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Proactive Community Case Management and Child Survival: Protocol for a Cluster Randomised Controlled Trial

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Proactive Community Case Management and Child Survival: Protocol for a Cluster Randomised Controlled Trial

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ABSTRACT

Background: The majority of maternal and child deaths in low- and middle-income countries are preventable with existing community-based interventions. Investing in community health workers (CHWs)—shown to improve access to care and reduce maternal, newborn, and child morbidity and mortality—is re-emerging as a key strategy to achieve health-related Sustainable Development Goals. However, recent evaluations of national programmes for CHW-led integrated Community Case Management (iCCM) of common childhood illnesses have not found benefits on access to care and child mortality. Developing innovative ways to maximise the potential benefits of iCCM is critical to achieving the SDGs.

Methods: A cluster-randomised controlled trial in rural Mali aims to test the efficacy of a proactive community case management (ProCCM) intervention in reducing under-five mortality, compared to a conventional iCCM approach. In the ProCCM arm, 69 village-clusters will have CHWs who conduct daily proactive case-finding home visits and deliver doorstep counsel, care, referral, and follow-up. In the iCCM arm, 68 village-clusters will have CHWs who provide the same services exclusively out of a fixed health post. A baseline population census will be conducted of all people living in the study area. All women of child-bearing age will be enrolled in the study and surveyed at baseline, 12, 24, and 36 months. The survey includes a life table tracking all live births

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and deaths occurring in the 59 months prior to enrolment through the 36 months of follow-up.

Discussion: This study is designed and implemented in partnership with the Malian Ministry of Health. We aim to answer questions of key concern among government partners in the design of the national-level iCCM program, including if ProCCM is cost-effective, equitable, and affordable at scale. Findings from this study could have important policy implications for CHW-led iCCM scale up across sub-Saharan Africa.

Trial registration: ClinicalTrials.gov, NCT02694055. Registered 13 January 2016, https://clinicaltrials.gov/show/NCT02694055.

Key words: Child health; Maternal health; Cluster randomized trial; Community Health Workers, integrated Community Case Management, Child mortality

Strengths and limitations of this study

- This is a cluster randomised controlled trial powered to detect a 25% difference in the incidence rate of under-five mortality between the two study arms.
- The trial will generate evidence on the efficacy, cost-effectiveness, and equity of community-based proactive case detection on access to care and child mortality.
- The intervention is designed to facilitate public sector adoption and scale-up if found to be effective.
- Unexpected events may occur that influence the extent to which the intervention can be implemented per protocol.

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BACKGROUND

The vast majority of maternal, newborn, and child deaths in low- and middle-income countries are preventable. Evidence-based and cost-effective methods for prevention and treatment are available for the leading causes of death, yet many still face barriers to obtaining timely, quality, appropriate care. If community-based interventions, such as the treatment of malaria with artemisinin compounds, oral rehydration solution for childhood diarrhoea, oral antibiotics for pneumonia, nutritional interventions during pregnancy, and hand washing with soap, were scaled to achieve 90% coverage in high-burden countries before 2020, an estimated 6.9 million maternal and child deaths could be averted.[1]

Integrated Community Case Management (iCCM) of common childhood illnesses entails a package of services to diagnose, treat and refer children under five with malaria, diarrhoea, pneumonia, or moderate malnutrition, delivered by community health workers (CHWs).[2] Community case management of common childhood illnesses has been shown to increase care seeking outside the home,[3] reduce treatment failure rates,[3] and reduce mortality due to malaria,[4] diarrhoea,[3,5,6] pneumonia,[3,7,8] as well as all causes.[4,6,7]

Many countries in sub-Saharan Africa have adopted iCCM as an evidence-based strategy to improve child health.[9] However, the expected benefits of iCCM have not been realized in all contexts.[10–12] Several recent evaluations of national iCCM programmes did not find impacts on care seeking or child mortality, in part, study authors conclude, due to low demand for CHW services.[13–16] These national programmes shared certain

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design and implementation features that may have contributed to the lack of overall effects by not addressing barriers to care, such as user fees for services, lack of frequent and dedicated CHW supervision for quality assurance, and community care provision exclusively (or primarily) for patients that seek care from a fixed health post. As more countries commit to scaling up CHW-led health care systems, it is critical that we understand how to best design and implement iCCM, and CHW services more broadly, in order to bring about their full potential.

To address this need, we designed a cluster randomised controlled trial to test a proactive model of CHW service delivery for comprehensive child, reproductive, and maternal health services (ProCCM) compared to the same set of comprehensive services delivered via the standard iCCM model relying on patient-initiated care-seeking.[17] The ProCCM approach is designed to overcome additional social, structural, and health system barriers that may impede or lead to delayed access, even under a community-based comprehensive iCCM approach. At a systems level, these include the direct and indirect costs of care, including distance to care. At the household level, lack of resources, mistrust in the health care system, and complex familial decision-making dynamics due to in part to gender inequality can contribute to delays in reaching care.[18,19] By proactively seeking out patients and linking community members to the health care system, ProCCM is designed to reduce the time from onset of condition to utilisation of health services, including direct provision of comprehensive primary care services for all household members, ultimately reducing mortality.

METHODS

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Study aims and hypothesis

Our cluster randomised controlled trial aims to:

(1) Estimate the effect of adding proactive case detection by CHWs to an iCCM intervention on under-five child mortality; we hypothesize that, after 36 months, the difference in the incidence rate of under-five mortality between the two study arms will be greater than 25%.

(2) Compared to iCCM, estimate the effect of ProCCM on utilisation of reproductive, maternal, and child health services.

(3) Evaluate the ProCCM model, compared to iCCM, in terms of cost-effectiveness, equity, and affordability at scale.

Study site

The trial will be conducted in the Bankass health district in eastern Mali, approximately 600 kilometres east of the nation's capital, Bamako. The district has a 2016 population of approximately 300,000 people and is served by a public secondary referral hospital located in Bankass, the largest town in the district.[20] Within the Bankass health district, the study is being conducted in seven (of 22) health catchment areas: Dimbal, Doundé, Ende, Kani Bozon, Koulongon, Lessagou, and Soubala (Figure 1). The study area has a 2016 population of approximately 100,000 people.[20] Each health catchment area is served by a primary health centre (PHC) operated by the Ministry of Health.

Study design

This is an unblinded, cluster-randomised controlled trial, with 69 village-clusters in the intervention arm and 68 village-clusters in the comparison arm. Clusters are randomised

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to receive either iCCM from stationary CHW(s) serving patients exclusively at a community health post (control) as per Mali's national iCCM strategy,[49] or ProCCM from CHW(s) conducting daily proactive case-finding home visits in addition to serving patients at a community health post. Only the intervention arm will receive door-to-door proactive case detection by CHWs, including doorstep care and home-based follow-up.

Intervention

Local community members—female candidates encouraged—who can read and write in French will be recruited, trained, supervised, and supported as CHWs from the village-cluster in which they will work. CHW coverage will be based on Mali's national iCCM strategy, which recommends one CHW for a population of 700 in the southern region, which includes the study area.[49] Clusters, therefore, may have one or multiple CHWs, depending on the size of the cluster population. Clusters with less than 200 people and within three kilometres of another cluster assigned to the same study arm will share a CHW, provided there is no geographic barrier (i.e., river) between the two clusters and no linguistic barrier for the CHW. CHWs will provide a comprehensive set of primary care services, including iCCM in accordance with national and international standards[21] and reproductive health for women of child-bearing age (see Table 1 for a full description of the CHW package of care). CHW services will include counselling, diagnostics, treatment, referral to reinforced PHCs, and follow-up care. User fees will be removed for all CHW and referral services for all patients in the study area. CHWs in both arms will receive a salary circa minimum wage and will be required to be on call, available to receive and care for patients who seek them out, 24 hours per day, seven days per week.

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A detailed description of the entire health system strengthening intervention in both arms is provided in the Online Supplementary Document.

Control arm: Conventional CHW service delivery

In clusters assigned to the control arm, CHWs will be stationed at a community health post to provide the comprehensive package of primary care services for at least four hours per day, six days per week, available to receive patients seeking care.

Intervention arm: Proactive CHW service delivery

In clusters assigned to the intervention arm, CHW(s) will be trained and deployed to conduct proactive case finding, door-to-door home visits for at least two hours each day, six days a week, with the goal of visiting each household at least two times each month. During the home visit, CHWs will screen all household members for recent illness or symptoms and provide services at the home, including follow-up for sick children and adults, pregnant women, newborns, and post-partum mothers. In addition to home visits, ProCCM CHWs will provide care at their health post for at least two hours a day, six days per week, according to a calendar shared with the community. At the health post, CHWs will provide the same services as those offered by CHWs in the control arm to care-seeking patients.

Cluster definition and randomisation

In order to identify distinct clusters, a field team visited all villages and hamlets in the study area and collected GPS coordinates at the public space where community-wide meetings, announcements, and festivities are held. GPS coordinates were mapped and the cardinal distances between neighbouring villages/hamlets were calculated. Villages and

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hamlets one kilometre or less from one another were grouped into clusters, resulting in 160 individual villages and hamlets grouped into 137 unique clusters.

Villages located 1.0 or more kilometres from a PHC were stratified by health catchment area and distance to the nearest PHC (1.0–5.0 kilometres vs. more than 5.0 kilometres). The cut-off point of 5.0 km was defined in accordance with national iCCM guidelines,[22] which deploys CHWs to deliver iCCM services only in communities greater than 5.0 km from a PHC. An additional stratum was defined for all villages where the PHC was located to ensure balanced assignment of PHC villages across arms. Within each strata, villages were randomly assigned to the control or treatment arm using a computer-generated random number conducted a member of the US-based research team who did not have any involvement in the implementation of the intervention or field operations.

Sample size and primary and secondary endpoints

Primary endpoint

The primary endpoint is under-five mortality, measured as deaths among children under five years of age per 1,000 person-years at risk of mortality. The sample size for the trial was based on this primary endpoint, derived using methods for cluster-randomised trials[23] in which each cluster was treated as an observation and the cluster-level outcome was defined as the under-five mortality rate per person-years at risk. We used a negative binomial model to simulate the number of deaths among children under five. According to 2014 national population estimates adjusted for 2016 using a 2.2% annual growth rate,[20] the seven health catchment areas encompassed a population of 103,848

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inhabitants. Assuming that 20% (n=20,767) of the population was children aged 0-59 months, we calculated a mean of 216 children per village. Person-years at risk were calculated assuming three years of prospective study follow-up with 10% attrition based on experience with previous trials in Mali.[24,25] We used a coefficient of variation of k=0.29[23] to model the extra variation due to clustering ($1/k^2$ is the size parameter in the negative binomial model). With these parameters, the trial will be able to detect a relative difference of 25% (alpha = 0.05, two-tailed test) in the under-five mortality incidence between treatment and control arms with 81.8% power after 36 months.

Secondary endpoints

We will also estimate the effect of the intervention on a number of secondary endpoints:

(a) Infant mortality (deaths per 1,000 live births among children aged 0-11 months);

(b) Newborn mortality (deaths per 1,000 live births among children aged 0-28 days);

(c) Receipt of oral rehydration therapy and zinc within 24 hours of diarrhea onset among children under five;

(d) Receipt of diagnostic testing and/or effective treatment for malaria within 24 hours of fever onset among children under five;

(e) Evaluation by a qualified provider within 24 hours of symptom onset among children under five with cough and/or fast breathing;

(f) Receipt of three or more doses of Sulfadoxine-Pyrimethamine as Intermittent Preventive Treatment during a woman's most recent pregnancy;

(g) Enrollment in ANC with a skilled provider in the first trimester during a woman's most recent pregnancy;

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(h) Completing four or more antenatal care (ANC) consultations with a skilled provider during a woman's most recent pregnancy;

(i) Use of a modern method of contraception among women of reproductive age.

Inclusion criteria

Any individual in the study area at any point during the study period, including visitors, are eligible to receive the health services offered through the intervention. Only permanent residents of the study area are eligible to be included in the household survey.

Sources of data

The effects of the ProCCM model of service delivery, compared to the iCCM model, for the primary and secondary endpoints will be assessed using data from three sources: (1) household surveys, (2) the CHW mobile application, and (3) facility records.

Household surveys

A household survey will be administered to all eligible women at baseline (prior to the launch of the intervention), and 12, 24, and 36 months after the intervention. Surveyors will not be members of the villages they survey, nor will they be members of the intervention health care delivery staff. All surveyors will be female, as the survey tool contains sensitive questions regarding contraception and reproductive health. The survey includes a household roster, which may be completed by the female head of household, and a questionnaire administered to consenting or assenting women of reproductive age (15-49) who are permanently residing in the household without foreseeable plans to move away from the area.

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The household survey instrument was adapted from the Mali Demographic and Health Survey. The baseline survey will include a birth history to capture all live births occurring in the 59 months prior, which will then be updated during each of the follow-up survey rounds. To track maternal mortality, the survey will record all household deaths occurring the previous year, with additional information on timing of death (during pregnancy, childbirth, after childbirth) for women of reproductive age. The survey also captures detailed information on household and individual socio-demographic characteristics, access and utilisation of reproductive and maternal health care, and care-seeking behaviours and investments for recently ill children under five. Follow-up surveys will add new household members to the study cohort (e.g., due to births, migration) and record absences due to out-migration or death. Surveyors will attempt to contact each eligible woman up to three additional times if she is absent at the first visit.

CHW mobile application data

CHWs in both study arms will be equipped with an Android smartphone and trained to use a mobile application to track services rendered. The app is also designed to be a job aid with integrated data validation and prompts to guide the CHW through the appropriate case management protocol. Population census data collected at baseline, including individual unique identifiers and demographic information, will be pre-populated into the CHW application so that each CHW can access the records of families in his/her service delivery zone. During each encounter with a prospective patient, the CHW will either identify the individual in the application or register newborns, new arrivals, or visitors, before selecting the appropriate form in the application for the specific health concern (e.g., malaria case management). The types of actions displayed

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under a patient's profile are linked to her sex and age (e.g., pregnancy follow-up is displayed only for women aged 15-49). The application will also alert the CHW of upcoming tasks related to patient follow-up, with an action calendar for 24-hour follow-up available starting at midnight each day.

Facility data

Each PHC will be equipped with five laptop computers, and the physician-in-chief, midwife, pharmacist, vaccine administration technician, and receptionist will be trained in data collection on an EMR system. Population census data collected at baseline will be imported into the EMR system, including individual unique identifiers and basic demographic information. When attending a PHC, patients will present first to reception, where their medical records will be identified using their unique identifier, name, family and/or village information. During the patient consultation, the service provider will record patient health information (i.e., diagnostic tests, results, treatment, posology) in both the EMR and in the paper facility registers, the source documents of the Malian Ministry of Health and required by law. Referral by a CHW will be recorded.

Analytical plan

Analyses of the primary and secondary endpoints will estimate intention-to-treat (ITT) effects. Using data collected prospectively in the 12-, 24- and 36-month follow-up surveys, we will test for the difference in the incidence of deaths among children under five across treatment and control clusters using a Poisson regression model. Children surveyed at baseline will contribute person-years of exposure from the start date of the trial (intervention launch). Children born during the trial will contribute person-years of exposure beginning at birth. All children included in the analysis will contribute person-

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years through the date of their death, or are right-censored on their fifth birthday or the end date of the trial, whichever comes first. The coefficient of interest with be the incidence rate ratio estimated on a dichotomous variable that indicates the child's residence in a treatment versus control cluster. We will control for the non-constant risk of mortality in early childhood by adding a term for age, measured in months.

ITT estimates for secondary endpoints will also be estimated via regression analyses testing the significance of the coefficient on the treatment assignment variable. Linking functions will be chosen based on the type of outcome variable analysed (i.e., logit for dichotomous outcomes). Given the number of secondary endpoints, we will correct for multiple hypothesis testing. To control the familywise error rate, we will implement a Bonferroni correction. We will identify the number of tests to be conducted (k) *a priori*. Using $\alpha=0.05$, we will calculate a corrected $\alpha=(0.05/k)$ to be used in all significance tests for secondary endpoints.

All regressions will be estimated using robust standard errors to account for serial correlation within clusters. We will also estimate ITT effects using an adjusted model that controls for any unbalanced observable characteristics measured at baseline, such as household wealth, education, or household size, among others. These will then be compared to estimates from a per-protocol analysis of the primary and secondary outcomes. Supplementary analyses will be conducted to assess the existence and magnitude of heterogenous treatment effects according to distance to PHC (less than five kilometres vs. five kilometres or more), village population size, household wealth.

Cost-effectiveness analysis

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Cost-effectiveness analysis (CEA) compares different programme alternatives in terms of their cost-effectiveness ratio, which can be thought of as the average cost per unit of impact or benefit (e.g., cost per life year saved). In most cases, CEA is used to determine whether or not a new alternative policy is better than the status quo, or whether the extra cost is worth the extra benefit. In such cases, the incremental cost-effectiveness ratio (ICER) is used, which takes the ratio between the incremental costs of the new programme with respect to the status quo, to the incremental benefits of the new programme with respect to the status quo. We will perform an ICER analysis to evaluate the relative cost-effectiveness of the ProCCM model with respect of the iCCM model.

We will calculate the total economic costs of both programmatic models, which will reflect the monetary value of programme and household resources used to deliver and access services, respectively. From the programme perspective, these will include personnel and other recurrent costs such as drugs, laboratory tests and other inputs used to provide services. These data will come from three sources: (1) the CHW mobile application, which reflects all services and supplies used by CHWs for service provision; (2) PHC EMR, which include the services rendered at the PHC and resources will be valued at prices paid by the Ministry of Health; (3) programme records, including CHW's value of work time vis-à-vis salaries, and productivity data from the mobile application for time and services given. From the household perspective, costs include time used to access health services, valued at their opportunity costs (i.e., time lost from work), as well as out-of-pocket expenses such as paying for drugs or health services. These data will be obtained from the household surveys, which asks about out-of-pocket expenditures, time spent accessing services, and earnings from paid work.

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Patient and public involvement

The study was designed in collaboration with national, district, and local health officials. Bankass health district was chosen in consultation with the Ministry of Health for three reasons: (i) health care utilisation (prenatal and curative consultations) was low and under-five mortality was high; (ii) there were no overlapping interventions by other nongovernmental organizations at the time and for intended period of the trial; and (iii) local authorities were highly engaged and interested in collaborating on study implementation. Research questions and outcome measures were also chosen in consultation, to answer questions of key concern to ministerial partners for informing the design of the national strategic plan for iCCM scale-up, including whether the intervention is equitable, cost-effective, affordable at scale. Community consultation and permission will be sought prior to trial commencement in meetings with representatives of the village-clusters, such as village chiefs and their advisories, politico-administrative authorities, religious leaders, and representatives of women's and youth associations. Representatives will then communicate with community members via open public meetings. Once the study has terminated, results will be disseminated to participants via dissemination workshops at all levels of local, regional, and national representation.

Ethical approval and trial oversight

This trial is registered with ClincialTrials.gov (NCT02694055). Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Pharmacy and Dentistry, University of Bamako (2016/03/CE/FMPOS). The University of California, San Francisco exempted secondary analysis of the trial data from ethical approval. A data safety and monitoring board (DSMB) will provide oversight throughout the trial.

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DISCUSSION

Supported by the emergence of global health guidelines and the accumulation of rigorous evidence on the efficacy of iCCM, countries across sub-Saharan Africa are scaling up iCCM to improve child health.[9] Yet, the most recent evaluations of national iCCM programmes suggest further improvements in the delivery of iCCM programmes are necessary to reduce under-five mortality.[13–16] Because the core design and implementation of CHW services varies across health systems, their optimal features must be identified and evaluated for iCCM to realise its full potential. This includes identifying how financing mechanisms, health system integration, packages and delivery of care, and CHW recruitment, training and supervision, and compensation relate to care outcomes where CHWs are deployed as frontline health workers. The current trial aims to address one of these gaps by testing a proactive case detection workflow against a passive approach on reducing under-five mortality risk. The results of the trial will thus be pertinent to policymakers and implementers to determine how CHWs may be better deployed for amplifying public health impact.

The current study was designed and will be implemented in partnership with the Mali Ministry of Health to facilitate adoption of lessons learned and scale-up in the public sector if the intervention is found to be effective. In addition to the primary objective related to CHW service delivery mechanisms, secondary objectives explore questions of key concern to ministerial partners for informing the design of the national strategic plan for iCCM scale-up, including whether the intervention is equitable, cost-effective, affordable at scale. The intervention itself is designed to be scalable as the planning and

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implementation of the intervention was executed in partnership with the Ministry of Health and district health officials, including operating through government PHCs.

Limitations

The large geographic area and three-year time frame leaves the study open to a number of potential confounding effects. Although contingency measures have been put into place for various situations that may arise, unexpected events may occur that influence the extent to which the study can be implemented per protocol. CHWs may have avenues for interacting with each other outside the structures of the intervention which may lead to contamination. Changes to the health system or other contextual factors in the intervention area, such as drug stock-outs, health centre staff strikes, and concurrent programme implementation by other actors, may be beyond the control of the study implementers. However, close partnership with national and local health authorities during study preparation will enable us to proactively track these events, implement contingency steps, and/or otherwise document them for later sensitivity analyses of the trial's effects.

Trial status

The household baseline survey was carried out from December 2016 to February 2017. Health facility improvements, CHW trainings, and provider trainings were completed by December 2016. Implementation of the intervention including the removal of user fees began in February 2017.

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DECLARATIONS

List of abbreviations

CEA ……..	Cost-Effectiveness Analysis
CHW …….	Community Health Worker
DHS ……...	Demographic Health Survey
DSMB ……...	Data Safety and Monitoring Board
EMR ……..	Electronic Medical Records
iCCM …….	Integrated Community Case Management
ICER ……..	Incremental Cost-Effectiveness Ratio
ITT …….	Intention to Treat
PHC ……...	Primary Health Centre
ProCCM …….....	Proactive Community Case Management
UNICEF ……	United Nations Children's Emergency Fund
WHO …….	World Health Organization

Ethics approval and consent to participate

This trial is registered with ClincialTrials.gov (NCT02694055). Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Pharmacy and Dentistry, University of Bamako (2016/03/CE/FMPOS). The University of California, San Francisco exempted secondary analysis of the trial data from ethical approval. Informed consent will be obtained from all participants entered into the trial, or from the participant's parent or guardian if she is a minor.

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Consent for publication

Not applicable.

Data sharing statement

No additional data available now. Data will be made publicly available after the conclusion of the trial.

Competing interests

CW, KK, and AJ declare grants from Child Relief International Foundation. KK and AJ declare grants from USAID Development Innovation Ventures. The funders had no role in study design, and will have no role in data collection, data analysis, data interpretation, or writing of future reports. All authors declare no other competing interests.

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Authors' contributions

CW, KK, BP, JXL, ET, and AJ drafted the original study protocol with input from SS, NP, SB, and MF. MF conducted the sample size calculations. CW and ET prepared the protocol manuscript. All authors reviewed and provided feedback on the final version of the manuscript.

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Tables and Figures

Figure 1: Map of study area; colours indicate the seven health catchment areas within which the trial is being conducted

Table 1: CHW package of care, provided at the patient's doorstep (ProCCM arm) or at the CHW's health post (ProCCM and iCCM arms)

CHW Intervention	Description
Diagnosis and treatment of malaria, all ages	- Diagnosis and treatment of simple cases of malaria for patients of all ages, and accompaniment of patients of all ages with severe malaria to public PHC
iCCM of common childhood illnesses	- Diagnosis and treatment of malaria, diarrhoeal disease, and acute respiratory infection for children 2-59 months, and acute moderate malnutrition for children 6 to 59 months according to standard iCCM protocols[21]
Detection of pregnancy	- Pregnancy testing for women whose last menstrual period occurred more than six weeks before the date of the visit
Family planning services	- Contraceptive counselling, administration (oral contraceptives, depo provera, condoms), or referral (IUD, implants, sterilisation) for women who test negative for pregnancy and women or men who request family planning
Accompaniment or referral to PHC for danger signs, all ages	- Screening of sick patients of all ages for a list of predefined danger signs that indicate either immediate accompaniment or referral to public PHC - Referral of pregnant women to public PHC for prenatal consultation, facility-based delivery, and post-natal care
Follow-up care	- 24 hour follow-up for patients of all ages after referral to public PHC - 24, 48 and 72 hour follow-up after treatment of malaria (all ages) or iCCM (children under five); additional follow-up according to standard iCCM protocols[21] - Follow-up and danger sign monitoring throughout pregnancy (two weeks throughout her pregnancy, and every week in the final month until delivery) and post-partum period (24 hours, 48 hours, five days, and once per week until 48 days after delivery)
Newborn assessment	- Conduct of newborn assessment to provide counselling and screen for danger signs at 24 hours, 48 hours, 120 hours, 7 days, 14 days, 21 days, and 28 days
Health promotion and disease prevention	- Counselling for patients and families for disease prevention using behaviour change communication techniques

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Online Supplementary Document

Description of the intervention

Reinforcement of facility-based care

Prior to the commencement of the trial, all clusters will receive a health system strengthening intervention implemented at all seven study PHCs. To meet anticipated increase in utilisation as a result of the trial, each PHC will receive targeted, physical infrastructure improvements, including having separate general and maternity units, separate observation rooms for men and women, a pharmacy, and solar panels for continuous electricity. All PHC staff from the seven participating sites will receive training in priority areas of clinical care, including integrated management of childhood illness according to WHO guidelines, antenatal and delivery care, post-natal and newborn care, family planning, and rational prescription. Each PHC will recruit a formally-trained midwife to complement the existing auxiliary midwives that were responsible for PHC maternity care prior to the study.

CHW recruitment

CHWs will be recruited from the cluster in which they will work. They must be between 18 to 45 years old, inclusive, and know how to read and write in French. Female candidates will be encouraged. Community leaders, including mayors, village chiefs, and members of the Community Health Association (the administrative body of the PHC) will nominate potential candidates who meet these criteria. If community leaders are unable to identify an eligible candidate from the cluster, a CHW from a nearby village will be recruited and will relocate to the cluster in which he/she will work.

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CHW candidates will participate in the pre-service training (described below) after which the final selection of CHWs will be made based on the trainer's evaluation of each candidate's mastery of the protocol, active listening ability, spirit of commitment, and communication skills. CHWs who previously worked in the study area will be recruited and retrained according to their randomised assignment. In both arms, the community leaders of the cluster will ensure that the selected CHW(s) has a health post, which will be located either at the CHW's home or at a separate site, depending on the resources and preferences of the community.

CHW training

All selected CHWs will undergo a six-week, full time pre-service training and a one-week full time annual reinforcement training, conducted separately by arm. Training curriculum for the following will be the same for both arms: iCCM of malaria, diarrhoea, acute respiratory infections, and malnutrition; newborn care; antenatal and post-partum care; contraception; vaccination schedules; CHW roles and responsibilities, including patient communication, good clinical practices, and stock management; and data collection on a phone-based CHW application. In the intervention arm, the training curriculum will include additional modules on proactive case detection, door-step care, and home-based follow-up.

CHW supervision

All participating CHWs will receive monthly one-on-one supervision and weekly group supervision with a dedicated CHW supervisor, recruited and trained for this exclusive purpose. Each supervisor will be responsible for between 15 and 20 CHWs, with an equal number of CHWs from intervention and control arms. In turn, CHW supervisors themselves will receive

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monthly one-on-one supervision and weekly group supervision from a manager, following the same strategy used for CHW supervision.

Group supervision sessions will be held separately for CHWs assigned to each study arm in order to minimize spill-over effects. Group supervision sessions will be held every week for the first three months after intervention launch and every two weeks after the first three months. During group supervision sessions, which will last approximately two hours, the supervisor and CHWs will discuss common challenges faced by CHWs in the field and potential solutions. At the final group session of the calendar month, the supervisor and CHWs will agree on a schedule of individual supervision sessions for the coming month. Each CHW will know in advance the date and time of his/her next individual supervision session, but not the location within his/her catchment area at which it will take place.

Monthly individual CHW supervision activities will include the following: (i) home visits conducted without the CHW in which the supervisor conducts household interviews in the absence of the CHW to elicit patient or caregiver perspectives of CHW care; (ii) direct observation in which the supervisor observes the CHW providing care (at the health post for CHWs in the control arm, during home visits for CHWs in the intervention arm); and (iii) one-on-one feedback in which the supervisor and CHW identify areas of strength and areas for improvement.

CHW reporting

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CHWs will record all patient encounters using a CHW mobile application on an Android smartphone. In addition to measuring aggregate process indicators, such as the number of children under five evaluated per month, the data collected by the CHW application will be used to generate CHW performance indicators, including coverage (percentage of population interfacing with the CHW per month), speed (percentage of sick children under five treated within one day of symptom onset), and quality of care (percentage of patient encounters conducted without protocol error). The data collected by the CHW application will also be used to identify system-level challenges, such as drug stock-outs.

CHWs who commit any protocol deviation (e.g., conducting proactive case finding home visits in the control arm, not conducting proactive case finding home visits in the intervention arm), will be required first to work closely with the supervisor to address the problem, and then will be summoned to a meeting with the administrative body of the PHC if the problem persists, and finally removed from his/her post if performance does not improve. Falsification of data or charging user fees to patients (verified through supervisory home visits without the CHW and/or patient data auditing) will constitute immediate termination.

CHW compensation

All CHWs will be compensated for their work with a monthly salary of 40,000 FCFA (approximately 70 USD), which is circa minimum wage. CHWs will receive an additional 3000 FCFA (approximately 5.40 USD) of monthly phone credit, and 1000 FCFA (approximately 1.80 USD) for each group supervision meeting to cover transportation costs. All CHWs will also be

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enrolled in Mali's payroll tax and social security retirement benefits (INPS) system. Compensation will be the same in both study arms.

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Proactive Community Case Management and Child Survival: Protocol for a Cluster Randomised Controlled Trial

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Proactive Community Case Management and Child Survival: Protocol for a Cluster Randomised Controlled Trial

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ABSTRACT

Introduction: Community health workers (CHWs)—shown to improve access to care and reduce maternal, newborn, and child morbidity and mortality—is re-emerging as a key strategy to achieve health-related Sustainable Development Goals. However, recent evaluations of national programmes for CHW-led integrated Community Case Management (iCCM) of common childhood illnesses have not found benefits on access to care and child mortality. Developing innovative ways to maximise the potential benefits of iCCM is critical to achieving the SDGs.

Methods and analysis: An unblinded, cluster randomised controlled trial in rural Mali aims to test the efficacy of the addition of door-to-door proactive case detection by CHWs compared to a conventional approach to iCCM service delivery in reducing under-five mortality. In the intervention arm, 69 village-clusters will have CHWs who conduct daily proactive case-finding home visits and deliver doorstep counsel, care, referral, and follow-up. In the control arm, 68 village-clusters will have CHWs who provide the same services exclusively out of a fixed community health site. A baseline population census will be conducted of all people living in the study area. All women of reproductive age will be enrolled in the study and surveyed at baseline, 12, 24, and 36 months. The survey includes a life table tracking all live births and deaths occurring prior to enrolment through the 36 months of follow-up in order to measure the primary endpoint: under-five mortality, measured as deaths among children under five years of age per 1,000 person-years at risk of mortality.

Ethics and dissemination: The trial has received ethical approval from the Ethics Committee of the Faculty of Medicine, Pharmacy and Dentistry, University of

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Bamako. The results will be disseminated through peer-reviewed publications, national and international conferences and workshops, and media outlets.

Trial registration: ClinicalTrials.gov, NCT02694055. Registered 13 January 2016, https://clinicaltrials.gov/show/NCT02694055.

Key words: Child health; Maternal health; Cluster randomized trial; Community Health Workers, integrated Community Case Management, Child mortality

Strengths and limitations of this study

- This is a cluster randomised controlled trial powered to detect a 25% relative difference in the incidence rate of under-five mortality between the two study arms.
- The trial will generate evidence on the efficacy, cost-effectiveness, and equity of door-to-door proactive case detection by CHWs on access to care and child mortality.
- The intervention is designed to facilitate public sector adoption and scale-up if found to be effective.
- The large geographic area and three-year time frame leave the study vulnerable to unexpected events that may influence the extent to which the intervention can be implemented per protocol.
- Changes to the health system or other contextual factors in the intervention area, such as drug stock-outs, health centre staff strikes, concurrent programme implementation by other actors, and political insecurity may be beyond the control of the study implementers.

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INTRODUCTION

The vast majority of maternal, newborn, and child deaths in low- and middle-income countries are preventable. Evidence-based and cost-effective methods for prevention and treatment are available for the leading causes of death, yet many still face barriers to obtaining timely, quality, appropriate care. If community-based interventions, such as the treatment of malaria with artemisinin compounds, oral rehydration solution for childhood diarrhoea, oral antibiotics for pneumonia, nutritional interventions during pregnancy, and hand washing with soap, were scaled to achieve 90% coverage in high-burden countries before 2020, an estimated 6.9 million maternal and child deaths could be averted.[1]

Integrated Community Case Management (iCCM) of common childhood illnesses entails a package of services to diagnose, treat and refer children under five with malaria, diarrhoea, pneumonia, or moderate malnutrition, delivered by community health workers (CHWs).[2] Community case management of common childhood illnesses has been shown to improve access to care[3–5] and treatment adherence,[3,6] and reduce mortality due to malaria,[7] diarrhoea,[3,8,9] pneumonia,[3,10,11] as well as all causes.[7,9,10]

Many countries in sub-Saharan Africa have adopted iCCM as an evidence-based strategy to improve child health.[12,13] However, the expected benefits of iCCM have not been realized in all contexts.[14–19] Several recent evaluations of national iCCM programmes did not find impacts on care seeking or child mortality, in part, study authors conclude, due to low demand for CHW services.[20–23] These national programmes shared certain design and implementation features that may have

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contributed to the lack of overall effects by not addressing barriers to care, such as user fees for services, lack of frequent and dedicated CHW supervision for quality assurance, and community care provision exclusively (or primarily) for patients that seek care from a fixed health site. As more countries commit to scaling up CHW-led health care systems, it is critical that we understand how to best design and implement iCCM, and CHW services more broadly, in order to bring about their full potential.

To address this need, we designed a cluster randomised controlled trial to test door-to-door proactive case detection by CHWs compared to a conventional approach to iCCM service delivery, which relies on patient-initiated care-seeking. In both arms of the trial, CHWs will provide an integrated package of child, reproductive, and maternal health services, primary health centres (PHCs) will be reinforced in infrastructure and capacity, and user fees will be removed at all levels of care. The difference between the intervention (ProCCM) arm and the control (iCCM) arm is the proactive versus conventional approach to the delivery of community-based services. The comparator was chosen to isolate and assess the effects of one design feature of CHW service delivery: proactive case detection.

The ProCCM approach is designed to overcome additional social, structural, and health system barriers that may impede or lead to delayed access, even under a community-based comprehensive iCCM approach. At a systems level, these include the direct and indirect costs of care, including distance to care. At the household level, lack of resources, mistrust in the health care system, and complex familial decision-making dynamics due to in part to gender inequality can contribute to delays in reaching care.[24,25] By proactively seeking out patients and linking community

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members to the health care system, ProCCM is designed to reduce the time from onset of condition to utilisation of health services, including direct provision of comprehensive primary care services for all household members, ultimately reducing mortality.

METHODS AND ANALYSES

Study aims and hypothesis

Our cluster randomised controlled trial aims to:

(1) Estimate the effect of adding door-to-door proactive case detection by CHWs to an enhanced iCCM intervention on under-five child mortality; we hypothesize that, after 36 months, the relative difference in the incidence rate of under-five mortality between the two study arms will be greater than 25%.

(2) Estimate the effect of adding door-to-door proactive case detection by CHWs to an enhanced iCCM intervention on utilisation of reproductive, maternal, and child health services.

(3) Evaluate the ProCCM intervention model, compared to the iCCM control model, in terms of cost-effectiveness, equity, and affordability at scale.

Study site

The trial will be conducted in the Bankass health district of the Mopti region in eastern Mali, approximately 600 kilometres east of the nation's capital, Bamako. The district has a 2016 population of approximately 300,000 people and is served by a public secondary referral hospital located in Bankass, the largest town in the district.[26] Within the Bankass health district, the study is being conducted in seven (of 22) health catchment areas: Dimbal, Doundé, Ende, Kani Bozon, Koulongon, Lessagou, and Soubala (Figure 1). The study area has a 2016 population of

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approximately 100,000 people.[26] Each health catchment area is served by a PHC operated by the Ministry of Health.

Study design

This is an unblinded, pragmatic, cluster-randomised controlled trial, with 69 village-clusters in the intervention arm and 68 village-clusters in the comparison arm. Clusters are randomised to receive either enhanced iCCM from stationary CHW(s) serving patients exclusively at a community health site (control) as per Mali's national iCCM strategy,[27] or ProCCM from CHW(s) conducting daily proactive case-finding home visits in addition to serving patients at a community health site. Only the intervention arm will receive door-to-door proactive case detection by CHWs, including doorstep care and home-based follow-up.

Intervention

Local community members—female candidates encouraged—who can read and write in French will be recruited, trained, supervised, and supported as CHWs from the village-cluster in which they will work. CHW coverage will be based on Mali's national iCCM strategy, which recommends one CHW for a population of 700 in the southern region where the study area is situated.[27] Clusters, therefore, may have one or multiple resident CHWs, depending on the size of the cluster population. Clusters with less than 200 people and within three kilometres of another cluster assigned to the same study arm will share a CHW, provided there is no geographic barrier (i.e., river) between the two clusters and no linguistic barrier for the CHW.

In both arms, CHWs will provide a comprehensive set of primary care services, including iCCM in accordance with national and international standards,[28] as well as maternal and reproductive health for women of reproductive age (see Table 1 for a

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full description of the CHW package of care). CHW services will include counselling, diagnostics, treatment, referral to reinforced PHCs, and follow-up care. CHWs will be required to be on call, available to receive and care for patients who seek them out, 24 hours per day, seven days per week. CHWs will receive a salary circa minimum wage (40,000 FCFA per month), and user fees will be removed for all CHW and referral services for all patients in the study area. A detailed description of the entire health system strengthening intervention in both arms is provided in the Online Supplementary Document.

Control arm: Conventional CHW service delivery

In clusters assigned to the control arm, CHWs will be stationed at a community health site to provide the comprehensive package of primary care services for at least four hours per day, six days per week, available to receive patients seeking care. The community health site is at the cluster level and separate from the PHC.

Intervention arm: Proactive CHW service delivery

In clusters assigned to the intervention arm, CHW(s) will be trained and deployed to conduct proactive case finding, door-to-door home visits for at least two hours each day, six days a week, with the goal of visiting each household at least two times each month. During the home visit, CHWs will screen all household members for recent illness or symptoms and provide services at the home, including follow-up for sick children and adults, pregnant women, newborns, and post-partum mothers. In addition to home visits, ProCCM CHWs will provide care at their community health site for at least two hours a day, six days per week, according to a calendar shared with the community. At the health site, CHWs will provide the same services as those offered by CHWs in the control arm to care-seeking patients.

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Cluster definition and randomisation

In order to identify distinct clusters, a field team visited all villages and hamlets in the study area and collected Global Positioning System (GPS) coordinates at the public space where community-wide meetings, announcements, and festivities are held. GPS coordinates were mapped and the cardinal distances between neighbouring villages/hamlets were calculated. Villages and hamlets one kilometre or less from one another were grouped into clusters, resulting in 160 individual villages and hamlets grouped into 137 unique clusters. A cluster definition based in geographic reality rather than administrative delineation helps to mitigate against contamination.

Clusters located 1.0 or more kilometres from a PHC were stratified by health catchment area and distance to the nearest PHC (1.0–5.0 kilometres vs. more than 5.0 kilometres). The cut-off point of 5.0 km was defined in accordance with national iCCM guidelines,[27] which deploys CHWs to deliver iCCM services only in communities greater than 5.0 km from a PHC. An additional stratum included all villages where the PHC was located to ensure balanced assignment of PHC villages across arms. Within each strata, clusters were randomly assigned to the control or treatment arm using a computer-generated random number. Randomisation was conducted by a member of the research team based in the United States who did not have any involvement in CHW recruitment or participant enrolment. Trial statisticians will remain blinded to cluster allocation until the end of the trial.

Sample size and primary and secondary endpoints

Primary endpoint

The primary endpoint is under-five mortality, measured as deaths among children under five years of age per 1,000 person-years at risk of mortality. In Mopti, the

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region of the study site, the ten-year under-five mortality rate (U5MR) was 111 deaths per 1,000 live births during the 2012-2013 DHS, which is higher than the national U5MR.[29] Since the 2013 DHS, intermittent prophylactic therapy in children for malaria has been rolled out across the region. As Intermittent Preventive Treatment in Children (IPTc) is associated with a risk ratio of all-cause under-five mortality of 0.66 in areas of seasonal transmission of malaria,[30] we estimate that baseline U5MR in the area of the intervention will be 111*0.66=72.6/1000.

The sample size for the trial was based on this primary endpoint, derived using methods for cluster-randomised trials[31] in which each cluster was treated as an observation and the cluster-level outcome was defined as the U5MR per person-years at risk. We used a negative binomial model to simulate the number of deaths among children under five. According to 2014 national population estimates adjusted for 2016 using a 2.2% annual growth rate,[26] the seven health catchment areas encompassed a population of 103,848 inhabitants. Assuming that 20% of the population was children aged 0-59 months and 22% was women aged 15 to 49, we calculated a mean of 152 children and 167 women per cluster. Person-years at risk were calculated assuming three years of prospective study follow-up with 10% attrition based on experience with previous trials in Mali.[32,33] We used a coefficient of variation of k=0.29[31] to model the extra variation due to clustering ($1/k^2$ is the size parameter in the negative binomial model). With these parameters, the trial will be able to detect a relative difference of 25% (alpha = 0.05, two-tailed test) in the under-five mortality incidence between treatment and control arms with 81.8% power after 36 months.

Secondary endpoints

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We will also estimate the effect of the intervention on a number of secondary endpoints:

(a) Infant mortality (deaths per 1,000 live births among children aged 0-11 months);

(b) Newborn mortality (deaths per 1,000 live births among children aged 0-28 days);

(c) Pregnancy-related mortality ratio (number of deaths among women while pregnant or within 42 days of delivery or termination per 100,000 live births per year) if there is sufficient and robust data to do so;

(d) Receipt of oral rehydration therapy and zinc within 24 hours of diarrhea onset among children under five;

(e) Receipt of diagnostic testing and/or effective treatment for malaria within 24 hours of fever onset among children under five;

(f) Evaluation by a qualified provider within 24 hours of symptom onset among children under five with cough and/or fast breathing;

(g) Receipt of three or more doses of Sulfadoxine-Pyrimethamine as Intermittent Preventive Treatment during a woman's most recent pregnancy;

(h) Enrollment in ANC with a skilled provider in the first trimester during a woman's most recent pregnancy;

(i) Completing four or more antenatal care (ANC) consultations with a skilled provider during a woman's most recent pregnancy;

(j) Use of a modern method of contraception among women of reproductive age.

Inclusion criteria

Any individual in the study area at any point during the study period, including visitors, are eligible to receive the health services offered through the intervention. Only permanent residents of the study area are eligible to be included in the household survey. All women aged 15 to 49 permanently residing in the study area at

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baseline who provide consent or assent and report no foreseeable plans to leave the study area are eligible to participate in the women's questionnaire of the household survey—the data source used for the measurement of primary and secondary endpoints. Women who did not meet the inclusion criteria at baseline but who become newly eligible during the course of the study are invited to participate at follow-up household survey rounds.

Sources of data

The effects of the ProCCM model of service delivery, compared to the iCCM model, for the primary and secondary endpoints will be assessed using data from three sources: (1) household surveys, (2) the CHW mobile application, and (3) facility records.

Household surveys

A household survey will be administered to all eligible women at baseline (prior to the launch of the intervention), and 12, 24, and 36 months after the intervention start. Surveyors will not be members of the villages they survey, nor will they be members of the intervention health care delivery staff. All surveyors will be female, as the survey tool contains sensitive questions regarding contraception and reproductive health. The survey includes a household roster, which may be completed by the female head of household, and a questionnaire administered to consenting or assenting women of reproductive age (15-49).

The household survey instrument was adapted from the Mali Demographic and Health Survey (DHS) and designed in Open Data Kit, which permits real-time quality and completeness control on data collection. The women's questionnaire will include

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a full birth history to capture all live births, which will then be updated during each of the follow-up survey rounds. To track maternal mortality, the survey will record all household deaths occurring the previous year, with additional information on timing of death (during pregnancy, childbirth, after childbirth) for women of reproductive age. The survey also captures detailed information on household and individual socio-demographic characteristics, access and utilisation of reproductive and maternal health care, and care-seeking behaviours and investments for recently ill children under five. Follow-up household survey rounds will add new household members to the study cohort (e.g., due to births, migration) and record absences due to out-migration or death. Surveyors will attempt to contact each eligible woman up to three additional times if she is absent at the first visit.

CHW mobile application data

CHWs in both study arms will be equipped with an Android smartphone and trained to use a mobile application to track services rendered. The app is also designed to be a job aid with integrated data validation and prompts to guide the CHW through the appropriate case management protocol. Population census data collected at baseline, including individual unique identifiers and demographic information, will be pre-populated into the CHW application so that each CHW can access the records of families in his/her service delivery zone. During each encounter with a prospective patient, the CHW will either identify the individual in the application or register newborns, new arrivals, or visitors, before selecting the appropriate form in the application for the specific health concern (e.g., malaria case management). The types of actions displayed under a patient's profile are linked to her sex and age (e.g., pregnancy follow-up is displayed only for women aged 15-49). The application will

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also alert the CHW of upcoming tasks related to patient follow-up, with an action calendar for 24-hour follow-up available starting at midnight each day.

Facility data

Each PHC will be equipped with five laptop computers, and the physician-in-chief, midwife, pharmacist, vaccine administration technician, and receptionist will be trained in data collection on an EMR system. Population census data collected at baseline will be imported into the EMR system, including individual unique identifiers and basic demographic information. When attending a PHC, patients will present first to reception, where their medical records will be identified using their unique identifier, name, family and/or village information. During the patient consultation, the service provider will record patient health information (i.e., diagnostic tests, results, treatment, posology) in both the EMR and in the paper facility registers, the source documents of the Malian Ministry of Health and required by law. Referral by a CHW will be recorded.

Analytical plan

Analyses of the primary and secondary endpoints will estimate intention-to-treat (ITT) effects.

Analysis of primary endpoint

Using data collected prospectively in the 12-, 24- and 36-month follow-up household surveys, we will test for the difference in the incidence of deaths among children under five across treatment and control arms using a Poisson regression model with cluster-level random effects, controlling for household distance to PHC (less than five kilometres vs. five kilometres or more). Children surveyed at baseline will contribute person-years of exposure from the start date of the trial's intervention launch; children

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born during the trial will contribute person-years of exposure beginning at birth. Children who enter the trial after baseline will contribute person-years of exposure beginning at the household survey interview date in which they are enrolled. All children included in the analysis will contribute person-years through the date of their death, or are right-censored on their fifth birthday or the end date of the trial, whichever comes first. The coefficient of interest with be the incidence rate ratio estimated on a dichotomous variable that indicates the child's residence in a treatment versus control cluster. We will control for the non-constant risk of mortality in early childhood by controlling for age (in months) constant over time, and will control for any individual-level characteristics that are unbalanced at baseline. To estimate mortality, a child's date of birth, date of interview, vital status at interview, and if applicable, date of death are required. We will replicate the procedures for missing mortality data used in the Demographic and Health Surveys, described in detail elsewhere.[34]

Analysis of secondary endpoints

The same modelling approach will be used to estimate ITT effects for secondary endpoints (excluding the covariate for child's age); regression analyses will test the significance of the regression coefficient on the treatment assignment variable. Linking functions will be chosen based on the type of outcome variable analysed (i.e., logit for dichotomous outcomes). If 10% or fewer observations have missing secondary outcome data, we will drop observations from analysis; otherwise, we will determine and apply sample weights to estimates derived from the complete sample of observations. For any secondary endpoints that differ significantly by arm at baseline, we will use a difference-in-differences estimation approach to account for this difference.

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Per-protocol estimates: ITT estimates will be compared to estimates from a per-protocol analysis of primary and secondary outcomes. Our per-protocol analysis will estimate the effects of the intervention only for households that received the ProCCM CHW services according to the intervention protocol. This will be defined as households, which report they have received two or more visits from a CHW in the month preceding the household survey for each year they participated in the survey, regardless of treatment assignment. Finally, exploratory analyses will be conducted to assess the existence and magnitude of heterogeneous treatment effects according to village population size and household wealth.

Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) compares different programme alternatives in terms of their cost-effectiveness ratio, which can be thought of as the average cost per unit of impact or benefit (e.g., cost per life year saved). In most cases, CEA is used to determine whether or not a new alternative policy is better than the status quo, or whether the extra cost is worth the extra benefit. In such cases, the incremental cost-effectiveness ratio (ICER) is used, which takes the ratio between the incremental costs of the new programme with respect to the status quo, to the incremental benefits of the new programme with respect to the status quo. We will perform an ICER analysis to evaluate the relative cost-effectiveness of the ProCCM model with respect of the iCCM model.

We will calculate the total economic costs of both programmatic models, which will reflect the monetary value of programme and household resources used to deliver and access services, respectively. From the programme perspective, these will include personnel and other recurrent costs such as drugs, laboratory tests and other inputs

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used to provide services. These data will come from three sources: (1) the CHW mobile application, which reflects all services and supplies used by CHWs for service provision; (2) PHC EMR, which include the services rendered at the PHC and resources will be valued at prices paid by the Ministry of Health; (3) programme records, including CHW's value of work time vis-à-vis salaries, and productivity data from the mobile application for time and services given. From the household perspective, costs include time used to access health services, valued at their opportunity costs (i.e., time lost from work), as well as out-of-pocket expenses such as paying for drugs or health services. These data will be obtained from the household surveys, which asks about out-of-pocket expenditures, time spent accessing services, and earnings from paid work.

Patient and public involvement

The study was designed and implemented in partnership with national, district, and local health officials of the Malian Ministry of Health. Bankass health district was chosen in consultation with the Ministry of Health for three reasons: (i) health care utilisation (prenatal and curative consultations) was low and under-five mortality was high; (ii) there were no overlapping interventions by other nongovernmental organizations at the time and for intended period of the trial; and (iii) local authorities were highly engaged and interested in collaborating on study implementation. Research questions and outcome measures were also chosen in consultation, to answer questions of key concern to government partners for informing the design of the national strategic plan for iCCM scale-up, including whether the intervention is equitable, cost-effective, and affordable at scale. Community consultation and permission will be sought prior to trial commencement in meetings with representatives of the village-clusters, such as village chiefs and their advisories,

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politico-administrative authorities, religious leaders, and representatives of women's and youth associations. Representatives will then communicate with community members via open public meetings. Once the study has terminated, results will be disseminated to participants via dissemination workshops at all levels of local, regional, and national representation.

Ethics and dissemination

This trial is registered with ClincialTrials.gov (NCT02694055). Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Pharmacy and Dentistry, University of Bamako (2016/03/CE/FMPOS). The University of California, San Francisco exempted secondary analysis of the trial data from ethical approval. External monitoring of the study will be assured by a Clinical Research Associate external to the trial team. Any substantial protocol amendments or deviations, or any unintended effects of trial interventions or conduct, will be submitted to the Ethics Committee and records reviewed by the CRA.

Surveyors will obtain informed consent from all household survey respondents prior to enrolment in the trial, or from the respondent's parent or guardian if she is a minor. Identifying information (i.e. proper name, phone number) will be stored separately from the survey data, linked by the registration ID. Access to identifying information will be restricted to the data collection and management team; trial statisticians and other external collaborators will access only de-identified data.

An independent data safety and monitoring board (DSMB) will provide oversight throughout the trial. The DSMB will oversee participant safety and evaluate interim results to determine if the trial should be stopped early. Interim analyses of the primary endpoint (under-five mortality) will be performed at 12 and 24 months,

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estimated using data from the first and second follow-up household surveys. The DSMB will terminate the study early if a 50% relative difference in under-five mortality is detected after 12 months (statistical significance at $p<0.001$) or a 35% relative difference in under-five mortality after 24 months ($p<0.001$), a stopping rule more stringent than Haybittle-Peto stopping rules.[35,36] At the end of the trial period, or if the trial is terminated early, all participating villages will receive the care with the condition identified in the superior study arm.

Trial results will be published in peer-reviewed journals following the International Committee of Medical Journal Editors (ICJME) guidelines. Findings will be disseminated via conferences and workshops with national and international stakeholders in community-based healthcare delivery including researchers, policymakers, and practitioners. De-identified data will be made publicly available after the conclusion of the trial and publication of the main effects.

DISCUSSION

Supported by the emergence of global health guidelines and the accumulation of rigorous evidence on the efficacy of iCCM, countries across sub-Saharan Africa are scaling up iCCM to improve child health.[12,13] Yet, the most recent evaluations of national iCCM programmes suggest further improvements in the delivery of iCCM programmes are necessary to reduce under-five mortality.[20–23] Because the core design and implementation of CHW services varies across health systems, their optimal features must be identified and evaluated for iCCM to realise its full potential. This includes identifying how financing mechanisms, health system integration, packages and delivery of care, and CHW recruitment, training, supervision, and compensation relate to care outcomes where CHWs are deployed as

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frontline health workers. The current trial aims to address one of these gaps by testing door-to-door proactive case detection by CHW against a conventional CHW service delivery approach on reducing under-five mortality risk. The results of the trial will thus be pertinent to policymakers and implementers to determine how CHWs may be better deployed for amplifying public health impact.

The current study was designed and will be implemented in partnership with the Mali Ministry of Health to facilitate adoption of lessons learned and scale-up in the public sector if the intervention is found to be effective. In addition to the primary objective related to CHW service delivery mechanisms, secondary objectives explore questions of key concern to ministerial partners for informing the design of the national strategic plan for iCCM scale-up, including whether the intervention is equitable, cost-effective, affordable at scale. The intervention itself is designed to be scalable as the planning and implementation of the intervention was executed in partnership with the Ministry of Health and district health officials, including operating through government PHCs. Findings from this study could have important policy implications for CHW-led iCCM scale up across sub-Saharan Africa.

Limitations

The large geographic area and three-year time frame leave the study open to a number of potential confounding effects. Although contingency measures have been put into place for various situations that may arise, unexpected events may occur that influence the extent to which the study can be implemented per protocol. CHWs may have avenues for interacting with each other outside the structures of the intervention which may lead to contamination. Changes to the health system or other contextual factors in the intervention area, such as drug stock-outs, health centre staff strikes,

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concurrent programme implementation by other actors, and political insecurity may be beyond the control of the study implementers. However, close partnership with national and local health authorities during study preparation will enable us to proactively track these events, implement contingency steps, and/or otherwise document them for later sensitivity analyses of the trial's effects.

Trial status

The household baseline survey was carried out from December 2016 to February 2017. Health facility improvements, CHW trainings, and provider trainings were completed by December 2016. Implementation of the intervention including the removal of user fees began in February 2017.

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DECLARATIONS

List of abbreviations

CEA ……..	Cost-Effectiveness Analysis
CHW …….	Community Health Worker
DHS ……...	Demographic Health Survey
DSMB ……...	Data Safety and Monitoring Board
EMR ……..	Electronic Medical Records
GPS ……..	Global Positioning System
iCCM …….	Integrated Community Case Management
ICER ……..	Incremental Cost-Effectiveness Ratio
ITT …….	Intention to Treat
PHC ……...	Primary Health Centre
ProCCM …….....	Proactive Community Case Management
UNICEF ……	United Nations Children's Emergency Fund
WHO …….	World Health Organization

Contributors

CW, KK, BP, JXL, ET, and AJ drafted the original study protocol with input from SS, NP, SB, and MF. MF conducted the sample size calculations. CW and ET prepared the protocol manuscript. All authors reviewed and provided feedback on the final version of the manuscript.

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intervention and assuring adherence to protocol. We thank Dr. Dansiné Diarra for the GPS mapping that allowed us to generate our clusters, and for providing Figure 1. We thank the community-based and facility-based health workers and their supervisors for their role in implementation, We are grateful to the Malian Ministry of Health, representatives from Community Health Associations at each PHC site, village leaders, and the communities of the Bankass District for their collaboration.

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Competing interests

CW, KK, and AJ declare grants from Child Relief International Foundation. KK and AJ declare grants from USAID Development Innovation Ventures. The funders and sponsor had no role in study design, and will have no role in data collection, data analysis, data interpretation, or writing of future reports. All authors declare no other competing interests.

Ethics approval

Ethics Committee of the Faculty of Medicine, Pharmacy and Dentistry, University of Bamako (2016/03/CE/FMPOS).

Provenance and peer review

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Tables and Figures

Figure 1: Map of study area; colours indicate the seven health catchment areas within which the trial is being conducted

Table 1: Community Health Worker package of care, provided at the patient's doorstep (intervention arm) or at the CHW's health site (both arms)

CHW Services	Description
Diagnosis and treatment of malaria, all ages[ð]	- Diagnosis and treatment of simple cases of malaria for patients of all ages, and accompaniment of patients of all ages with severe malaria to public PHC
iCCM of common childhood illnesses[ð]	- Diagnosis and treatment of malaria, diarrhoeal disease, and acute respiratory infection for children 2-59 months, and acute moderate malnutrition for children 6 to 59 months according to standard iCCM protocols[28]
Detection of pregnancy	- Pregnancy testing for women whose last menstrual period occurred more than six weeks before the date of the visit
Family planning services[ð]	- Contraceptive counselling, administration (oral contraceptives, depo provera, condoms), or referral (IUD, implants, sterilisation) for women who test negative for pregnancy and women or men who request family planning
Accompaniment or referral to PHC for danger signs, all ages[ð]	- Screening of sick patients of all ages for a list of predefined danger signs that indicate either immediate accompaniment or referral to public PHC - Referral of pregnant women to public PHC for prenatal consultation, facility-based delivery, and post-natal care
Follow-up care	- 24-hour follow-up for patients of all ages after referral to public PHC - 24, 48 and 72 hour follow-up after treatment of malaria (all ages) or iCCM (children under five); additional follow-up according to standard iCCM protocols[28] - Follow-up and danger sign monitoring throughout pregnancy (two weeks throughout her pregnancy, and every week in the final month until delivery) and post-partum period (24 hours, 48 hours, five days, and once per week until 48 days after delivery)
Newborn assessment[ð]	- Conduct of newborn assessment to provide counselling and screen for danger signs at 24 hours, 48 hours, 120 hours, 7 days, 14 days, 21 days, and 28 days
Health promotion and disease prevention[ð]	- Counselling for patients and families for disease prevention using behaviour change communication techniques

Notes:
[ð]These services are also offered by conventional CHWs in the Malian context, according to the Ministry of Health's policy on CHW care.
Abbreviations: iCCM=integrated Community Case Management; IUD=intrauterine device; PHC=primary health centre.

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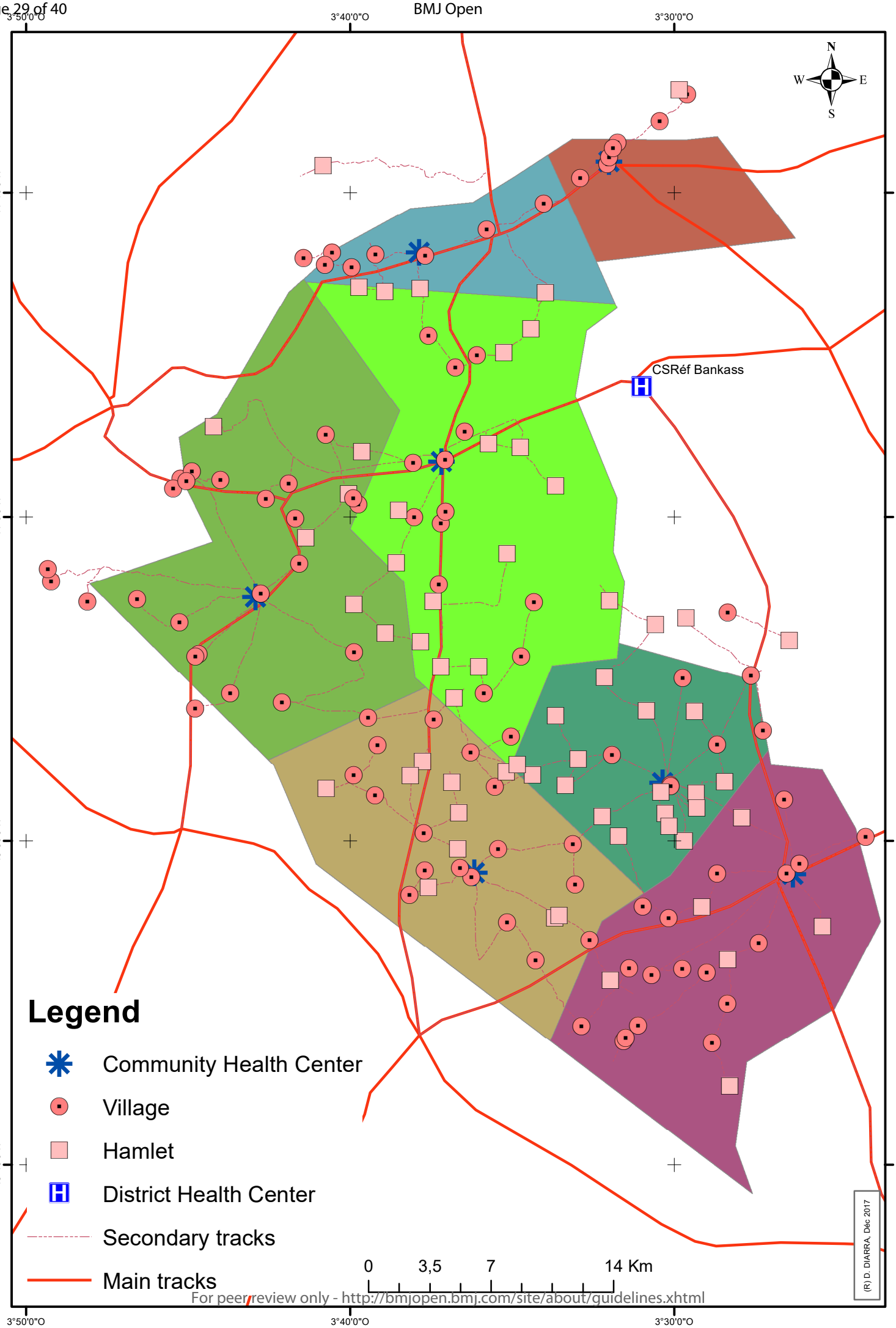

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Online Supplementary Document

Description of the intervention

Reinforcement of facility-based care

Prior to the commencement of the trial, all clusters will receive a health system strengthening intervention implemented at all seven study PHCs. To meet anticipated increase in utilisation as a result of the trial, each PHC will receive targeted, physical infrastructure improvements, including having separate general and maternity units, separate observation rooms for men and women, a pharmacy, and solar panels for continuous electricity. All PHC staff from the seven participating sites will receive training in priority areas of clinical care, including integrated management of childhood illness according to WHO guidelines, antenatal and delivery care, post-natal and newborn care, family planning, and rational prescription. Each PHC will recruit a formally-trained midwife to complement the existing auxiliary midwives that were responsible for PHC maternity care prior to the study.

CHW recruitment

CHWs will be recruited from the cluster in which they will work. They must be between 18 to 45 years old, inclusive, and know how to read and write in French. Female candidates will be encouraged. Community leaders, including mayors, village chiefs, and members of the Community Health Association (the administrative body of the PHC) will nominate potential candidates who meet these criteria. If community leaders are unable to identify an eligible candidate from the cluster, a CHW from a nearby village will be recruited and will relocate to the cluster in which he/she will work.

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CHW candidates will participate in the pre-service training (described below) after which the final selection of CHWs will be made based on the trainer's evaluation of each candidate's mastery of the protocol, active listening ability, spirit of commitment, and communication skills. CHWs who previously worked in the study area will be recruited and retrained according to their randomised assignment. In both arms, the community leaders of the cluster will ensure that the selected CHW(s) has a health post, which will be located either at the CHW's home or at a separate site, depending on the resources and preferences of the community.

CHW training

All selected CHWs will undergo a six-week, full time pre-service training and a one-week full time annual reinforcement training, conducted separately by arm. Training curriculum for the following will be the same for both arms: iCCM of malaria, diarrhoea, acute respiratory infections, and malnutrition; newborn care; antenatal and post-partum care; contraception; vaccination schedules; CHW roles and responsibilities, including patient communication, good clinical practices, and stock management; and data collection on a phone-based CHW application. In the intervention arm, the training curriculum will include additional modules on proactive case detection, door-step care, and home-based follow-up.

CHW supervision

All participating CHWs will receive monthly one-on-one supervision and weekly group supervision with a dedicated CHW supervisor, recruited and trained for this exclusive purpose. Each supervisor will be responsible for between 15 and 20 CHWs, with an equal number of CHWs from intervention and control arms. In turn, CHW supervisors themselves will receive

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monthly one-on-one supervision and weekly group supervision from a manager, following the same strategy used for CHW supervision.

Group supervision sessions will be held separately for CHWs assigned to each study arm in order to minimize spill-over effects. Group supervision sessions will be held every week for the first three months after intervention launch and every two weeks after the first three months. During group supervision sessions, which will last approximately two hours, the supervisor and CHWs will discuss common challenges faced by CHWs in the field and potential solutions. At the final group session of the calendar month, the supervisor and CHWs will agree on a schedule of individual supervision sessions for the coming month. Each CHW will know in advance the date and time of his/her next individual supervision session, but not the location within his/her catchment area at which it will take place.

Monthly individual CHW supervision activities will include the following: (i) home visits conducted without the CHW in which the supervisor conducts household interviews in the absence of the CHW to elicit patient or caregiver perspectives of CHW care; (ii) direct observation in which the supervisor observes the CHW providing care (at the health post for CHWs in the control arm, during home visits for CHWs in the intervention arm); and (iii) one-on-one feedback in which the supervisor and CHW identify areas of strength and areas for improvement.

CHW reporting

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CHWs will record all patient encounters using a CHW mobile application on an Android smartphone. In addition to measuring aggregate process indicators, such as the number of children under five evaluated per month, the data collected by the CHW application will be used to generate CHW performance indicators, including coverage (percentage of population interfacing with the CHW per month), speed (percentage of sick children under five treated within one day of symptom onset), and quality of care (percentage of patient encounters conducted without protocol error). The data collected by the CHW application will also be used to identify system-level challenges, such as drug stock-outs.

CHWs who commit any protocol deviation (e.g., conducting proactive case finding home visits in the control arm, not conducting proactive case finding home visits in the intervention arm), will be required first to work closely with the supervisor to address the problem, and then will be summoned to a meeting with the administrative body of the PHC if the problem persists, and finally removed from his/her post if performance does not improve. Falsification of data or charging user fees to patients (verified through supervisory home visits without the CHW and/or patient data auditing) will constitute immediate termination.

CHW compensation

All CHWs will be compensated for their work with a monthly salary of 40,000 FCFA (approximately 70 USD), which is circa minimum wage. CHWs will receive an additional 3000 FCFA (approximately 5.40 USD) of monthly phone credit, and 1000 FCFA (approximately 1.80 USD) for each group supervision meeting to cover transportation costs. All CHWs will also be

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enrolled in Mali's payroll tax and social security retirement benefits (INPS) system.

Compensation will be the same in both study arms.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	https://clinicaltrials.gov/show/NCT02694055
Protocol version	3	Date and version identifier	Document name
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	22
	5b	Name and contact information for the trial sponsor	23
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18-19
Introduction			

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Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5, 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5, 7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6, Fig 1
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11-12 for participants; 7 and Suppl file for recruitment of CHWs
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8 and Suppl file for more information
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	19
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	18
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA 7: this is a pragmatic trial

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Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	21 for trial status
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9

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Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	SOPs available upon request
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-17, SAP available upon request
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-17, SAP available upon request
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-17, SAP available upon request

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19, DSMB charter available upon request
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18-19

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Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19

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	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	These are available upon request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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