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Protocol for a quasi-experimental study to assess the feasibility, acceptability and costs of multiple first-lines artemisinin-based combination therapies for uncomplicated malaria in the health district of Kaya, Burkina Faso.

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1. Abstract:

Introduction

A simultaneous deployment of multiple first-line therapies (MFT) for uncomplicated malaria using artemisinin-based combination therapies (ACTs), as demonstrated by mathematical models, may extend the useful therapeutic life of the current ACTs. This is possible by reducing drug pressure and slowing the spread of resistance without putting patients' life at risk. We hypothesized that a simultaneous deployment of three different ACTs, is feasible, acceptable and can achieve high coverage rate if potential barriers are well identified and well addressed.

Methods and analysis

We plan to conduct a quasi-experimental study in the health district of Kaya, in Burkina Faso. We will be investigating a simultaneous deployment of three ACTs, Artemether-Lumefantrin, Pyronaridine-Artesunate, Dihydroartesinin-Piperaquine, targeting three segments of the population: Pregnant women, children under five and individuals of five years old and above. The study will be rolled out through four overlapping phases: formative phase, the MFT deployment phase, the monitoring and evaluation phase and the post-evaluation phase. The formative phase will help to generate baseline information and to develop MFT deployment tools. It will be followed by the the MFT deployment in the catchment area. The monitoring and evaluation phase will start in parallel with the deployment of MFT. Cross-sectional surveys using desk review, qualitative and quantitative research methods will be used to assess study outcomes. A statistical analysis plan will be written and agreed according to the principal features stated in the protocol before the closure of the databases for statistical analysis. Content analysis will be used for the qualitative data.

Ethics and dissemination

The ethics committee for health research in Burkina Faso approved the study (Clearance N°2018-8-113). Study findings will be disseminated through feedback meetings with local communities, national workshop, oral presentations at congresses, seminars and publication in peer-reviewed scientific journals.

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2. Strengths and limitations of this study

- Theoretical models have shown that simultaneous deployment of ACTs for uncomplicated malaria case management may extend the useful therapeutic life of the current ACTs by reducing drug pressure and slowing the spread of resistance without putting lives at risk.
- This quasi-experimental study aims at assessing the feasibility, the acceptability and the cost of MFT strategy deploying three ACTs targeting three segments of the population for managing uncomplicated malaria.
- This study will provide shreds of evidence for policymakers to facilitate the rapid uptake of the strategy aiming at preventing the emergence and the spread of *P. falciparum* resistance to the ACTs in malaria-endemic areas.
- The study will not look at the changes in molecular markers of resistance of ACTs before and after the deployment of the MFT.

3. Introduction

Despite consolidated control efforts, malaria still remains the leading cause of morbidity and mortality in Burkina Faso. The transmission is intense and perennial but peaks during the rainy season. In 2016, a total of 9,362,608 uncomplicated malaria cases, 423,214 severe malaria cases and 3,974 malaria imputable deaths were recorded in all health facilities in Burkina Faso. Malaria was then responsible for 45% and 31% of outpatients visits at the peripheral health facilities and at medical centres/hospitals level respectively. At the peripheral health facilities, 60.4% of all-causes hospital admission and 40% of all-causes deaths were associated with malaria.(**1**) The main malaria vectors are *Anopheles gambiae, Anopheles arabiensis and Anopheles funestus.*(**2**)

Malaria control strategy in Burkina relies on: i) an integrated approach combining vector control tools, ii) chemoprevention in vulnerable groups (intermittent preventive treatment during pregnancy (IPTp) and the seasonal malaria chemoprevention (SMC) in children less than five years of age); and iii) prompt and adequate malaria case management both at community (CCMm) and health facility levels. (**2**)

One of the main threats to malaria control and elimination is the emergence and the spread of artemisinin-resistant *P. falciparum* parasites. Artemisinin resistance was first reported in Western Cambodia characterised by slow parasite clearance,(**3**,**4**) increased artemisinin-based combination therapies (ACTs) treatment failure rates,(**5**) and recently linked with point mutations in the “propeller” region of a *P. falciparum* Kelch protein.(**6**) Artemisinin resistance has since spread, emerged independently, or both in other areas of mainland Southeast Asia (**7**–**12**). To address this real threat, different approaches have been proposed, or are being developed such as the research and development of new antimalarial agents,(**13**) the concept of triple combination therapy in which two slowly eliminated partner drugs are combined with an artemisinin derivative,(**14**) the deployment of multiple first-line therapies (MFT) containing drugs with different or opposing selection pressures.(**15**) Although current ACTs still remain effective across sub-Saharan African countries, there is a need to promote new strategies optimising their use when slow progress is made in the development of new alternatives drugs.

In this study, we will evaluate to what extent the MFT strategy is feasible and acceptable. We will also document how much it will cost to the health system to deploy such strategy.

4. Methods and analysis

4.1 Study site

The study will be conducted in the health district of Kaya. A research platform, the Kaya Health and Demographic Surveillance System (Kaya-HDSS) has been established in this district since 2007 by the "Institut de Recherche en Sciences de la Santé" (IRSS) team. The district is located in the north-central region, 100 km from Ouagadougou, the capital of Burkina Faso. It covers four municipalities, including one urban and three rural with an estimated population of 365,585 inhabitants in 2016. (**1**) The district has forty (40) first-level public health facilities including 39 primary healthcare centres and one medical centre with a surgery unit. In addition, there are four private and confessional health facilities. The health district has the regional hospital of Kaya, which is the referral hospital for the north-central region. In 2016, the number of uncomplicated malaria cases recorded in the district was 150,796. The incidences of malaria in 2016 were 1.1 per person-year and 0.4 per person-year, respectively, in children less than five years of age and in the total population. The number of malaria cases treated with ACTs was 149,256 in the same year. (**1**)

In the district, healthcare is provided by the primary health centres, the medical centre and the regional hospital centre. Outpatient and inpatient services, vaccination services, child healthcare and antenatal care services are available 24 hours per day and 7 days per week. All health centres maintain a drug store where generic drugs are available. A free health care policy is in place in Burkina Faso since April 2016, covering children under five years of age and pregnant women.

As per World Health Organisation (WHO) recommendation, all cases of clinical malaria in Burkina Faso should be biologically confirmed with a malaria rapid diagnostic test (mRDT) or microscopy, when available, before any treatment. As per National Malaria Control programme guidelines, Artesunate-Amodiaquine or Artemether-Lumefantrin or Dihydroartemisinin-Piperaquine are the recommended first-line drugs for the treatment of uncomplicated malaria.(**16**)

4.2 Study design

This is a quasi-experimental study aiming at assessing the feasibility, acceptability and the costs of an MFT programme for uncomplicated malaria. The programme will be rolled out through four overlapping phases: the formative phase, the MFT deployment phase, the monitoring and evaluation phase and the post-evaluation phase as illustrated in ***figure 1***. A mixed-method, desk reviews, quantitative and qualitative surveys will be conducted to assess the programme outcomes. The programme is anticipated to last 22 months.

Three ACTs will be deployed at the health facility level. Each of them will be assigned to the management of uncomplicated malaria in a segment of the population as follows: Pyronaridine-Artesunate (Pyr-AS) for children under five, Artemether-Lumefantrin (AL) for pregnant women and Dihydroartesinin-Piperaquine (DHA-PQ) for individuals equal or more than 5 years. All these three ACTs are registered in Burkina Faso. The community case management of malaria will continue to be carried out following the current recommendations of the national malaria control programme, with the AL given across all age categories except pregnant women. Sufficient stocks of ACTs will be secured for the MFT deployment period to avoid both stock-outs and expiring of drugs. The supply chain of the ACTs will comply with the official drugs distribution channel illustrated in ***figure 2***. No parallel supply chain will be admitted. Any personnel involved in the implementation of the MFT programme will be identified and provided appropriate training for his/her role and responsibilities.

4.3 Study objectives

The objectives of the different phases of the programme are as follows:

- ***Formative phase***
  - General objective

    To generate baseline information and develop intervention tools for the MFT programme for uncomplicated malaria.
  - Specific objectives
    - To consolidate the programme working group;
    - To assess the perceptions and expectations of the Heath system's key stakeholders and the community members about the MFT programme;
    - To document any perceived or existing obstacles/threats to the implementation of the MFT programme;
    - To assess the treatment-seeking behaviour for febrile episodes /malaria;
    - To assess the morbidity and the mortality related to febrile episodes/malaria;
    - To develop a training manual, promotional and educational tools for optimising the implementation and uptake of the programme;
    - To develop tools for the monitoring and evaluation of the MFT programme implementation.

- ***MFT deployment phase***
  - General objective

To implement the MFT for uncomplicated malaria that is feasible, acceptable and can achieve a high coverage rate.

- Specific objectives
  - To train and sensitise the key stakeholders/implementers of the MFT programme;
  - To ensure continuous availability of study medicines delivered through the official drug supply chain system in Burkina Faso;
  - To promote adherence to the MFT programme within the study communities.

- ***Monitoring and evaluation phase***
  - General objective

    To assess the feasibility, the acceptability, the costs and the effects of the MFT programme for the management of uncomplicated malaria cases.
  - Specific objectives
    - To ensure continuous monitoring of the MFT deployment progress;
    - To assess the implementation of the MFT for uncomplicated malaria;
    - To determine the coverage of febrile episodes/malaria promptly and appropriately managed by health workers;
    - To determine the adherence of caregivers/febrile patients to ACT treatment regimen;
    - To assess the acceptability of the MFT deployment strategy;
    - To determine the costs for the implementation of the MFT programme at district level;
    - To assess the quality of care provided / performance of health workers;
    - To assess the impact of the MFT programme on the morbidity and mortality related to febrile episodes/malaria;
    - To assess the effects of the MFT programme on treatment-seeking behaviour for fever episodes/malaria.

4.4 Study outcomes

The study outcomes, the methods of assessment, the time-points for assessment, the targeted populations and the data collections tools are summarised in ***table 1 (***Supplemental materials).

4.5 Sampling strategies

Quantitative surveys

The true prevalence of fever episode/malaria at the community level in the programme settings and in the context of seasonal malaria chemoprevention is not well known. Considering a prevalence ranging between 30% and 60% during the high transmission season of malaria before the deployment of the MFT programme and a modest reduction of 10% during the deployment of the MFTs, a sample size of 450 in each survey group (children under five, children 5-15 years of age and 16-40 years of age) will be needed, with a confidence level of 95% and a desired power of 80% and an imponderable rate of 10%.

There is no formal sample size calculation for pregnant women. These will be recruited exhaustively as long as the fieldworkers identify them during the surveys at the community level. We will not perform any pregnancy testing at home. Pregnant women will be enrolled only with proof of ongoing pregnancy as documented in their antenal visit cards.

Qualitative surveys

The sampling strategy for the collection of the qualitative data are summarised in ***table 2***.

4.6 Data collection approaches

Quantitative surveys

Household surveys

A two-stage sampling process will be used. First, a sample of the targeted villages will be randomly selected from the list of all the villages in the health district of Kaya. Within selected villages, households will be randomly visited using a “random walk” method. Children less than five years of age, pregnant women, individuals aged 5 to 15 years and individuals aged 16 to 40 years (adult population) will be invited to take part in the survey until the sample size of the village is reached. A household is defined as a family unit where the head of the household and his spouse (s) and other relatives live together and share their income.

A paper questionnaire will be used to collect information from caregivers of children less than five years old, pregnant women, individuals, aged 5 to 15 years and 16 to 40 years.

Healthcare services utilisation

Information on the utilisation of health facilities by the community will be collected from the health facility registers and through interviews with target populations during the household surveys. The registers will provide a utilisation rate of the health facility, using as the denominator the total number of individuals in the target age groups living in the study area obtained from the HDSS. The interviews with target population will provide a coverage rate. For example, the proportion of fever episodes or confirmed malaria cases treated by the health workers according to the MFT programme. The denominator will be the total number of fever episodes or confirmed malaria cases that occurred in the four weeks preceding the

household surveys or the total number of cases of fever episodes/malaria seen at the health facility level.

Update of HDSS data

An exhaustive assessment of malaria-related morbidity and mortality will be conducted through the updates of the HDSS and comparing data from the year before the project with those generated during the year of deployment of the pilot MFT programme.

Qualitative surveys

In-depth interviews

In-depth individual interviews (IDI) will be conducted with diverse respondents including stakeholders of the Heath system (Central, intermediate and peripheral level), health system managers, health care providers and community members (key opinion leaders, pregnant women, mothers of children under 5 years of age, and adult population). IDI will be completed to establish the range of perceptions on the pilot MFT programme, and sources of care and overview of the intervention. The interviews will be conducted in the local language or in the language best- spoken by the participant and by trained social scientists using structured interview guides

Focus group discussion

Focus group discussions (FGDs) will be held with household heads (male participants), mothers (female caregivers), and adult's population, the potential beneficiaries of the care at the health facility level and health workers (HWs) in the programme catchment area. The aim will be to obtain data on perceptions of the pilot MFT programme and perceptions of fever/malaria case and its management. The discussion will be conducted in the language or the best-spoken language by the participants, using structured interview guides. The discussions will be recorded and then transcribed and translated into English for analysis. The FGDs will gather 8-12 participants per session.

Assessment of the cost to the health service of offering the MFT programme

The time utilised by HWs will be captured by asking them (possibly a sample) to keep a time log of their activities on the programme (diary). The value of their time will be obtained from estimates of opportunity costs (minimum wage, the average salary of the area). The programme accounting system will provide information on expenditures over the one and half year of the programme. Many of the resources such as programme personnel salaries, supplies, utilities and transport as well as mRDTs and ACTs will be considered. A visit to the

programme offices will serve to develop an inventory of capital goods like equipment, furniture, vehicles and size of offices.

For the personnel not directly involved in the intervention but still providing time for the programme, a questionnaire will be designed to capture their time during oral interviews at their place of work (health centres, regional offices…). With regards to the various preparatory activities during the start-up phase, the research team will develop and keep an inventory of all the resources utilised for identifying training workshops for HWs, development of IEC material and community mobilisation campaigns.

4.7 Data management and analysis

Quantitative data

Every month, health facilities-based summary data will be collected by the field supervisors using a standard data extraction form and monitoring report template. These data will be shared with the district health office and a copy will be sent to the research institution. Poor quality data issues and other queries will be managed regularly rather than at the end of the study to maximize data completeness and quality, and the timeliness of final analysis. All the data collected at both the health facility and the community level will be checked before being double entered independently in the database.

Efforts will be made during the study to track missing data and minimize its degree as no attempt will be made to impute for missing data during the final analysis. All the data entered will be checked for inconsistencies and corrections will be made accordingly. A statistical analysis plan will be written and agreed in accordance with the principal features stated in the protocol before freezing the database for statistical analysis.

Qualitative data

Data management will begin during data collection by transcribing and translating each audio-recorded IDI and FGD and expanded notes when audio recordings are not available. All transcripts will be typed into a word processing programme and stored on password-protected computers. All participants will be assigned unique identification codes to facilitate data tracking and no identifiable information will be collected. Data management logs may be created to track and monitor data collection and transcription.

As soon as possible after the interviews are conducted, each transcript will be read carefully by the study investigators in order to: (1) ask any question from the text that may be unclear; (2) point out areas in which interviewing and transcription techniques could be improved and (3) identify recurrent themes and areas for future probing.

Data-derived codes developed through inductive coding and retrieving will be used during analysis. A priori codes for retrieving text for key concepts related to the overall objectives also will be applied to the data. Investigators will determine a coding frame to be used based on the topic guides and the first few transcripts available for analysis. New codes will be added as necessary during transcript analysis. The qualitative data software program QSR NVivo, will be used to organize all qualitative data and prepare them for analysis. Procedures will be put into place to check for inter-coding discrepancies. Once all the transcripts will be coded, textual coding reports will be produced. Data reduction techniques will be used to examine codes in detail for sub-themes and patterns across the transcripts.

5. Ethics and dissemination

The study protocol and informed consent documents were approved by the National Ethics Committee for the Research on Health in Burkina Faso. The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza in 2013.

All participants in the different surveys of the formative and evaluation phases will be asked to voluntarily give written informed consent before any study-specific data collection. A copy of the informed consent form will be shared with each participant. Participant's full name will not be written on any data collection instruments and an identification codes will be assigned to each participant. Participants names will not be written in the transcripts of the interviews. Unique identification numbers will also be assigned to each participant during data analysis activities. All electronic files will be password protected and stored on password-protected computers. The copies of all the informed consent forms will be stored securely in a locked cabinet at the research institution offices, separately from study questionnaires or interview transcripts. Names will not be included in any formal or informal presentation and in any manuscript.

There are few anticipated risks associated with participation in the different surveys. Some participants may feel uncomfortable or embarrassed when asked questions about their current practices or their attitudes towards malaria case management. The research staff will make all the effort to protect individual participants' privacy and confidentiality. There are no direct benefits to participants from taking part in the various surveys. However, the information provided by the participants will be immediately used to inform the design of MFT pilot programme and later will be useful to generate evidence to support decision-makers on the adoption of the MFT strategy for uncomplicated malaria.

Any protocol's amendment will be agreed upon between the investigators and MMV project management team in the form of a written amendment. Amended protocols will then be submitted for ethical clearance.

The findings of this study will be disseminated through feedback meetings for reporting to local communities, national workshop with researchers, policy-makers, and oral presentations at national and international congresses, conferences, and seminars. We will also submitted the results to peer-reviewed scientific journals for publications.

6. Patient and public involvement

Study participants were not involved in the development of the research question, outcome measures, and in the design of the study. They will not be also involved in the recruitment procedures. Data will be collected from households, study participants both at the community level and at the health facility level. Households in the study area will be randomly selected and potential subjects living within the selected households and who meet the eligibility criteria will be invited to participate in the study after obtaining informed consent. Study results will be disseminated to the study populations through feedback meetings with the communities' leaders and representatives.

7. Discussion

The MFT programme has not yet been implemented in a structured way in sub-Saharan Africa. This study will be among the first to generate evidence of the feasibility, acceptability and cost of MFT stragtegy.

The MFT is one of the potential strategy that could effectively mitigate the enormous threat in the figth against malaria which is the emergence and spread of artemisinin resistance. Indeed, the loss of artemisinin effectiveness would likely result in the loss of all ACTs. Therefore, there is urgent need to identify and to implement in sub-Saharan Africa a better way to optimise the use of these ACTs that could provide a much higher long-term barrier to the emergence and/or the spread of resistance and thus protecting them. Theoretical models showed that the simultaneous deployment of MFT for uncomplicated malaria is a promising strategy to extend the useful therapeutic life of the current ACTs by reducing drug pressure and slowing the spread of resistance without putting lives at risk. The development of feasible strategies for implementing MFT is therefore recommended.(**17**,**18**) Treating half of the population with one ACT and the other half with a different ACT would reduce the fitness of resistant parasites approximately as well as treating half as many patients.(**19**) Therefore, there is an advantage in deploying two or more ACTs. There are several scenarios for

implementing MFT strategy depending on the target: i) the partition of the ACTs market by segments of the same population: paediatric patients, pregnant women, adults patients, ii) the distribution of one ACT for home-based care and use a different ACT in the clinic, iii) the mosaic distribution of ACTs i.e. an alternating distribution of different ACTs in the same population over a given period of time… (**20**)

The deployment of the MFT, whatever the strategy, would present several challenges including planning for the right distribution channel of the ACTs, the management of the logistics, the compensation of the higher costs of some ACTs, the adjustment of health system delivery due to a lower preference for some drugs. Findings from this research are pivotal to inform stakeholders on the future of this strategy.

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10. Authors' contributions

MS, AMT, IS and SBS conceived the study. MS, AMT, IS, ABT and SBS developed the study protocol. YN, AKK, NB, AH, YS, SK participated in the finalization of the protocol. MS wrote the first draft of the manuscript. MS, AMT, IS, JMTK, YN, DH, AKK, NB, AB, AH, FD, YS, SK, ABT, SBS critically reviewed the manuscript. MS, AMT, IS, JMTK, YN, DH, AKK, NB, AB, AH, FD, YS, SK, ABT, SBS approved the final version of the manuscript.

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12. Competing interests' statement: None declared.

13. Ethics approval: Comité d'éthique pour la recherché en santé (CERS), Burkina Faso

14. Provenance and peer review: Not commissioned, externally peer reviewed.

Figures and tables

Table 2: Sampling strategy

Target group	Data Collection methods and sample size	Sampling strategy
The national malaria control programme	3 IDI	All personnel with a key role in malaria case management strategy delivery
Central essential drugs store (CAMEG)	3 IDI	All personnel with a key role in ACTs ordering and inventory management
North-central health region (Head of the health region, Lead pharmacist, Responsible of the disease control service)	3 IDI	All personnel with a key role in malaria case management strategy delivery
Heath district management team of Kaya (Head of the health district, Lead pharmacist Responsible for the district-level healthcare provision)	3 IDI	All personnel with a key role in malaria case management strategy delivery
Head of the local health facilities	5 IDI, 4 FGD	5 heads of the local health facilities in the health district of Kaya will be randomly selected and invited for the IDI. The 40 heads of local health facilities will be allocated randomly into for groups for FGD.
Essential drugs stores managers at health facilities level	5 IDI, 4 FGD	5 essential drugs storekeepers of the local health facilities in the health district of Kaya will be randomly selected and invited for the IDI. The 40 essential drugs storekeepers of local health facilities will be allocated randomly into for groups for FGD.
Local health workers	10 FGD	10 local health facilities in the health district of Kaya will be randomly selected and the local health workers in charge of malaria case management in pregnant women, children under five and individuals of five years old and above, will be grouped for the conduct of the FGD.
Community key opinion leaders	10 IDI, 4 FGD	10 local health facilities in the health district of Kaya will be randomly selected, and the head of the health facilities will appoint a community leader per their respective health area for the conduct of the IDI. Subsequently, 4 community leaders per 10 health facility previously selected will be identified by the head of the health facility to constitute the group for the conduct of the FGD.
Heads of household (male participants)	5 FGD	During the household surveys, villages will be selected at random within the health district of Kaya. Households will be selected at random via the random walk method, with the interval selected dependent on village size and the head of households (males) will be invited for the conduct of FGD.

Caregivers of children under five (female participants)	5 FGD	During the household surveys, villages will be selected at random within the health district of Kaya. Caregivers (mothers of children under five) will be selected at random via the random walk method, with the interval selected dependent on village size and will be invited for the conduct of FGD.
Pregnant women	5 FGD	During the household surveys, villages will be selected at random within the health district of Kaya. Pregnant women will be selected at random via the random walk method, with the interval selected dependent on village size and will be invited for the conduct of FGD.
Adult participants	5 FGD	During the household surveys, villages will be selected at random within the health district of Kaya. Adult potential participants will be selected at random via the random walk method, with the interval selected dependent on village size and will be invited for the conduct of FGD.
Total of interviews	**32 IDI and 42 FGD**	

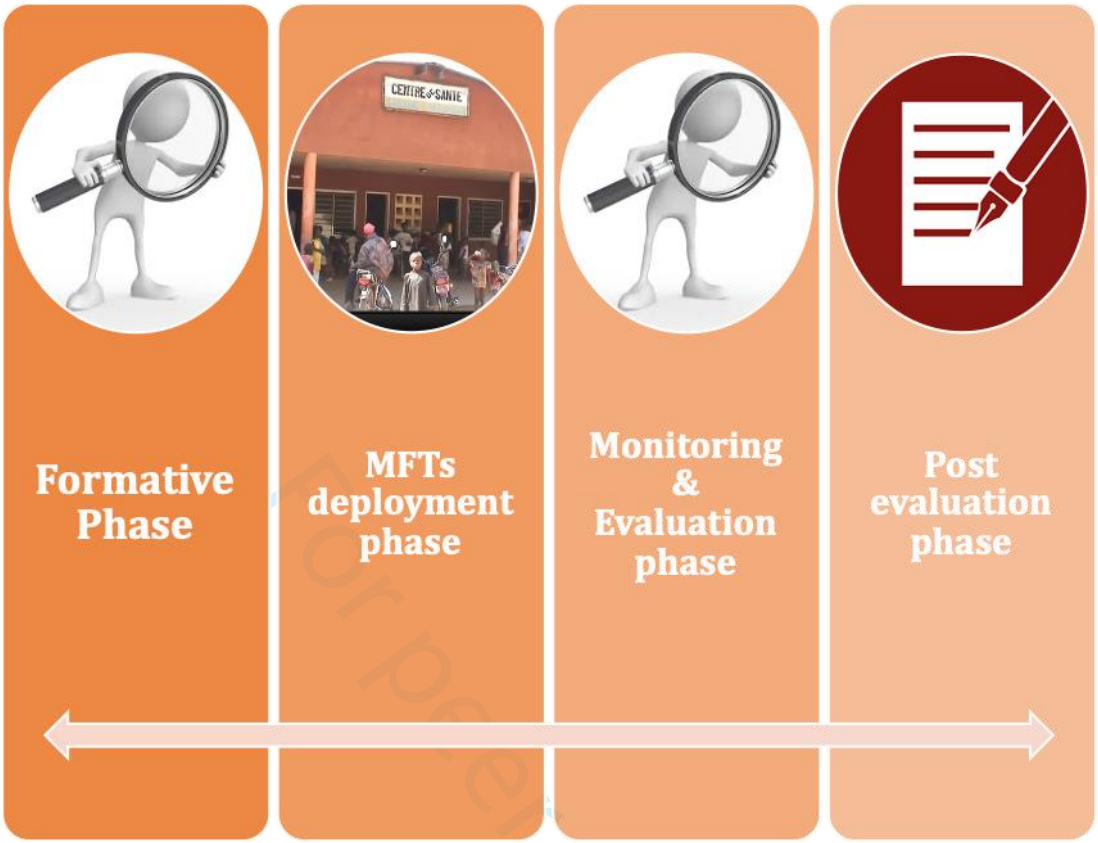
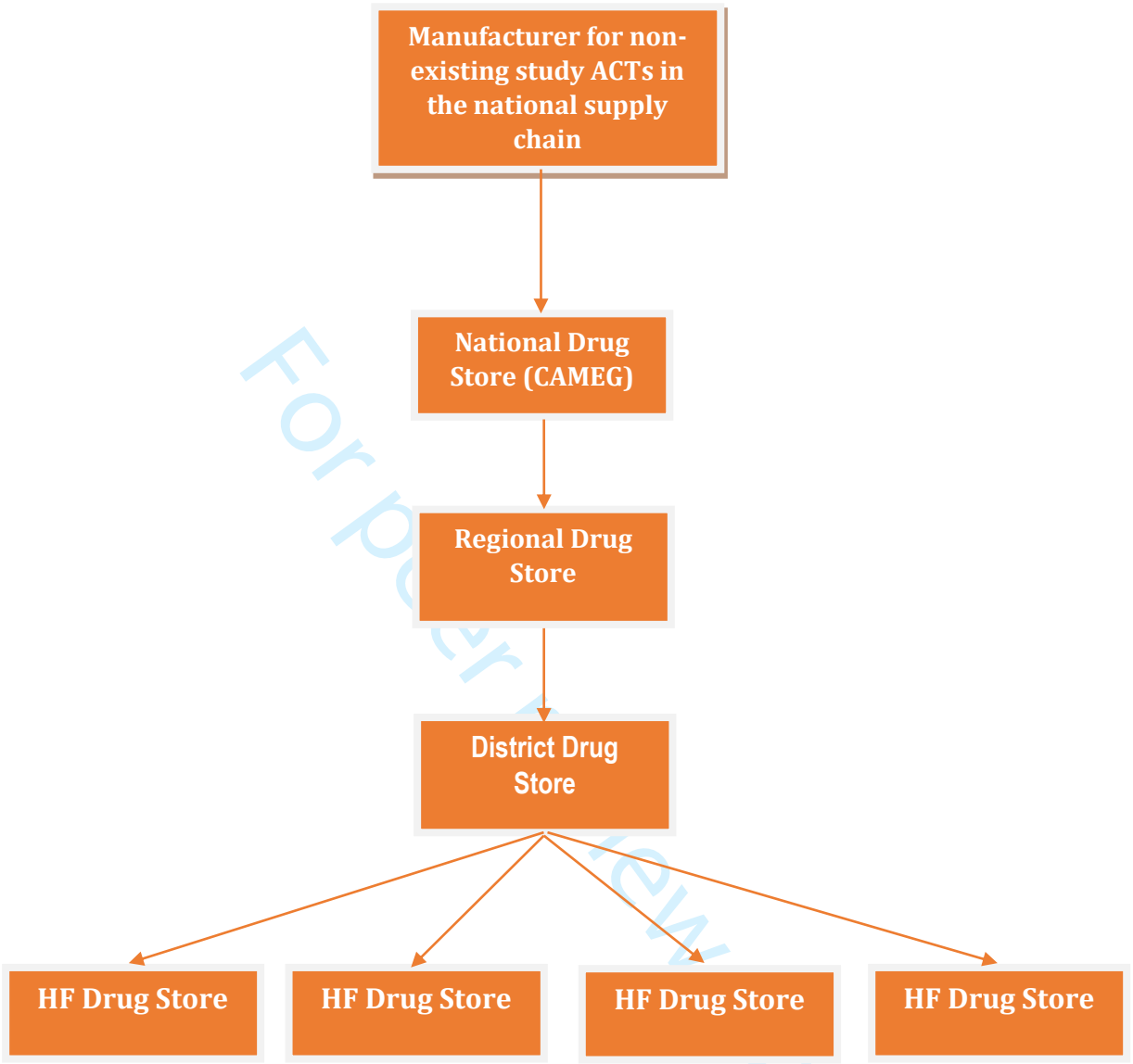


Figure 1: Design of the programme



HF: health facility

Figure 2: Artemisinin-based combination therapies flow in the framework of the MFT programme

Table 1: Outcomes to be measured during the monitoring and evaluation phase

Outcomes	Indicators	Numerator/ Denominator	Methods of assessment	Time point for assessment	Targeted populations	Data collection tools
Outcome 1: the implementation of the MFT pilot programme	- Average number of monitoring visits per health facility and drugs stores involved in the study per annum	Numerator: Number of monitoring visits per health facility and drugs stores involved in the study per annum Denominator: Number of health facility and drugs stores involved in the study	Health facility-based survey Central, regional and district-based surveys	End of MFTs deployment phase	Heath facilities Drugs stores	Monitoring visit report template
	- Average number of monitoring visit on which drugs stores have stock out of any dose of study ACTs per annum	Numerator: Number of monitoring visit on which drugs stores have stock out of any dose of study ACTs per annum Denominator: Number of drugs stores involved in the study	Health facility-based survey Central, regional and district-based surveys	End of MFTs deployment phase	Drugs stores	Monitoring visit report template
	- Average number of monitoring visit on which health facilities have stock out of mRDTs per annum	Numerator: Number of monitoring visit on which health facilities have stock out of mRDTs per annum Denominator: Number of health facilities involved in the study	Health facility-based survey Central, regional and district-based surveys	End of MFTs deployment phase	Drugs stores	Monitoring visit report template
Outcome 2: The coverage of febrile episode/malaria promptly and appropriately managed by health workers according to the MFT pilot programme	- Proportion of febrile episode seen at the health facility level	Numerator: Number of febrile episodes taken to a health facility Denominator: Number of febrile episodes	Household survey	During MFTs deployment phase at peak malaria season	Caregivers, pregnant women, adults	KAP questionnaire
	- Proportion of febrile episode seen at health facility level (HFL) within 24 hours	Numerator: Number of febrile episodes taken to a health facility within 24h Denominator: Number of febrile episodes	Household survey Health facility-based survey	During MFTs deployment phase at peak malaria season	Caregivers, pregnant women, adults Registers of health facility	KAP questionnaire Data extraction forms

				End of MFTs deployment phase		
	- Proportion of febrile episode seen at HFL within 24 hours and tested for parasitemia	Numerator: Number of febrile episodes seen at the health facility and tested for parasitemia Denominator: Number of febrile episodes taken to a health facility	Household survey Health facility-based survey	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, pregnant women, adults Registers of health facility	KAP questionnaire Data extraction forms
	- Proportion of febrile episode seen at HFL within 24 hours with positive diagnostic test who were given ACT according to the MFTs strategy	Numerator: Number of febrile episodes seen at a health facility with a positive diagnostic test and treated with ACT according to the MFTs strategy Denominator: Number of febrile episodes with a positive diagnostic test	Household survey Health facility-based survey	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, pregnant women, adults Registers of health facility	KAP questionnaire Data extraction forms
	- Proportion of febrile episode seen at HFL within 24 hours with a negative diagnostic test who did not receive any antimalarial.	Numerator: Number of febrile episodes seen at a health facility with a negative diagnostic test and not treated with ACT according to the MFTs strategy Denominator: Number of febrile episodes with a negative diagnostic test	Household survey Health facility-based survey	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, pregnant women, adults Registers of health facility	KAP questionnaire Data extraction forms
	- Proportion of febrile episode seen at HFL within 24 hours with a negative diagnostic test who received an ACT.	Numerator: Number of febrile episodes seen at a health facility with a negative diagnostic test and treated with ACT Denominator: Number of febrile episodes with a negative diagnostic test	Household survey Health facility-based survey	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, pregnant women, adults Registers of health facility	KAP questionnaire Data extraction forms

Outcome 3: the adherence of caregivers/febrile patients to ACTs treatment schedule provided by health workers according to MFTs pilot programme	Proportion of febrile episodes treated with ACTs adhering to ACT treatment schedule (timing and doses) by HWs according to MFTs strategy	Numerator: Number of febrile episodes treated with ACT provided by health workers according to MFTs strategy adhering to ACT treatment schedule (timing and dosing) Denominator: Number of febrile episodes treated with ACT provided by health workers according to MFTs strategy	Household surveys	During MFTs deployment phase at peak malaria season	Caregivers, adults, pregnant women	KAP Questionnaire
Outcome 4: The acceptability of the MFT pilot programme	- Number of favourable and unfavourable opinions from various profiles of informants about the intervention, including health agents of different levels and authorities, concerning the MFTs pilot programme. - Proportion of community resources people (mothers/caregivers, health agents, heads of household (male participants) community leaders) with favourable opinions to the MFTs pilot programme and their reasons - Proportion of community resources people (mothers/caregivers, health agents, heads of household (male participants) community leaders) with unfavourable opinions to the MFTs pilot programme and their reasons	Numerator: Exploration of selected informants' opinions Comparison of different opinions Denominator: Caregivers, pregnant women, adults, community leaders, health workers, health authorities	Qualitative surveys Household surveys	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, adults, pregnant women, key community leaders, health workers, health authorities	FGD, IDI guides KAP questionnaire
Outcome 5: the cost of the MFT pilot programme	- Cost per additional febrile episode receiving prompt treatment or confirmed negative diagnosis	Numerator: Total economic cost, cost savings Denominator: Additional number of febrile episodes given ACT with a negative parasitological test within 24 hours	Household survey Health facility-based survey	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, pregnant women, adults Health workers	Cost data collection forms KAP questionnaire Data extraction forms at the health facility level

					Registers of health facility	
	- Cost per additional inappropriate antimalarial treatment avoided	Numerator: Total economic cost, cost savings Denominator: Additional number of confirmed negative episodes not treated with an ACT	Household survey Health facility-based survey	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, pregnant women, adults Health workers Registers of health facility	Cost data collection forms KAP questionnaire Data extraction forms at the health facility level
	- Cost per additional febrile episode appropriate managed for malaria with a confirmed diagnosis	Numerator: Total economic cost, cost savings Denominator: Additional number of febrile episodes treated with ACT or with a negative parasitological test within 24 hours	Household surveys Health facility-based surveys	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, adults, pregnant women, health workers Registers of health facilities,	KAP Questionnaire, Cost data collection forms Data extraction forms at the health facility level
	- Cost per capita of intervention (provider and societal perspective)	Numerator: Total economic cost-Cost savings Total financial cost-cost saving Denominator: Population of the area	Household surveys Health facility-based surveys	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, pregnant women, adults Health workers Registers of health facility	Cost data collection forms Census data collection forms

	- Cost to the HWs to participate in the MFTs strategy	Numerator: Economic costs to HWs participating in the MFTs strategy Denominator: Number of HWs	Health facility-based surveys	End of MFTs deployment phase	Health workers Registers of health facility	Cost data collection forms
Outcome 6: the quality of care provided /performance of health workers	- Proportion of episode of uncomplicated fever seen by HWs tested for malaria parasitemia	Numerator: Number of episodes of uncomplicated fever seen by HWs tested with mRDT/blood smear Denominator: Number of uncomplicated fever episodes/malaria fever seen by HWs	Health facility-based surveys Household surveys	End of MFTs deployment phase During MFTs deployment phase at peak malaria season	Registers of health facilities Caregivers, adults, pregnant women, health workers	Data extraction forms KAP questionnaire
	- Proportion of uncomplicated fever episodes/malaria seen by HW, tested positive and treated with the correct dose of ACT according to MFTs pilot programme	Numerator: Number of uncomplicated fever episodes/Malaria seen by HWs, tested positive and treated with the correct dose of ACT according to MFTs pilot programme Denominator: Number of uncomplicated fever episodes/malaria seen by HWs and tested positive.	Health facility-based surveys Household surveys	End of MFTs deployment phase During MFTs deployment phase at peak malaria season	Registers of health facilities Caregivers, adults, pregnant women, health workers	Data extraction forms KAP questionnaire
	- Proportion of febrile episodes treated with ACTs according to MFTs pilot programme by HWs provided with appropriate dosing advice	Numerator: Number of uncomplicated febrile episodes/malaria treated with ACTs according to MFTs approach by HWs provided with appropriate dosing advice Denominator: Number of uncomplicated febrile episodes/malaria treated with ACTs according to MFTs pilot programme by HWs	Health facility-based surveys Household surveys	End of MFTs deployment phase During MFTs deployment phase at peak malaria season	Registers of health facilities Caregivers, adults, pregnant women, health workers	Data extraction forms KAP questionnaire

	- Proportion of uncomplicated febrile episodes/malaria seen by HWs provided with advice on danger signs	Numerator: Number of uncomplicated febrile episodes/malaria seen by HWs provided with advice on danger signs Denominator: Number of uncomplicated febrile episodes/malaria seen by HWs	Health facility-based surveys Household surveys	End of MFTs deployment phase During MFTs deployment phase at peak malaria season	Registers of health facilities Caregivers, adults, pregnant women, health workers	Data extraction forms KAP questionnaire
Outcome 7: the impact of MFT pilot programme on malaria incidence	- Incidence of uncomplicated febrile episode/malaria within 4 weeks preceding the survey, before and during the MFTs deployment	- Numerator: Number of uncomplicated febrile episode/malaria within 4 weeks preceding the survey, before and during the MFTs deployment - Denominator: Number of persons per segments of the population	Household surveys,	MFTs deployment phase at the peak of the malaria season	Caregivers, adults, pregnant women	KAP Questionnaire,
	- Proportion of uncomplicated febrile episode/malaria seen at health facility level before and during the MFTs deployment in the study area	- Numerator: Number of uncomplicated febrile episodes/malaria seen by HWs at HFL during study periods (before and during the MFTs deployment) per segments of the population - Denominator: Number of person-years per segments of the population during the study periods	Health facility level	End of MFTs deployment phase	Registers of health facilities	Data extraction forms
Outcome 8: the impact of the MFT pilot programme on malaria mortality	- Mortality rate related to febrile episode/malaria before and during the pilot MFTs deployment	- Numerator: Number of malaria-associated deaths before and during the pilot MFTs deployment phase per segments of the population - Denominator: Number of person-years per segments of the population	Household surveys, Health facility level	End of MFTs deployment phase	Caregivers, adults, pregnant women Registers of health facilities	HDSS mortality data collection forms Data extraction forms
Outcome 9: the effect of MFT pilot programme on	- Proportion of individuals with fever in the last four weeks for whom advice or treatment was sought	- Numerator: Number of individuals with fever in the last four weeks for whom advice or treatment was sought	Household surveys	MFTs deployment phase at the	Caregivers, adults,	KAP Questionnaire

treatment-seeking behaviour for fever episodes/malaria		- Denominator: Number of individuals with fever in the last four weeks		peak of the malaria season	pregnant women	
	- Proportion of individuals with fever in the last four week who sought treatment at HFL within 24 hours	- Numerator: Number of individuals with fever in the last four weeks who sought treatment at HFL within 24 hours - Denominator: Number of individuals with fever in the last four weeks	Household surveys	MFTs deployment phase at the peak of the malaria season	Caregivers, adults, pregnant women	KAP Questionnaire
	- Source of advice or care for those suffering from fever in the last four weeks	- Numerator: Number per type of source of advice or care for those suffering from fever in the last four weeks - Denominator: Number of individual suffering from fever in the last four weeks who sought advice or care	Household surveys	MFTs deployment phase at the peak of the malaria season	Caregivers, adults, pregnant women	KAP Questionnaire

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Protocol for a quasi-experimental study to assess the feasibility, acceptability and costs of multiple first-lines artemisinin-based combination therapies for uncomplicated malaria in the health district of Kaya, Burkina Faso.

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Keywords:	Tropical medicine < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, CHEMOTHERAPY, Epidemiology < INFECTIOUS DISEASES, Epidemiology < TROPICAL MEDICINE

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Protocol for a quasi-experimental study to assess the feasibility, acceptability and costs of multiple first-lines artemisinin-based combination therapies for uncomplicated malaria in the health district of Kaya, Burkina Faso.

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1. Abstract:

Introduction

A simultaneous deployment of multiple first-line therapies (MFT) for uncomplicated malaria using artemisinin-based combination therapies (ACTs), as demonstrated by mathematical models, may extend the useful therapeutic life of the current ACTs. This is possible by reducing drug pressure and slowing the spread of resistance without putting patients' life at risk. We hypothesized that a simultaneous deployment of three different ACTs, is feasible, acceptable and can achieve high coverage rate if potential barriers are well identified and well addressed.

Methods and analysis

We plan to conduct a quasi-experimental study in the health district of Kaya, in Burkina Faso. We will be investigating a simultaneous deployment of three ACTs, Artemether-Lumefantrin, Pyronaridine-Artesunate, Dihydroartesinin-Piperaquine, targeting three segments of the population: Pregnant women, children under five and individuals of five years old and above. The study will be rolled out through four overlapping phases: formative phase, the MFT deployment phase, the monitoring and evaluation phase and the post-evaluation phase. The formative phase will help to generate baseline information and to develop MFT deployment tools. It will be followed by the the MFT deployment in the catchment area. The monitoring and evaluation phase will start in parallel with the deployment of MFT. Cross-sectional surveys using desk review, qualitative and quantitative research methods will be used to assess study outcomes. Univariate, bivariate and multivariate analysis including logistic regression and interrupted time series analysis approach will be used to assess quantitative study outcomes.Content analysis will be used for the qualitative data.

Ethics and dissemination

The ethics committee for health research in Burkina Faso approved the study (Clearance N°2018-8-113). Study findings will be disseminated through feedback meetings with local communities, national workshop, oral presentations at congresses, seminars and publication in peer-reviewed scientific journals.

ClinicalTrials.gov Identifier: NCT04265573

2. Strengths and limitations of this study

- Theoretical models have shown that simultaneous deployment of ACTs for uncomplicated malaria case management may extend the useful therapeutic life of the current ACTs by reducing drug pressure and slowing the spread of resistance without putting lives at risk.
- This quasi-experimental study aims at assessing the feasibility, the acceptability and the cost of MFT strategy deploying three ACTs targeting three segments of the population for managing uncomplicated malaria.
- This study will provide shreds of evidence for policymakers to facilitate the rapid uptake of the strategy aiming at preventing the emergence and the spread of *P. falciparum* resistance to the ACTs in malaria-endemic areas.
- The study will not look at the changes in molecular markers of resistance of ACTs before and after the deployment of the MFT.

3. Introduction

Despite consolidated control efforts, malaria still remains the leading cause of morbidity and mortality in Burkina Faso. The transmission is intense and perennial but peaks during the rainy season. In 2018, a total of 11,463,808 uncomplicated malaria cases, 506,513 severe malaria cases and 4,294 malaria imputable deaths were recorded in all health facilities in Burkina Faso. Malaria was then responsible for 41.3% and 25.9% of outpatients visits at the peripheral health facilities and at medical centres/hospitals level respectively. At the peripheral health facilities, 57% of all-causes hospital admission and 36.3% of all-causes deaths were associated with malaria.(**1**) The main malaria vectors are *Anopheles gambiae, Anopheles arabiensis and Anopheles funestus.*(**2**)

Malaria control strategy in Burkina relies on: i) an integrated approach combining vector control tools, ii) chemoprevention in vulnerable groups (intermittent preventive treatment during pregnancy (IPTp) and the seasonal malaria chemoprevention (SMC) in children less than five years of age); and iii) prompt and adequate malaria case management both at community (CCMm) and health facility levels. (**2**)

As per World Health Organisation (WHO) recommendation, all cases of clinical malaria in Burkina Faso should be biologically confirmed with a malaria rapid diagnostic test (mRDT) or microscopy, when available, before any treatment. As per National Malaria Control Programme (NMCP) guidelines, three artemisinin based combination therapies (ACTs), Amodiaquine-Artesunate (AQ-AS) or Artemether-Lumefantrin (AL) or Dihydroartemisinin-Piperaquine (DHA-PQ) are the recommended first-line drugs for the treatment of uncomplicated malaria. (**3**) The granules for oral suspension of Pyronaridine-Artesunate (PYR-AS) prequalified by WHO, has been registered in Burkina Faso and is available at private pharmacies across the country. Several studies conducted in sub-Saharan Africa including Burkina Faso have demonstrated the safety and the efficacy of these four ACTs (AS-AQ, AL, DHA-PQ and PYR-AS) against uncomplicated malaria. (**4–7**) Oral quinine is recommended for the management of uncomplicated malaria cases in pregnant woman as well as ACTs except the first trimester of pregnancy. Four ACTs (DHA-PQ, AL, AS-AQ and Artesunate-Mefloquine) shown to be safe and effective in pregnant women in sub-Saharan Africa including Burkina Faso as reported by the PREGACT Study group. (**8**)

One of the main threats to malaria control and elimination is the emergence and the spread of artemisinin-resistant *P. falciparum* parasites. Artemisinin resistance was first reported in Western Cambodia characterised by slow parasite clearance,(**9,10**) increased ACTs treatment failure rates,(**11**) and recently linked with point mutations in the “propeller” region

of a *P. falciparum* Kelch protein.(**12**) Artemisinin resistance has since spread, emerged independently, or both in other areas of mainland Southeast Asia (**13–18**). To address this real threat, different approaches have been proposed, or are being developed such as the research and development of new antimalarial agents,(**19**) the concept of triple combination therapy in which two slowly eliminated partner drugs are combined with an artemisinin derivative,(**20**) the deployment of multiple first-line therapies (MFT) containing drugs with different or opposing selection pressures.(**21**) Although current ACTs still remain effective across sub-Saharan African countries, there is a need to promote new strategies optimising their use when slow progress is made in the development of new alternatives drugs.

In this study, we will evaluate to what extent the MFT strategy is feasible and acceptable. We will also document how much it will cost to the health system to deploy such strategy.

4. Methods and analysis

4.1 Study site

The study will be conducted in the health district of Kaya. A research platform, the Kaya Health and Demographic Surveillance System (Kaya-HDSS) has been established in this district since 2007 by the "Institut de Recherche en Sciences de la Santé" (IRSS) team. (**22**) The district is located in the north-central region, 100 km from Ouagadougou, the capital of Burkina Faso. It covers four municipalities, including one urban and three rural with an estimated population of 1,687,858 inhabitants in 2018. (**1**) The district has forty (40) first-level public health facilities including 39 primary healthcare centres and one medical centre with a surgery unit. In addition, there are four private and confessional health facilities. The health district has the regional hospital of Kaya, which is the referral hospital for the north-central region. In 2018, the number of uncomplicated malaria cases recorded in the district was 191,771. The incidences of malaria in 2018 were 1.27 per person-year and 0.4 per person-year, respectively, in children less than five years of age and in the total population. The number of malaria cases treated with ACTs was 188,527 in the same year. (**1**)

In the district, healthcare is provided by the primary health centres, the medical centre and the regional hospital centre. Outpatient and inpatient services, vaccination services, child healthcare and antenatal care services are available 24 hours per day and 7 days per week. All health centres maintain a drug store where generic drugs are available. A free health care policy is in place in Burkina Faso since April 2016, covering children under five years of age and pregnant women.

4.2 Study design

This is a quasi-experimental study aiming at assessing the feasibility, acceptability and the costs of a MFT programme for uncomplicated malaria. The programme will be rolled out through four overlapping phases: the formative phase, the MFT deployment phase, the monitoring and evaluation phase and the post-evaluation phase as illustrated in ***figure 1***. A mixed-method, desk reviews, quantitative and qualitative surveys will be conducted to assess the programme outcomes. The programme is anticipated to last 22 months, from 2019 to 2021.

Three ACTs will be deployed at the health facility level. Each of them will be assigned to the management of uncomplicated malaria in a segment of the population as follows: PYR-AS for children under five, AL for pregnant women and DHA-PQ for individuals equal or more than 5 years. The community case management of malaria will continue to be carried out following the current recommendations of the NMCP, with the AL given across all age categories except pregnant women. Sufficient stocks of ACTs will be secured for the MFT deployment period to avoid both stock-outs and expiring of drugs. The supply chain of the ACTs will comply with the official drugs distribution channel illustrated in ***figure 2***. No parallel supply chain will be admitted. Any personnel involved in the implementation of the MFT programme will be identified and provided appropriate training for his/her role and responsibilities. The inclusion and non-inclusion criteria for the three study ACTs are, as follows:

- For PYR-AS: inclusion criteria is the age less that five years and weight equal and more than 5 kilogrammes. The non – inclusion criteria is the know hypersensitivity to a component of PYR-AS.
- For DHA-PQ: inclusion criteria is the age equal and more than five years and non-inclusion is the know hypersensitivity to a component of DHA-PQ.
- For AL: inclusion criteria is pregnant woman and non-inclusion criteria is first trimester of pregnancy and know hypersensitivity to one component of AL.

4.3 Study objectives

The objectives of the different phases of the programme are as follows:

- ***Formative phase***
  - General objective

    To generate baseline information and develop intervention tools for the MFT programme for uncomplicated malaria.
  - Specific objectives
    - To consolidate the programme working group;

- To assess the perceptions and expectations of the Heath system's key stakeholders and the community members about the MFT programme;
- To document any perceived or existing obstacles/threats to the implementation of the MFT programme;
- To assess the treatment-seeking behaviour for febrile episodes /malaria;
- To assess the morbidity and the mortality related to febrile episodes/malaria;
- To develop a training manual, promotional and educational tools for optimising the implementation and uptake of the programme;
- To develop tools for the monitoring and evaluation of the MFT programme implementation.

- ***MFT deployment phase***
  - General objective

    To implement the MFT for uncomplicated malaria that is feasible, acceptable and can achieve a high coverage rate.
  - Specific objectives
    - To train and sensitise the key stakeholders/implementers of the MFT programme;
    - To ensure continuous availability of study medicines delivered through the official drug supply chain system in Burkina Faso;
    - To promote adherence to the MFT programme within the study communities.

- ***Monitoring and evaluation phase***
  - General objective

    To assess the feasibility, the acceptability, the costs and the effects of the MFT programme for the management of uncomplicated malaria cases.
  - Specific objectives
    - To ensure continuous monitoring of the MFT deployment progress;
    - To assess the implementation of the MFT for uncomplicated malaria;
    - To determine the coverage of febrile episodes/malaria promptly and appropriately managed by health workers;
    - To determine the adherence of caregivers/febrile patients to ACT treatment regimen;

- To assess the acceptability of the MFT deployment strategy;
- To determine the costs for the implementation of the MFT programme at district level;
- To assess the quality of care provided / performance of health workers;
- To assess the impact of the MFT programme on the morbidity and mortality related to febrile episodes/malaria;
- To assess the effects of the MFT programme on treatment-seeking behaviour for fever episodes/malaria.

4.4 Study outcomes

The study outcomes, the methods of assessment, the time-points for assessment, the targeted populations and the data collections tools are summarised in ***Supplementary table 1*** .

4.5 Sampling strategies

Quantitative surveys

The true prevalence of fever episode/malaria at the community level in the programme settings and in the context of seasonal malaria chemoprevention is not well known. Considering a prevalence ranging between 30% and 60% during the high transmission season of malaria before the deployment of the MFT programme and a modest reduction of 10% during the deployment of the MFT, a sample size of 450 in each survey group (children under five, children 5-15 years of age and 16-40 years of age) will be needed, with a confidence level of 95% and a desired power of 80% and an imponderable rate of 10%.

There is no formal sample size calculation for pregnant women. These will be recruited exhaustively as long as the fieldworkers identify them during the surveys at the community level. We will not perform any pregnancy testing at home. Pregnant women will be enrolled only with proof of ongoing pregnancy as documented in their antenal visit cards.

Qualitative surveys

The sampling strategy for the collection of the qualitative data are summarised in ***table 1***.

4.6 Data collection approaches

Quantitative surveys

Household surveys

A two-stage sampling process will be used. First, a sample of the targeted villages will be randomly selected from the list of all the villages in the health district of Kaya. Within selected

villages, households will be randomly visited using a “random walk” method. Children less than five years of age, pregnant women, individuals aged 5 to 15 years and individuals aged 16 to 40 years (adult population) will be invited to take part in the survey until the sample size of the village is reached. A household is defined as a family unit where the head of the household and his spouse (s) and other relatives live together and share their income.

A paper questionnaire will be used to collect information from caregivers of children less than five years old, pregnant women, individuals, aged 5 to 15 years and 16 to 40 years.

Healthcare services utilisation

Information on the utilisation of health facilities by the community will be collected from the health facility registers and through interviews with target populations during the household surveys. The registers will provide a utilisation rate of the health facility, using as the denominator the total number of individuals in the target age groups living in the study area obtained from the Kaya-HDSS. The interviews with target population will provide a coverage rate. For example, the proportion of fever episodes or confirmed malaria cases treated by the health workers according to the MFT programme. The denominator will be the total number of fever episodes or confirmed malaria cases that occurred in the four weeks preceding the household surveys or the total number of cases of fever episodes/malaria seen at the health facility level.

Update of Kaya-HDSS data

An exhaustive assessment of malaria-related morbidity and mortality will be conducted through the updates of the Kaya-HDSS and comparing data from the year before the project with those generated during the year of deployment of the MFT programme.

Qualitative surveys

The qualitative surveys will be carried out by socials scientists (interviewers/facilitators) holding a Bachelor/Master degree in socio-anthropology under the coordination of a senior social scientist. They will be recruited through a call for application and then well-trained on the objectives of the study, the specific standard operating procedures, the data collection tools and the process of consent taking. The training sessions will be followed by pre-tests on the ground in order to address any misunderstanding of the interview guides, the process of data collection and to adapt the interview guides before the commencement of surveys.

In-depth interviews

In-depth individual interviews (IDI) will be conducted with diverse respondents including stakeholders of the Heath system (Central, intermediate and peripheral level), health system managers, health care providers and community members (key opinion leaders, pregnant women, mothers of children under 5 years of age, and adult population). IDI will be completed to establish the range of perceptions on the MFT programme, and sources of care

and overview of the intervention. The interviews will be conducted in the local language or in the language best- spoken by the participant and by trained social scientists using structured interview guides

Focus group discussion

Focus group discussions (FGDs) will be held with household heads (male participants), mothers (female caregivers), and adult's population, the potential beneficiaries of the care at the health facility level and health workers (HWs) in the programme catchment area. The aim will be to obtain data on perceptions of the MFT programme and perceptions of fever/malaria case and its management. The discussion will be conducted in the language or the best-spoken language by the participants, using structured interview guides. The discussions will be recorded and then transcribed and translated into French for analysis. The FGDs will gather 8-12 participants per session.

Assessment of the cost to the health service of offering the MFT programme

The time utilised by HWs will be captured by asking them (possibly a sample) to keep a time log of their activities on the programme (diary). The value of their time will be obtained from estimates of opportunity costs (minimum wage, the average salary of the area). The programme accounting system will provide information on expenditures over the one and half year of the programme. Many of the resources such as programme personnel salaries, supplies, utilities and transport as well as mRDTs and ACTs will be considered. A visit to the programme offices will serve to develop an inventory of capital goods like equipment, furniture, vehicles and size of offices.

For the personnel not directly involved in the intervention but still providing time for the programme, a questionnaire will be designed to capture their time during oral interviews at their place of work (health centres, regional offices…). With regards to the various preparatory activities during the start-up phase, the research team will develop and keep an inventory of all the resources utilised for identifying training workshops for HWs, development of communication material and community mobilisation campaigns.

4.7 Data management and analysis

Quantitative data

Every month, health facilities-based summary data will be collected by the field supervisors using a standard data extraction form and monitoring report template. These data will be shared with the district health office and a copy will be sent to the research institution. Poor quality data issues and other queries will be managed regularly rather than at the end of the

study to maximize data completeness and quality, and the timeliness of final analysis. All the data collected at both the health facility and the community level will be checked before being double entered independently in the database.

Efforts will be made during the study to track missing data and minimize its degree as no attempt will be made to impute for missing data during the final analysis. All the data entered will be checked for inconsistencies and corrections will be made accordingly. Basic descriptive univariate and bivariate analysis will be undertaken to describe socio-demographic and economic characteristics of the study populations, communities' knowledge, attitudes and practices regarding febrile episodes/malaria and access to effective malaria case management including diagnostic and treatment before and during the MFT deployment. Appropriate statistics including proportions, means, medians, interquartile ranges, standard deviations and confidence intervals will be computed. The effect of the MFT on treatment seeking behavior for febrile episode/ malaria and on the malaria incidence will be assessed using multivariate analysis including logistic regression and the approach of interrupted time series analysis respectively. The effect of the MFT on febrile episode/malaria related mortality will be assessed using the mortality rate ratios derived from data collected one calendar year before and one calendar year along the implementation of the study.

Qualitative data

Data management will begin during data collection by transcribing and translating each audio-recorded IDI and FGD and expanded notes when audio recordings are not available. All transcripts will be typed into a word processing programme and stored on password-protected computers. All participants will be assigned unique identification codes to facilitate data tracking and no identifiable information will be collected. Data management logs will be created to track and monitor data collection and transcription.

As soon as possible after the interviews are conducted, each transcript will be read carefully by the study investigators in order to: (1) ask any question from the text that may be unclear; (2) point out areas in which interviewing and transcription techniques could be improved and (3) identify recurrent themes and areas for future probing.

Data-derived codes developed through inductive coding and retrieving will be used during analysis. A priori codes for retrieving text for key concepts related to the overall objectives also will be applied to the data. Investigators will determine a coding frame to be used based on the topic guides and the first few transcripts available for analysis. New codes will be added as necessary during transcript analysis. The qualitative data software program QSR NVivo, will be used to organize all qualitative data and prepare them for analysis. Procedures will be put into place to check for inter-coding discrepancies. Once all the transcripts will be

coded, textual coding reports will be produced. Data reduction techniques will be used to examine codes in detail for sub-themes and patterns across the transcripts.

5. Ethics and dissemination

The study protocol and informed consent documents were initially approved by the National Ethics Committee for the Research on Health in Burkina Faso (Clearance N°2018-8-113). The approval has a lifespan of one year and therefore must be renewed every year. The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza in 2013.

All participants in the different surveys of the formative and evaluation phases will be asked to voluntarily give written informed consent before any study-specific data collection. A copy of the informed consent form will be shared with each participant. Participant's full name will not be written on any data collection instruments and an identification codes will be assigned to each participant. Participants names will not be written in the transcripts of the interviews. Unique identification numbers will also be assigned to each participant during data analysis activities. All electronic files will be password protected and stored on password-protected computers. The copies of all the informed consent forms will be stored securely in a locked cabinet at the research institution offices, separately from study questionnaires or interview transcripts. Names will not be included in any formal or informal presentation and in any manuscript.

There are few anticipated risks associated with participation in the different surveys. Some participants may feel uncomfortable or embarrassed when asked questions about their current practices or their attitudes towards malaria case management. The research staff will make all the effort to protect individual participants' privacy and confidentiality. There are no direct benefits to participants from taking part in the various surveys. However, the information provided by the participants will be immediately used to inform the design of MFT programme and later will be useful to generate evidence to support decision-makers on the adoption of the MFT strategy for uncomplicated malaria.

Any protocol's amendment will be agreed upon between the investigators and MMV project management team in the form of a written amendment. Amended protocols will then be submitted for ethical clearance.

The findings of this study will be disseminated through feedback meetings for reporting to local communities, national workshop with researchers, policy-makers, and oral

presentations at national and international congresses, conferences, and seminars. We will also submit the results to peer-reviewed scientific journals for publications.

6. Patient and public involvement

Study participants were not involved in the development of the research question, outcome measures, and in the design of the study. They will not be also involved in the recruitment procedures. Data will be collected from households, study participants both at the community and at the health facility levels. Households in the study area will be randomly selected and potential subjects living within the selected households and who meet the eligibility criteria will be invited to participate in the study after obtaining informed consent. Study results will be disseminated to the study populations through feedback meetings with the communities' leaders and representatives.

7. Discussion

The MFT strategy has not yet been implemented in a structured way in sub-Saharan Africa. This study will be among the first to generate evidence of the feasibility, acceptability and cost of MFT stragtegy.

The MFT is one of the potential strategy that could effectively mitigate the enormous threat in the figth against malaria which is the emergence and spread of artemisinin resistance. Indeed, the loss of artemisinin effectiveness would likely result in the loss of all ACTs. Therefore, there is urgent need to identify and to implement in sub-Saharan Africa a better way to optimise the use of these ACTs that could provide a much higher long-term barrier to the emergence and/or the spread of resistance and thus protecting them. Theoretical models showed that the simultaneous deployment of MFT for uncomplicated malaria is a promising strategy to extend the useful therapeutic life of the current ACTs by reducing drug pressure and slowing the spread of resistance without putting lives at risk. The development of feasible strategies for implementing MFT is therefore recommended.(**23,24**) Treating half of the population with one ACT and the other half with a different ACT would reduce the fitness of resistant parasites approximately as well as treating half as many patients.(**25**) Therefore, there is an advantage in deploying two or more ACTs. There are several scenarios for implementing MFT strategy depending on the target: i) the partition of the ACTs market by segments of the same population: paediatric patients, pregnant women, adults patients, ii) the distribution of one ACT for home-based care and use a different ACT in the clinic, iii) the mosaic distribution of ACTs i.e. an alternating distribution of different ACTs in the same population over a given period of time… (**26**)

In this study, we opted for the segmentation of the total population and we allocated an ACT to each given segment of the population to be able to take account the ACTs registered and available in the country. PYR-AS, AL and DHA-PQ and will be assigned respectively to children less than five years of age, pregnant women after the first semester of pregnancy and individuals five years of age and above. Indeed, AS-AQ will not be used in this study because the SMC is underway in the country using the sulfadoxine-pyrimethamine + amodiaquine. In order to avoid much pressure on amodiaquine and to protect the molecule, the NMCP in Burkina Faso is planning to remove it in the near future in its guidelines for uncomplicated malaria case management. The choice of AL for pregnant women is justified by its effectiveness and its good safety profile as well in this vulnerable population. (8) In addition, the CCMm strategy is also underway in the country using AL. Then, we aim to alleviate the pressure on AL, by reducing its use at the health facility level and assigning it to a small proportion of the population (pregnant women). PYR-AS will be assigned to the children under - five for several reasons such as, the good effectiveness and safety profile, (**4–6,27**) the availability of a child friendly formulation which does not interact with food intake and the easy dosage of the drug (single daily dose for three days) that can improve treatment compliance. Finally, DHA-PQ will be assigned to the rest of the population, individuals five years of age and above. This drug also has shown to be safe, efficacious and effective in preventing incident infections. (**5,7,27**) The absence of pediatric formulation prevents its use in children less than five.

The deployment of the MFT, whatever the strategy, would present several challenges including planning for the right distribution channel of the ACTs, the management of the logistics, the compensation of the higher costs of some ACTs, the adjustment of health system delivery due to a lower preference for some drugs. A potential limitation of this study is that it will look at the changes in molecular markers of resistance of ACTs before and after the deployment of the MFT. Findings from this research are pivotal to inform stakeholders on the future of this strategy.

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10. Authors' contributions

MS, AMT, IS and SBS conceived the study. MS, AMT, IS, ABT and SBS developed the study protocol. YN, AKK, NB, AH, YS, SK participated in the finalization of the protocol. MS wrote the first draft of the manuscript. MS, AMT, IS, JMTK, YN, DH, AKK, NB, AB, AH, FD, YS, SK, ABT, SBS critically reviewed the manuscript. MS, AMT, IS, JMTK, YN, DH, AKK, NB, AB, AH, FD, YS, SK, ABT, SBS approved the final version of the manuscript.

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12. Competing interests' statement: None declared.

13. Ethics approval: Comité d'éthique pour la recherché en santé (CERS), Burkina Faso

14. Provenance and peer review: Not commissioned, externally peer reviewed.

Figures:

Figure 1: Design of the programme

Figure 2: Artemisinin-based combination therapies flow in the framework of the MFT programme

Table:

Table 1: Sampling strategy for qualitative surveys

Target group	Data Collection methods and sample size	Sampling strategy
The national malaria control programme	3 IDI	All personnel with a key role in malaria case management strategy delivery
Central essential drugs store (CAMEG)	3 IDI	All personnel with a key role in ACTs ordering and inventory management
North-central health region (Head of the health region, Lead pharmacist, Responsible of the disease control service)	3 IDI	All personnel with a key role in malaria case management strategy delivery
Heath district management team of Kaya (Head of the health district, Lead pharmacist Responsible for the district-level healthcare provision)	3 IDI	All personnel with a key role in malaria case management strategy delivery
Head of the local health facilities	5 IDI, 4 FGD	5 heads of the local health facilities in the health district of Kaya will be randomly selected and invited for the IDI. The 40 heads of local health facilities will be allocated randomly into for groups for FGD.
Essential drugs stores managers at health facilities level	5 IDI, 4 FGD	5 essential drugs storekeepers of the local health facilities in the health district of Kaya will be randomly selected and invited for the IDI. The 40 essential drugs storekeepers of local health facilities will be allocated randomly into for groups for FGD.
Local health workers	10 FGD	10 local health facilities in the health district of Kaya will be randomly selected and the local health workers in charge of malaria case management in pregnant women, children under five and individuals of five years old and above, will be grouped for the conduct of the FGD.
Community key opinion leaders	10 IDI, 4 FGD	10 local health facilities in the health district of Kaya will be randomly selected, and the head of the health facilities will appoint a community leader per their respective health area for the conduct of the IDI. Subsequently, 4 community leaders per 10 health facility previously selected will be identified by the head of the health facility to constitute the group for the conduct of the FGD.
Heads of household (male participants)	5 FGD	During the household surveys, villages will be selected at random within the health district of Kaya. Households will be selected at random via the random walk method, with the interval selected dependent on village size and the head of households (males) will be invited for the conduct of FGD.

Caregivers of children under five (female participants)	5 FGD	During the household surveys, villages will be selected at random within the health district of Kaya. Caregivers (mothers of children under five) will be selected at random via the random walk method, with the interval selected dependent on village size and will be invited for the conduct of FGD.
Pregnant women	5 FGD	During the household surveys, villages will be selected at random within the health district of Kaya. Pregnant women will be selected at random via the random walk method, with the interval selected dependent on village size and will be invited for the conduct of FGD.
Adult participants	5 FGD	During the household surveys, villages will be selected at random within the health district of Kaya. Adult potential participants will be selected at random via the random walk method, with the interval selected dependent on village size and will be invited for the conduct of FGD.
Total of interviews	**32 IDI and 42 FGD**	

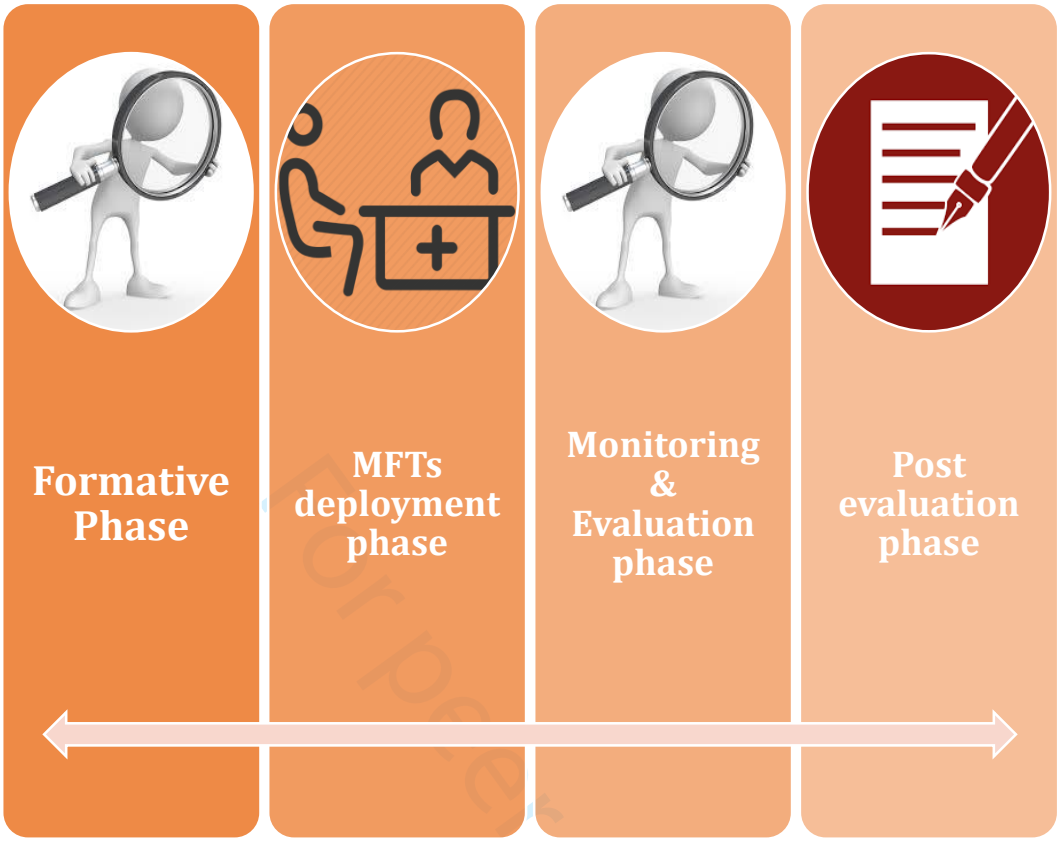
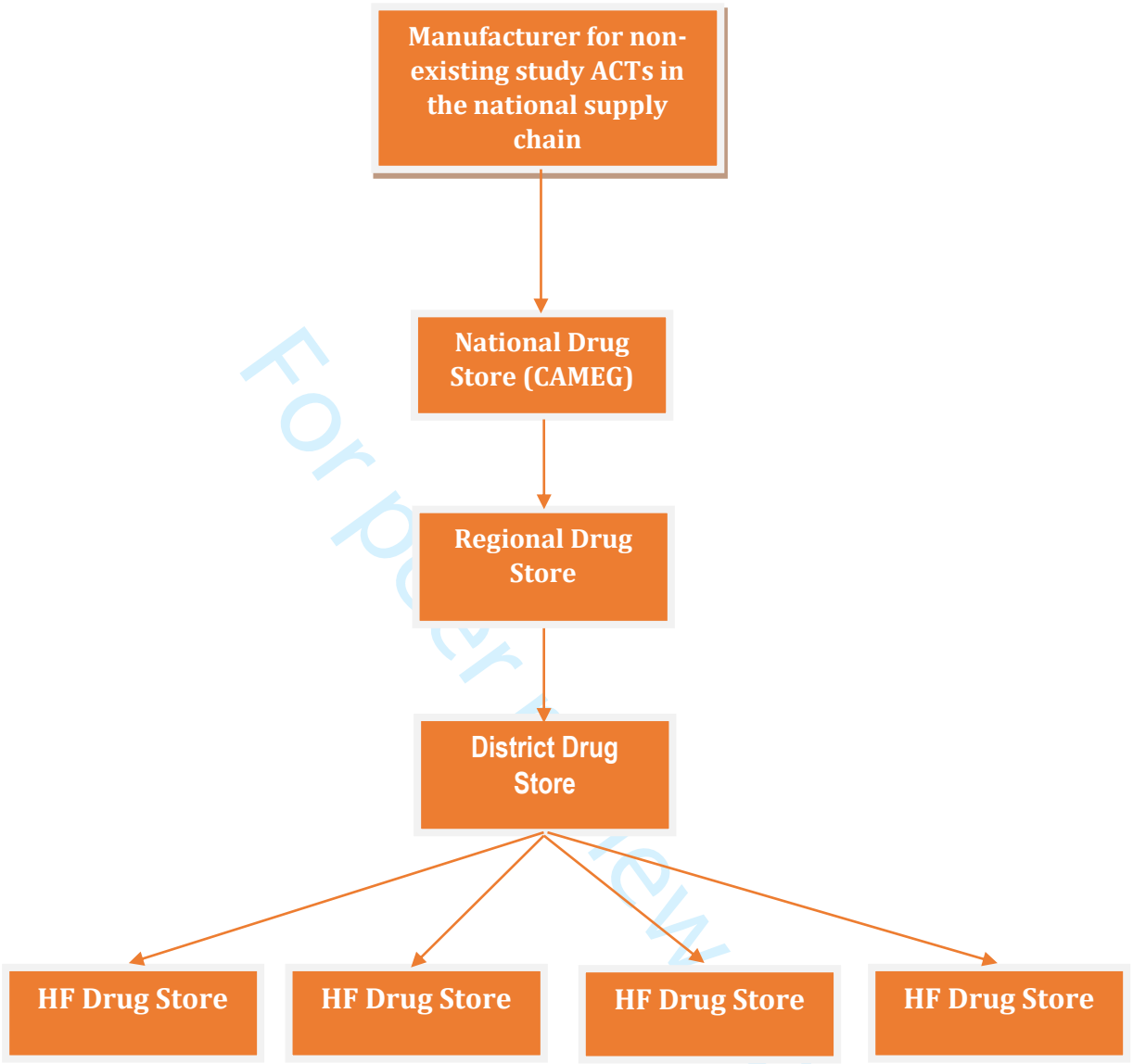


Figure 1: Design of the programme



HF: health facility

Figure 2: Artemisinin-based combination therapies flow in the framework of the MFT programme

Table 1: Outcomes to be measured during the monitoring and evaluation phase

Outcomes	Indicators	Numerator/ Denominator	Methods of assessment	Time point for assessment	Targeted populations	Data collection tools
Outcome 1: the implementation of the MFT pilot programme	- Average number of monitoring visits per health facility and drugs stores involved in the study per annum	Numerator: Number of monitoring visits per health facility and drugs stores involved in the study per annum Denominator: Number of health facility and drugs stores involved in the study	Health facility-based survey Central, regional and district-based surveys	End of MFTs deployment phase	Heath facilities Drugs stores	Monitoring visit report template
	- Average number of monitoring visit on which drugs stores have stock out of any dose of study ACTs per annum	Numerator: Number of monitoring visit on which drugs stores have stock out of any dose of study ACTs per annum Denominator: Number of drugs stores involved in the study	Health facility-based survey Central, regional and district-based surveys	End of MFTs deployment phase	Drugs stores	Monitoring visit report template
	- Average number of monitoring visit on which health facilities have stock out of mRDTs per annum	Numerator: Number of monitoring visit on which health facilities have stock out of mRDTs per annum Denominator: Number of health facilities involved in the study	Health facility-based survey Central, regional and district-based surveys	End of MFTs deployment phase	Drugs stores	Monitoring visit report template
Outcome 2: The coverage of febrile episode/malaria promptly and appropriately managed by health workers according to the MFT pilot programme	- Proportion of febrile episode seen at the health facility level	Numerator: Number of febrile episodes taken to a health facility Denominator: Number of febrile episodes	Household survey	During MFTs deployment phase at peak malaria season	Caregivers, pregnant women, adults	KAP questionnaire
	- Proportion of febrile episode seen at health facility level (HFL) within 24 hours	Numerator: Number of febrile episodes taken to a health facility within 24h Denominator: Number of febrile episodes	Household survey Health facility-based survey	During MFTs deployment phase at peak malaria season	Caregivers, pregnant women, adults Registers of health facility	KAP questionnaire Data extraction forms

				End of MFTs deployment phase		
	- Proportion of febrile episode seen at HFL within 24 hours and tested for parasitemia	Numerator: Number of febrile episodes seen at the health facility and tested for parasitemia Denominator: Number of febrile episodes taken to a health facility	Household survey Health facility-based survey	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, pregnant women, adults Registers of health facility	KAP questionnaire Data extraction forms
	- Proportion of febrile episode seen at HFL within 24 hours with positive diagnostic test who were given ACT according to the MFTs strategy	Numerator: Number of febrile episodes seen at a health facility with a positive diagnostic test and treated with ACT according to the MFTs strategy Denominator: Number of febrile episodes with a positive diagnostic test	Household survey Health facility-based survey	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, pregnant women, adults Registers of health facility	KAP questionnaire Data extraction forms
	- Proportion of febrile episode seen at HFL within 24 hours with a negative diagnostic test who did not receive any antimalarial.	Numerator: Number of febrile episodes seen at a health facility with a negative diagnostic test and not treated with ACT according to the MFTs strategy Denominator: Number of febrile episodes with a negative diagnostic test	Household survey Health facility-based survey	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, pregnant women, adults Registers of health facility	KAP questionnaire Data extraction forms
	- Proportion of febrile episode seen at HFL within 24 hours with a negative diagnostic test who received an ACT.	Numerator: Number of febrile episodes seen at a health facility with a negative diagnostic test and treated with ACT Denominator: Number of febrile episodes with a negative diagnostic test	Household survey Health facility-based survey	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, pregnant women, adults Registers of health facility	KAP questionnaire Data extraction forms

Outcome 3: the adherence of caregivers/febrile patients to ACTs treatment schedule provided by health workers according to MFTs pilot programme	Proportion of febrile episodes treated with ACTs adhering to ACT treatment schedule (timing and doses) by HWs according to MFTs strategy	Numerator: Number of febrile episodes treated with ACT provided by health workers according to MFTs strategy adhering to ACT treatment schedule (timing and dosing) Denominator: Number of febrile episodes treated with ACT provided by health workers according to MFTs strategy	Household surveys	During MFTs deployment phase at peak malaria season	Caregivers, adults, pregnant women	KAP Questionnaire
Outcome 4: The acceptability of the MFT pilot programme	- Number of favourable and unfavourable opinions from various profiles of informants about the intervention, including health agents of different levels and authorities, concerning the MFTs pilot programme. - Proportion of community resources people (mothers/caregivers, health agents, heads of household (male participants) community leaders) with favourable opinions to the MFTs pilot programme and their reasons - Proportion of community resources people (mothers/caregivers, health agents, heads of household (male participants) community leaders) with unfavourable opinions to the MFTs pilot programme and their reasons	Numerator: Exploration of selected informants' opinions Comparison of different opinions Denominator: Caregivers, pregnant women, adults, community leaders, health workers, health authorities	Qualitative surveys Household surveys	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, adults, pregnant women, key community leaders, health workers, health authorities	FGD, IDI guides KAP questionnaire
Outcome 5: the cost of the MFT pilot programme	- Cost per additional febrile episode receiving prompt treatment or confirmed negative diagnosis	Numerator: Total economic cost, cost savings Denominator: Additional number of febrile episodes given ACT with a negative parasitological test within 24 hours	Household survey Health facility-based survey	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, pregnant women, adults Health workers	Cost data collection forms KAP questionnaire Data extraction forms at the health facility level

					Registers of health facility	
	- Cost per additional inappropriate antimalarial treatment avoided	Numerator: Total economic cost, cost savings Denominator: Additional number of confirmed negative episodes not treated with an ACT	Household survey Health facility-based survey	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, pregnant women, adults Health workers Registers of health facility	Cost data collection forms KAP questionnaire Data extraction forms at the health facility level
	- Cost per additional febrile episode appropriate managed for malaria with a confirmed diagnosis	Numerator: Total economic cost, cost savings Denominator: Additional number of febrile episodes treated with ACT or with a negative parasitological test within 24 hours	Household surveys Health facility-based surveys	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, adults, pregnant women, health workers Registers of health facilities,	KAP Questionnaire, Cost data collection forms Data extraction forms at the health facility level
	- Cost per capita of intervention (provider and societal perspective)	Numerator: Total economic cost-Cost savings Total financial cost-cost saving Denominator: Population of the area	Household surveys Health facility-based surveys	During MFTs deployment phase at peak malaria season End of MFTs deployment phase	Caregivers, pregnant women, adults Health workers Registers of health facility	Cost data collection forms Census data collection forms

	- Cost to the HWs to participate in the MFTs strategy	Numerator: Economic costs to HWs participating in the MFTs strategy Denominator: Number of HWs	Health facility-based surveys	End of MFTs deployment phase	Health workers Registers of health facility	Cost data collection forms
Outcome 6: the quality of care provided /performance of health workers	- Proportion of episode of uncomplicated fever seen by HWs tested for malaria parasitemia	Numerator: Number of episodes of uncomplicated fever seen by HWs tested with mRDT/blood smear Denominator: Number of uncomplicated fever episodes/malaria fever seen by HWs	Health facility-based surveys Household surveys	End of MFTs deployment phase During MFTs deployment phase at peak malaria season	Registers of health facilities Caregivers, adults, pregnant women, health workers	Data extraction forms KAP questionnaire
	- Proportion of uncomplicated fever episodes/malaria seen by HW, tested positive and treated with the correct dose of ACT according to MFTs pilot programme	Numerator: Number of uncomplicated fever episodes/Malaria seen by HWs, tested positive and treated with the correct dose of ACT according to MFTs pilot programme Denominator: Number of uncomplicated fever episodes/malaria seen by HWs and tested positive.	Health facility-based surveys Household surveys	End of MFTs deployment phase During MFTs deployment phase at peak malaria season	Registers of health facilities Caregivers, adults, pregnant women, health workers	Data extraction forms KAP questionnaire
	- Proportion of febrile episodes treated with ACTs according to MFTs pilot programme by HWs provided with appropriate dosing advice	Numerator: Number of uncomplicated febrile episodes/malaria treated with ACTs according to MFTs approach by HWs provided with appropriate dosing advice Denominator: Number of uncomplicated febrile episodes/malaria treated with ACTs according to MFTs pilot programme by HWs	Health facility-based surveys Household surveys	End of MFTs deployment phase During MFTs deployment phase at peak malaria season	Registers of health facilities Caregivers, adults, pregnant women, health workers	Data extraction forms KAP questionnaire

	- Proportion of uncomplicated febrile episodes/malaria seen by HWs provided with advice on danger signs	Numerator: Number of uncomplicated febrile episodes/malaria seen by HWs provided with advice on danger signs Denominator: Number of uncomplicated febrile episodes/malaria seen by HWs	Health facility-based surveys Household surveys	End of MFTs deployment phase During MFTs deployment phase at peak malaria season	Registers of health facilities Caregivers, adults, pregnant women, health workers	Data extraction forms KAP questionnaire
Outcome 7: the impact of MFT pilot programme on malaria incidence	- Incidence of uncomplicated febrile episode/malaria within 4 weeks preceding the survey, before and during the MFTs deployment	- Numerator: Number of uncomplicated febrile episode/malaria within 4 weeks preceding the survey, before and during the MFTs deployment - Denominator: Number of persons per segments of the population	Household surveys,	MFTs deployment phase at the peak of the malaria season	Caregivers, adults, pregnant women	KAP Questionnaire,
	- Proportion of uncomplicated febrile episode/malaria seen at health facility level before and during the MFTs deployment in the study area	- Numerator: Number of uncomplicated febrile episodes/malaria seen by HWs at HFL during study periods (before and during the MFTs deployment) per segments of the population - Denominator: Number of person-years per segments of the population during the study periods	Health facility level	End of MFTs deployment phase	Registers of health facilities	Data extraction forms
Outcome 8: the impact of the MFT pilot programme on malaria mortality	- Mortality rate related to febrile episode/malaria before and during the pilot MFTs deployment	- Numerator: Number of malaria-associated deaths before and during the pilot MFTs deployment phase per segments of the population - Denominator: Number of person-years per segments of the population	Household surveys, Health facility level	End of MFTs deployment phase	Caregivers, adults, pregnant women Registers of health facilities	HDSS mortality data collection forms Data extraction forms
Outcome 9: the effect of MFT pilot programme on	- Proportion of individuals with fever in the last four weeks for whom advice or treatment was sought	- Numerator: Number of individuals with fever in the last four weeks for whom advice or treatment was sought	Household surveys	MFTs deployment phase at the	Caregivers, adults,	KAP Questionnaire

treatment-seeking behaviour for fever episodes/malaria		- Denominator: Number of individuals with fever in the last four weeks		peak of the malaria season	pregnant women	
	- Proportion of individuals with fever in the last four week who sought treatment at HFL within 24 hours	- Numerator: Number of individuals with fever in the last four weeks who sought treatment at HFL within 24 hours - Denominator: Number of individuals with fever in the last four weeks	Household surveys	MFTs deployment phase at the peak of the malaria season	Caregivers, adults, pregnant women	KAP Questionnaire
	- Source of advice or care for those suffering from fever in the last four weeks	- Numerator: Number per type of source of advice or care for those suffering from fever in the last four weeks - Denominator: Number of individual suffering from fever in the last four weeks who sought advice or care	Household surveys	MFTs deployment phase at the peak of the malaria season	Caregivers, adults, pregnant women	KAP Questionnaire

Standards for Reporting Implementation Studies: the StaRI checklist for completion

The StaRI standard should be referenced as: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths CJ, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor SJC for the StaRI Group. Standards for Reporting Implementation Studies (StaRI) statement. *BMJ* 2017;356:i6795

The detailed Explanation and Elaboration document, which provides the rationale and exemplar text for all these items is: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths C, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor S, for the StaRI group. Standards for Reporting Implementation Studies (StaRI). Explanation and Elaboration document. *BMJ Open* 2017 2017;7:e013318

Notes: A key concept of the StaRI standards is the dual strands of describing, on the one hand, the implementation strategy and, on the other, the clinical, healthcare, or public health intervention that is being implemented. These strands are represented as two columns in the checklist.

The primary focus of implementation science is the implementation strategy (column 1) and the expectation is that this will always be completed.	The evidence about the impact of the intervention on the targeted population should always be considered (column 2) and either health outcomes reported or robust evidence cited to support a known beneficial effect of the intervention on the health of individuals or populations.

The StaRI standardsrefers to the broad range of study designs employed in implementation science. Authors should refer to other reporting standards for advice on reporting specific methodological features. Conversely, whilst all items are worthy of consideration, not all items will be applicable to, or feasible within every study.

Checklist item		Reported on page #	Implementation Strategy	Reported on page #	Intervention
			"Implementation strategy" refers to how the intervention was implemented		"Intervention" refers to the healthcare or public health intervention that is being implemented.
Title and abstract					
Title	**1**	1	Identification as an implementation study, and description of the methodology in the title and/or keywords		
Abstract	**2**	2	Identification as an implementation study, including a description of the implementation strategy to be tested, the evidence-based intervention being implemented, and defining the key implementation and health outcomes.		
Introduction					
Introduction	**3**	4-5	Description of the problem, challenge or deficiency in healthcare or public health that the intervention being implemented aims to address.		
Rationale	**4**	4-5	The scientific background and rationale for the implementation strategy (including any underpinning theory/framework/model, how it is expected to achieve its effects and any pilot work).		The scientific background and rationale for the intervention being implemented (including evidence about its effectiveness and how it is expected to achieve its effects).

Aims and objectives	**5**	6-8	The aims of the study, differentiating between implementation objectives and any intervention objectives.		
Methods: description					
Design	**6**	6	The design and key features of the evaluation, (cross referencing to any appropriate methodology reporting standards) and any changes to study protocol, with reasons		
Context	**7**	5	The context in which the intervention was implemented. (Consider social, economic, policy, healthcare, organisational barriers and facilitators that might influence implementation elsewhere).		
Targeted 'sites'	**8**	5	The characteristics of the targeted 'site(s)' (e.g locations/personnel/resources etc.) for implementation and any eligibility criteria.		The population targeted by the intervention and any eligibility criteria.
Description	**9**	6	A description of the implementation strategy		A description of the intervention
Sub-groups	**10**	6	Any sub-groups recruited for additional research tasks, and/or nested studies are described		
Methods: evaluation					
Outcomes	**11**	8	Defined pre-specified primary and other outcome(s) of the implementation strategy, and how they were assessed. Document any pre-determined targets		Defined pre-specified primary and other outcome(s) of the intervention (if assessed), and how they were assessed. Document any pre-determined targets
Process evaluation	**12**	8-12	Process evaluation objectives and outcomes related to the mechanism by which the strategy is expected to work		
Economic evaluation	**13**	8-12	Methods for resource use, costs, economic outcomes and analysis for the implementation strategy		Methods for resource use, costs, economic outcomes and analysis for the intervention
Sample size	**14**	8	Rationale for sample sizes (including sample size calculations, budgetary constraints, practical considerations, data saturation, as appropriate)		
Analysis	**15**	10-12	Methods of analysis (with reasons for that choice)		
Sub-group analyses	**16**	11-12	Any a priori sub-group analyses (e.g. between different sites in a multicentre study, different clinical or demographic populations), and sub-groups recruited to specific nested research tasks		

Results					
Characteristics	**17**	Not applicable	Proportion recruited and characteristics of the recipient population for the implementation strategy		Proportion recruited and characteristics (if appropriate) of the recipient population for the intervention
Outcomes	**18**	Not applicable	Primary and other outcome(s) of the implementation strategy		Primary and other outcome(s) of the Intervention (if assessed)
Process outcomes	**19**	Not applicable	Process data related to the implementation strategy mapped to the mechanism by which the strategy is expected to work		
Economic evaluation	**20**	Not applicable	Resource use, costs, economic outcomes and analysis for the implementation strategy		Resource use, costs, economic outcomes and analysis for the intervention
Sub-group analyses	**21**	Not applicable	Representativeness and outcomes of subgroups including those recruited to specific research tasks		
Fidelity/ adaptation	**22**	Not applicable	Fidelity to implementation strategy as planned and adaptation to suit context and preferences		Fidelity to delivering the core components of intervention (where measured)
Contextual changes	**23**	Not applicable	Contextual changes (if any) which may have affected outcomes		
Harms	**24**	Not applicable	All important harms or unintended effects in each group		
Discussion					
Structured discussion	**25**	13-14	Summary of findings, strengths and limitations, comparisons with other studies, conclusions and implications		
Implications	**26**	14	Discussion of policy, practice and/or research implications of the implementation strategy (specifically including scalability)		Discussion of policy, practice and/or research implications of the intervention (specifically including sustainability)
General					
Statements	**27**	12-13	Include statement(s) on regulatory approvals (including, as appropriate, ethical approval, confidential use of routine data, governance approval), trial/study registration (availability of protocol), funding and conflicts of interest		