PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	An innovative public-private partnership to target subsidized antimalarials: a study protocol for a cluster randomized controlled trial to evaluate a community intervention in Western Kenya
AUTHORS	Laktabai, Jeremiah; Lesser, Adriane; Platt, Alyssa; Maffioli, Elisa; Mohanan, Manoj; Menya, Diana; O'Meara, Wendy; Turner, Elizabeth Louise

VERSION 1 - REVIEW

REVIEWER	Elizabeth Allen LSHTM UK
REVIEW RETURNED	11-Oct-2016

GENERAL COMMENTS	This is a clear well written protocol and I have very few comments all of which are minor. 1. There is no mention of a DMC – I see no need for one in this study but the SPIRIT guidelines are explicit and say that an explanation of why one is not needed should be given in the protocol. Ideally some details of the governance structure should also be given. 2. They authors state that they will allow for clustering in the analysis but it would be helpful to know how. 3. How will the randomisation be done? By computer? and by whom 4. A slightly more detailed description of usual care would help.

REVIEWER	S. Patrick KACHUR Centers for Disease Control and Prevention Atlanta, Georgia USA
REVIEW RETURNED	13-Nov-2016

GENERAL COMMENTS	This is a well-conceived study and a well presented research design. However, I am not certain that it will be suitable to the broad readership of BMJ. In a journal with a more specialized or regional focus, it would be more likely to come to the attention of researchers and public health program managers with closely aligned interests in expanding malaria diagnosis and treatment through public-private sector innovations. If accepted for publication, I suggest the following minor revisions: * I would strongly recommend that the background be expanded to describe the current state of availability and cost of quality assured ACTs in the private retail sector across Kenya and particularly in Bungoma and TransNzoia Counties. There is a gap in the

	description of programming between the close of the AMFm pilot in 2012 and the time of the study. It would also be important to note what role the investigators have/ will continue to play in ensuring supplies, quality and price of treatment drugs in the private sector. * Explain whether the CUs are existing, recognized administrative units or functional designations for the operations of health programs, or if they were constructed solely for the purposes of the research. What proportion of the total population/ geography of the subCounties do the 32 CUs selected for the study represent? * Please explain the extent to which the CHVs are purely volunteer or remunerated. And what are their responsibilities aside from malaria diagnostic testing? * On page 4 line 59 it is stated that all patients with a negative RDT will be referred to a health facility--this strikes me as potentially a very large number of cases that could overwhelm the health facilities, or at the very least that could result in a very low rate of referral completion. Will the study team evaluate this potential and consider how scalable such a model might be? * On page 5, lines 59-60 it is indicated that communities are aware of their CHVs and that "anyone desiring an RDT is advised to contact a CHV". I wonder if this is reasonable or even advisable as a public health strategy as it leaves the decision about testing to the consumer. Wouldn't it be more advisable to recommend that anyone with a febrile illness contact their CHV (or go directly to a health facility), and leave the decision about testing to the CHV or facility based health worker? * As I understand it, the study outcomes are almost all based on self-report at the time of 4 follow-up surveys with 6 month recall intervals. For questions about specific tests (a malaria test vs. a blood test for anemia or HIV), test results, specific drugs, and adherence--there is likely to be imperfect recall which could complicate the investigators' ability to see an intervention impact. Although I believe the design is robust enough to minimize the risk of systematic bias with regard to this concern.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Elizabeth Allen
Institution and Country: LSHTM, UK
Competing Interests: None

This is a clear well written protocol and I have very few comments all of which are minor.

Thank you for your comments and suggestions.

1. There is no mention of a DMC – I see no need for one in this study but the SPIRIT guidelines are explicit and say that an explanation of why one is not needed should be given in the protocol. Ideally some details of the governance structure should also be given.

We have added a section before the final paragraph (pg. 9) as follows:

“Trial oversight

The trial management committee (TMC) includes all co-authors of this protocol paper, with leadership provided by the study principal investigator, Dr. O'Meara. Other specific roles are CHV oversight (Dr. Menya), retail sector liaison and oversight (Dr. Laktabai), data analysis oversight (Dr. Turner), data management and data analysis (Ms. Platt), study coordination (Ms. Lesser) and advisory roles on economics (Dr. Mohanan and Ms. Maffioli). The TMC meets weekly to monitor field activities. No data safety and monitoring committee was created since the rapid diagnostic tests administered by CHVs are routinely used in a range of different settings and are considered safe when used by those carefully trained to use them, such as the CHVs in our study. Since no interim analyses are planned and data quality is monitored by the TMC through (blinded) periodic reports, no data monitoring committee was created."

2. They authors state that they will allow for clustering in the analysis but it would be helpful to know how.

We have expanded on our methods to state the following:

"We will use a mixed effects modeling approach with a random intercept for each CU (to account for clustering) and fixed effects for strata (to account for the stratified design)."

3. How will the randomisation be done? By computer? and by whom

We have added the following details to pg. 5 of the text:

"Randomization was performed by the lead statistician (ELT) using Stata SE 14.O Software (College Station: TX: Statcorp LP)."

4. A slightly more detailed description of usual care would help.

We have expanded the text on pg. 4 as follows:

"Individuals in the control arm receive usual care; they have access to standard community health volunteer (CHV) visits as per the Kenya Community Strategy Implementation guidelines[16]. In practice, usual care means that control arm individuals decide whether they seek treatment in the formal sector (i.e. testing and treatment via a health facility) or in the informal sector (i.e. private retailers) in which no testing is currently available but where government-subsidized anti-malarials are available."

Reviewer: 2
Reviewer Name: S. Patrick KACHUR
Institution and Country: Centers for Disease Control and Prevention, Atlanta, Georgia, USA
Competing Interests: None declared

This is a well-conceived study and a well presented research design. However, I am not certain that it will be suitable to the broad readership of BMJ. In a journal with a more specialized or regional focus, it would be more likely to come to the attention of researchers and public health program managers with closely aligned interests in expanding malaria diagnosis and treatment through public-private sector innovations.

If accepted for publication, I suggest the following minor revisions:

Thank you for your positive feedback and recommendations. Given our choice of a c-RCT design with repeated cross-sectional surveys, we hope that our protocol paper will appeal to a broad audience, including those that evaluate effectiveness of complex health interventions that include similar elements such as ours such as those that use task-shifting, a behavioral focus and/or with a public-private partnership. By publishing in BMJ Open, these features of our design could be accessible to a broad audience.

* I would strongly recommend that the background be expanded to describe the current state of availability and cost of quality assured ACTs in the private retail sector across Kenya and particularly

in Bungoma and TransNzoia Counties. There is a gap in the description of programming between the close of the AMFm pilot in 2012 and the time of the study. It would also be important to note what role the investigators have/ will continue to play in ensuring supplies, quality and price of treatment drugs in the private sector.

When AMFm ended in 2012, the subsidy was partly continued by the government but not at the same level. The final price for the consumer increased about 3-fold. We have added this information in the background on pg. 3 so that the text now reads as:

"The Kenyan Ministry of Health continued the private-sector subsidy but not at the same level as during the AMFm program. As a result, while ACTs are still sold over-the-counter and are widely available in the private retail sector, the retail price of ACTs increased approximately three-fold[12 13]."

With regards to the role of the investigators in the retail sector, we take no action to ensure availability of anti-malarials i.e. we do nothing to stock the retail stores. We ensure quality by only subsidizing green-leaf (quality-assured) ACTs and we control the price to the study participants because the study voucher ensures a fixed price to the consumer (see Table 1). In order to ensure a fixed price to the consumer, we agreed a price with the vendors at the beginning of the study so that we would pay them the difference between the fixed price to the client (see Table 1) and their agreed price, plus a 5 Kenyan shilling additional fee to them for each sale. We also agreed to re-evaluate these agreements should the wholesale price change considerably during the course of the study. In fact, we renegotiated the prices several months into the study following such a change in wholesale price.

* Explain whether the CUs are existing, recognized administrative units or functional designations for the operations of health programs, or if they were constructed solely for the purposes of the research. What proportion of the total population/ geography of the subCounties do the 32 CUs selected for the study represent?

The CUs are existing government units that pre-date the study. CU eligibility criteria was to already have active, trained CHVs in the CU. We have amended the text on "Overall Study Design" to read:

"We used a stratified cluster-randomized controlled trial design to assign all 32 eligible community units (CUs) in the area to either the intervention or control arm. A community unit is an existing administrative unit that averages about 1000 households (approximately 5000 people). In order to be eligible for the study, a CU had to have an existing system of trained community health volunteers (CHVs) in place. In practice, each eligible CU has approximately 20 CHVs and one community health extension worker (CHEW) who supervises the work of the CHVs, although the number of households and active CHVs per CU varies from place to place."

Additionally, in "Setting" (pg. 5-6), we have amended the text so that it is easier to read by having the same format for each Sub-county. We also now state approximately what fraction of the population of each Sub-county is covered by the study (i.e. 40% in Kiminini and 35% in Bungoma East). Importantly, we enrolled all of the eligible CUs in these sub-counties.

* Please explain the extent to which the CHVs are purely volunteer or remunerated. And what are their responsibilities aside from malaria diagnostic testing?

In the same "Overall Study Design" section we have expanded on our description in order to address your comment.

"In the existing structure, CHVs are a volunteer workforce involved in short-term health campaigns and health promotion with no salary from the Ministry of Health. They occasionally receive remuneration for periodic donor-funded activities. Intervention-arm CHVs are reimbursed for study-related travel for supervision and the community-based organizations that they have established receive a small bonus twice per year. "

* On page 4 line 59 it is stated that all patients with a negative RDT will be referred to a health facility--this strikes me as potentially a very large number of cases that could overwhelm the health

facilities, or at the very least that could result in a very low rate of referral completion. Will the study team evaluate this potential and consider how scalable such a model might be?

Thank you for highlighting how our choice of language does not clearly reflect exactly what we do. All individuals who receive an RDT (whether positive or negative) from an intervention-arm CHV receive a document with the test results, including their name, age, who tested them, the date and the test result. Those with a negative (i.e. who would not receive a subsidy for anti-malarials) would be advised to visit a health facility but we do not have a formal referral mechanism in place to ensure that this occurs. We have amended the text (pg. 5) to:

"In the intervention arm, the CHV administers an RDT to each eligible participant who presents with a fever or malaria-like symptoms at any point during the 18-month implementation period. All participants receive a paper form with the results of their RDT clearly stated. Those with a negative RDT are advised to visit a health facility with documented test results."

What the intervention seeks to do is to divert people who would go directly to the private retail sector without a test to have a test first. Our goal is not to divert them from the private sector to the health facilities. Therefore, we do not expect the health facilities to be overwhelmed by people who were not planning on visiting the health facility anyway. It is acceptable for the intervention to operate in this way since this group of people are those who would usually not go to the health facility anyway. Additionally, from our previous work, we know that health facilities frequently prescribe anti-malarials to test-negative individuals and/or to those without a test but who complain of a malaria-like illness (e.g. our community surveys showed that approximately 70% of all acute illnesses in the last 4 weeks took an ACT, that 49% of the test-negatives took an ACT and that 66% of the untested took an ACT).

* On page 5, lines 59-60 it is indicated that communities are aware of their CHVs and that "anyone desiring an RDT is advised to contact a CHV". I wonder if this is reasonable or even advisable as a public health strategy as it leaves the decision about testing to the consumer. Wouldn't it be more advisable to recommend that anyone with a febrile illness contact their CHV (or go directly to a health facility), and leave the decision about testing to the CHV or facility based health worker?

Thank you for highlighting this point. Our language was a little ambiguous, as the intervention is not designed to leave the decision about testing to the consumer but instead with the CHV. We have amended the text from "anyone desiring an RDT is advised to contact a CHV" to "anyone feeling ill with a malaria-like illness is advised to contact the CHV".

The PPP intervention aims to target individuals who would usually seek treatment in the retail sector without testing. We wish to ensure that tests are administered to such individuals so that they can make treatment decisions with information from the RDT.

* As I understand it, the study outcomes are almost all based on self-report at the time of 4 follow-up surveys with 6 month recall intervals. For questions about specific tests (a malaria test vs. a blood test for anemia or HIV), test results, specific drugs, and adherence--there is likely to be imperfect recall which could complicate the investigators' ability to see an intervention impact. Although I believe the design is robust enough to minimize the risk of systematic bias with regard to this concern.

Thank you for highlighting a missing piece of information. All outcomes are measured only in individuals who report a fever within the previous 4 weeks and not in the entire 6-month interval between surveys. Whilst 4-week recall is imperfect, most individuals are expected to recall febrile illnesses and we do not expect differential recall between study arms. In addition, we request to confirm the individual's self-report by reviewing any health records whenever possible.

We have amended both the abstract and the text to highlight this important point.

In the abstract we now state:

"Study outcomes in individuals with a febrile illness in the previous 4 weeks will be ascertained through population-based cross-sectional household surveys at four time points: baseline, 6, 12 and 18 months post-baseline."

Similarly, in the Outcomes section of the text (pg. 6) we now state:

“All study outcomes will be measured in individuals who have experienced a febrile illness in the previous 4 weeks. These outcomes will be ascertained through four cross-sectional household surveys (baseline, 6, 12, and 18 months).”

In the Survey procedures section, we now state:

“For only one reported fever per household for the previous 4-week period, the survey team records the type and source of any drug(s) taken, and self-reported test results of any diagnostic test for malaria (RDT or microscopy) performed prior to treatment.”

VERSION 2 – REVIEW

REVIEWER	S. Patrick Kachur Centers for Disease Control and Prevention United States
REVIEW RETURNED	28-Dec-2016

GENERAL COMMENTS	The authors have carefully and completely addressed all of my concerns and those of the other reviewer and editorial staff.