Study design

## This is a two-arm cRCT carried out in 3 woredas in SNNPR in Ethiopia. Clusters, defined by health center (the lowest administrative unit where HEW services are coordinated), are randomized into either the *conditional* or *universal* follow-up arm. All children seeking care from the HEW health posts in these clusters are potential recipients of the interventions, in addition to having access to routine care available from private and public health services. Caregivers of children who meet the inclusion criteria (fever without malaria, pneumonia, diarrhea, or other symptoms requiring referral) are counseled to follow one of two pathways, based on which intervention cluster the HEW belongs to. There are 25 clusters; 13 clusters in the universal follow-up arm and 12 in the conditional follow-up arm.

## Study site

This research study will be conducted in three woredas (districts), namely Boloso Sore, Damot Gale, and Halaba in the Wolayita zone of SNNPR in Southwest Ethiopia (Figure 1). The iCCM program is functioning in all districts of SNNPR through support to the Regional Health Bureau, from Save the Children International and the Integrated Family Health Program. It will therefore be an ideal environment to implement this research, as iCCM services are stable and the program is implemented by the Regional Health Bureau which will provide technical oversight to this project.

According to the latest Malaria Indicator Surveys, the rate of prompt care-seeking for fever is currently low, with only 46.3% of children U5 with fever taken for early treatment [[22](#_ENREF_22)]. However, care seeking at health post level shows an upward trend, presumably as a result of the increased awareness of the availability and proximity of child health services [[12](#_ENREF_12)]. In addition, Malaria Consortium, with funding from the James Percy Foundation, has recently started implementing the Integrated Community-based Interventions for Malaria Services (ICIMS) project in SNNPR. Activities include case detection by the volunteer Health Development Army who will work to ensure that all children with fever receive prompt diagnosis and treatment, and that children with danger signs get referred. As part of this grant, refresher training will also be provided to HEWs to negotiate optimal practices using behavior change communication tools and facilitation skills in community conversation. It is anticipated that these changes will lead to an increased use of HEWs in the study area.

The three woredas will be selected based on a) strength of iCCM program (i.e. consistency in HEW supervision and supply), b) HEW use rate among caregivers (>50 children assessed for fever each month over a 12 month period), and c) concurrent community mobilization activities under other grants (to ensure that demand was kept high during the study period). There are 25 health centers and 144 health posts with 282 HEWs in the three selected woredas.

## The interventions

Children 2-59 months with fever (≥37.5 degrees Celsius) or a history of fever, a negative mRDT, no other symptoms of pneumonia or diarrhea, and no danger signs will be eligible to participate in the study. Figure 2 outlines the areas which consenting caregivers will be counseled on, which include:

### Intervention arm 1 – Conditional follow-up (recommended in the Ethiopian IMNCI guidelines)

1. How to detect danger signs and seek care immediately from a health center if danger signs develop or the illness worsens,
2. Fever reductions strategies, such as tepid sponging, and paracetamol
3. Returning at any point to the HEW at the health post for re-assessment if symptoms persist or deteriorate
4. The day seven study visit to assess clinical outcomes

### Intervention arm 2 – Universal follow-up (common practice)

In the universal follow-up arm, caregivers will be counseled on 1, 2, and 4 above but advised to return on day three to the HEW for a follow-up assessment, even if the child has recovered.

At the day three reassessment visit in the universal follow-up arm and at any spontaneous visit in both arms, the child will have a full re-assessment of their condition and the HEW will fill out a child assessment form. Caregivers will be asked whether the child remains febrile or whether the illness has resolved. If the child still has unclassified fever and a negative mRDT on re-assessment, the child will be referred to the nearest health center, as recommended in the national IMNCI guidelines. If the illness has resolved, the child will be sent home.

A clinically trained independent evaluator (IE) who is blinded to the study arm will visit all enrolled children at their home on day seven to assess their clinical outcome. If caregivers report that the child no longer is ill and no fever is recorded, the child will be considered cured and no more follow-up will be done. If the caregiver reports that the child still has symptoms or if fever and/or other illness symptoms are detected during the assessment, the IE will follow the IMNCI algorithm and refer/treat the child accordingly. The IE will then follow up again via a home visit on day 14 and, if the child is still ill, on day 28.

At the day seven visit, the IE will use a questionnaire to ask about individual and household characteristics, care-seeking and other treatments for the current illness episode, and reasons for returning/not returning to the HEW for follow-up care.

Qualitative component

Caregivers’ recognition and responses to childhood fevers; and HEWs’ views and experiences of their position in the healthcare system during previous and in particular the current recommendations in the respective intervention arms will be explored using semi-structured interviews at a time point when the interventions are fully adopted by the HEWs (determined based on a stable enrolment rate). A subset of mothers and HEWs in both arms will be selected for inclusion in these interviews to help put the findings into context.

## Randomization

Cluster randomization will be at the health center level, corresponding to the lowest administrative unit where HEW services are coordinated; there are 25 clusters in the three study woredas, with an average of 5 health posts and 7.5 HEWs per cluster. All clusters will be eligible for randomization. Restricted randomization will be performed to minimize the difference between intervention and control arms on key indicators, including average under-five population size, cluster distance to nearest zonal referral hospital, and number of unclassified fevers in children U5 seen by HEWs [[23](#_ENREF_23)]. A validity matrix will be produced to confirm that no pairs will be more or less likely to appear together than they would by chance. Sorting of clusters and random selection of schemes will be carried out in STATA 13 (STATA Corp, College Station, TX, USA).

## Sample size

The primary outcome on which sample size is based is the percentage of children with persistent fever, persistent illness, or decline (hospital, danger signs develop, death) at day seven. It is assumed that about 5% of children in both groups will still be ill at day seven (based on rates of ~3% and 8% in previous studies [[16](#_ENREF_16), [24](#_ENREF_24)]) and that this percentage will be approximately equivalent between groups. To calculate sample size, the outcome rate (ill at day seven) in the universal follow-up group is set to 5%, and it is assumed that the (true) corresponding outcome percentage in the conditional follow up group will be no more than 6%. For the purposes of concluding that the conditional follow up is non-inferior to the universal follow up approach, the upper bound of a one-sided 95% confidence interval around the absolute difference in outcome rate (conditional minus universal) must not exceed 4% (non-inferiority margin), assuming a power of 80% and an alpha of 5%. A design effect of 3 is used to account for clustering at HEW and health facility levels, generating a total sample size of 4284 children, with 2142 in each arm. To compensate for 10% loss to follow-up at day seven and an additional 5% loss between day seven and day 14, a total of 4900 children will be enrolled. Enrolment will occur over a one-year period to account for seasonality of various causes of febrile illness; starting in December 2015 and is expected to be completed around December 2016

## Outcomes

All enrolled children will have a day seven study visit in their home with an IE to assess their clinical outcome. Children who have not recovered on day seven are re-assessed on day 14, and those whose illness persists on day 14 will be re-assessed on day 28. In addition, all enrolled children will be followed-up via a phone call for vital status on day 28. Management of illness at any follow-up visit (i.e. return to HEW on any day, return to HEW for universal day three visit, or day seven, 14, and 28 assessment) will follow established national IMNCI guidelines.

The primary outcome is treatment failure on day seven, defined as the proportion of children with unclassified fever who subsequently declined clinically (death, hospitalization, one or more danger signs or persistent fever).

Secondary outcomes include:

* Clinical presentation in those with unresolved illness at day seven in each arm
* Treatment failure on day 14 and 28, defined as the proportion of children with unclassified fever who subsequently declined clinically (death, hospitalization, one or more danger signs or persistent fever)
* Percentage of children who present to the HEW for the follow-up visit on day three in the universal follow-up arm
* Percentage of children who spontaneously re-present to HEW for persistence or worsening of symptoms in the conditional follow-up arm, and the timing of these visits
* Percentage of children receiving secondary treatment (antimicrobial medicines prescribed during visits to any providers after initial presentation to HEW) in each arm between enrolment and day seven
* Caregiver and HEW acceptability of universal and conditional follow-up recommendations

## Data collection

HEWs will collect data using an Open Data Kit (ODK) [[25](#_ENREF_25)] data collection form on mobile phones. Data will include date of enrolment, child identifiers and clinical indicators (fever/axillary temperature, cough, respiratory rate, diarrhea and danger signs). The enrolment data will be synchronized with a server which is accessed by a data manager who will download enrolments on a daily basis and schedule follow-up visits for six IEs using an online Google calendar.

The IEs will be equipped with tablets programmed with three ODK data collection forms; one for the day seven visit, one for any extra visits (on day 14 or 28), and one vital status form for day 28. The data that will be collected during the household follow-up visits on day seven, 14, and 28 will include clinical data for the children following the IMNCI algorithm (e.g. fever/axillary temperature, cough, respiratory rate, diarrhea, MUAC measure, and danger signs), any secondary treatment (antimicrobial medicines prescribed during visits to any providers after initial presentation to HEWs), hospitalization, care-seeking history, and costs, as well as caregiver and household characteristics. For children who cannot be found at home at the time of the home visit, two more attempts will be made over the two following days. After this, the child will be registered as a loss-to-follow-up for the primary outcome.

Three research assistants will enter data collected by HEWs for children who come back to the HEW spontaneously (universal and conditional arm) or on day three (universal arm) into an ODK sick child assessment form every two weeks.

A rigorous monitoring system will be implemented by the study team was part of the continuous quality assurance. The data manager will review forms submitted to the server daily, and check for duplicates, completeness, and accuracy before storing them in the project database. Discrepancies, overdue follow-up visits, and other issues will be resolved by phone calls to the IEs and during weekly supervision meetings with field research staff. Biweekly field supervision visits to all HEWs will be carried out, and district HEW supervisors will be trained to monitor HEW trial activities during routine weekly group supervisions. A minimum of 10 percent of all enrolled cases and 50 percent of children with treatment failure will have a quality control re-assessment by a research assistant. The final data set will be exported to STATA 13 (STATA Corp, College Station, TX, USA).

Semi-structured interviews with HEWs and caregivers of children enrolled in the study will be conducted when a stable enrolment rate has been established in the study (assumed to be after 3 months). HEW interviews focus on what decentralization of healthcare mean to HEWs, how changes in follow-up recommendations are perceived, how they describe their roles in the communities and how health system changes affect this role and their work situation. Caregiver interviews will aim to improve the understanding of caregiver perceptions of childhood illnesses, their perceived causes and treatment options in the three woredas. Interview guides will capture how caregivers (assume primarily mothers) of sick children experience illness episodes and treatment seeking inside and outside the household. Focus will be on how caregivers describe the illness episode from the beginning to the recovery/current health status, actions that are taken or not taken when a young child gets fever, who is involved in the care of the child and what their perceptions and experiences are with the recommended follow-up action they have been exposed to when visiting the HEW. Half of the HEWs and mothers to be interviewed will be from the study arm using the universal follow-up advice and the other half follow the conditional follow-up recommendation. HEWs will be purposively selected, based on who has enrolled the highest number of children for the cRCT. Mothers of children enrolled in the study in the two weeks preceding to the start of the qualitative data collection will be included using on simple random sampling. A minimum of 1 week should have passed since the day seven visit was completed to avoid study fatigue.

Interview guides will be separately prepared for the HEW and caregiver interview and translated into Amharic. Two male, Amharic speaking interviewers will conduct the HEW interviews and one additional male Amharic interviewer will be recruited for the caregiver interviews.