PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a quasi-experimental study to assess the feasibility, acceptability and costs of multiple first-lines artemisinin-based combination therapies for uncomplicated malaria in the health district of Kaya, Burkina Faso.
AUTHORS	SIRIBIE, Mohamadou; Tchouatieu, André-Marie; Soulama, Issiaka; Kaboré, Jean Moise Tanga; Nombré, Yacouba; Hien, Denise; Kiba Koumaré, Alice; Barry, Nouhoun; Baguiya, Adama; Héma, Alimatou; Dianda, Frédéric; Sawadogo, Yacouba; Kouanda, Seni; Tiono, Alfred B.; Sirima, Sodiomon Bienvenu

VERSION 1 – REVIEW

REVIEWER	José Manuel Ramos Rincón Universidad Miguel Hernández de Elche
REVIEW RETURNED	24-Jun-2020

GENERAL COMMENTS	The manuscript presents the protocol of s quasi-experimental study aims at assessing the feasibility, the acceptability and the cost of MFT strategy deploying three ACTs targeting hree segments of the population for managing uncomplicated malaria in health district of Kaya, Burkina Faso Recommendation: acceptation The protocol is well written and meets all the standards of a quasi-experimental study protocol. The manuscript could be approved in the current version

REVIEWER	Aung Pyae Phyo Myanmar Oxford Clinical Research Unit Myanmar
REVIEW RETURNED	09-Jul-2020

GENERAL COMMENTS	Major comments 1. In page-8, the choice of ACT is Pyronaridine-Artesunate (Pyr-AS) for children under five, Artemether-Lumefantrin (AL) for 156 pregnant women and Dihydroartesinin-Piperaquine (DHA-PQ) for individuals equal or more than 5 years. Can the author specify the rationale for the choice of ACT which is not in line with the National Guideline where the first-line ACT are Artesunate-Amodiaquine, Artemether-Lumefantrine and Dihydroartemisinin-Piperaquine. (Page 7, line 140) Again the choice of ACT is not reflecting the protocol title "Multiple first-lines ACTs" since Pyronaridine-Artesunate is not the first line ACT in Burkina Faso. 2. In page 9, Objective section said, to assess to assess the

	feasibility, acceptability, costs and "effects" of multiple first-lines ACTs. But author didn't describe tools/variables to measure the effect of multiple first-lines ACTs. How will the effect be evaluated? Effect on malaria prevalence or mortality? In page 11, the author roughly stated that "exhaustive assessment of malaria-related morbidity and mortality will be conducted through the updates of the HDSS and comparing data from the year before the project with those generated during the year of deployment of the pilot MFT programme". Please clearly specify variables and exact time period to be compared. And will the current sample size allow to compare the statistically significant effect of the multiple first-line ACTs? Again this objective is not in line with the protocol title where it said "to assess the feasibility, acceptability and costs of multiple first-lines". The protocol title doesn't mention to assess the "effect" of multiple first-lines ACTs. 3. In assessing the acceptability interviews and FGDs, will there be any question addressing the safety and tolerability of ACTs especially Pyronaridine-Artesunate which could be one of the pivotal factors in treatment policy decision. Minor comments 1. Please add more updated data about population and malaria prevalence/incidence if available later than 2016. (Page 7) 2. Please add anticipated study period (Start-End). 3. Specific objective (Page 9) said "To train and sensitise the key stakeholders of the MFT programme". Please elaborate the term "sensitise" and tools to evaluate this objective. 4. Please add ethics approval validity. It was approved in 2018 (N°2018-8-113). 5. Please mention how the interviewers or FGD facilitator will be trained/selected. Also state how the IDI/FGD participants will be selected.

REVIEWER	Solange Whegang Youdom University of Dschang, Department of Public Health, Faculty of medicine and pharmaceutical sciences, University of Dschang
REVIEW RETURNED	02-Aug-2020

GENERAL COMMENTS	The topic presented by the authors is very crucial in a context of ACT resistance. The deployment of multi-treatment effectively can contribute to the reduction of recrudescence and reinfection. Cost-effectiveness is also an important part to address. lines 139 to 144 should be in the background not the study site. in these lines it is mentioned the first line drugs in Burkina Faso. In the context of this country, I will suggest the author to add more rationale in the background to explain whether these combinations have been tested through randomized controlled trials or not, and state whether they are are effective in Burkina Faso. One of the best way to evaluate these three drugs could be through a randomized controlled trial, showing the gain in the efficacy with new ACT compared to existing ones. Is pyronaridine-artesunate already in use in Burkina Faso? I would have suggested that, rather than using a quasi-experimental study over 22 months, why not using an experimental study with ASPY as a new combination, and make use of the WHO guideline?

	Study outcomes (line 219) It is mentioned that study outcomes are reported on Table 1, but the first table is Table 2, this should be checked. Add a paragraph in how the study will be handle with Covid19 going on. How will the outcome listed be linked with the multi-treatment effectiveness? The study was registered and the funding details provided; a Consort summary/ or a diagram regarding how the sample size will be obtained could have been better to summarize the sampling strategies. My suggestions to improve the abstract is to add the current ACT treatment in Burkina Faso for malaria, and state whether they had been found non effective in any study. This statement will complete the main results from theoretical model. Regarding your analysis plan, I will suggest that you draft the plan before starting collecting the data as well the table shells and figures to go fast, not to wait before having the data base. I suggest that the authors make it clear whether they will use theoretical models on the data base to validate the background hypothesis, or not. There are several objectives listed but no timeline and it becomes difficult to assess whether they will fit in the proposed duration of the work (22 months). 22 months seems very long. The author would need to clarify this. They would need to add some expected results if any and the timeline. Minor revisions are to be made by the authors, and I recommend the protocol to be accepted by the editors.

REVIEWER	Deus Ishengoma National Institute for Medical Research (NIMR), Tanzania
REVIEW RETURNED	10-Aug-2020

GENERAL COMMENTS	General comment: The proposed protocol addresses an important subject in malaria case management due to the current threat of artemisinin resistance and ACT treatment failure, even in Africa as recently reported in Rwanda. Despite presentation of clear outcomes, the study design and methods are not well presented. The paper will require a major review before it can meet the required standards for publication. Specific comments: The following issues need to be clearly addressed. Abstract: Authors should briefly state what they will do to attain the goals of the study. The current version presents the objectives and outcomes but not the methodological details of the study. Introduction: 1. A thorough assessment and presentation of the current status and issues related to multiple first line ACTs or triple combination therapy should be presented. Recently, the subject has been well discussed and some papers published. These should reviewed and cited. 2. Authors presented country data of 2016 which is over 4years old. I would suggest to present more recent data to show the current status of malaria in Burkina Faso. Methods:

	1. The study site is reported to be under DSS since 2007 but authors decided to present the data of 2016. Is the area still under DSS? If yes, why not incorporate the most recent data? 2. On lines 139 – 141, authors cite WHO guidelines for parasitological confirmation of malaria before treatment. However, it is not stated if the same guidelines have been adopted and used in Burkina Faso. 3. Authors stated that three ACTs (amodiaquine-artesunate, artemether-lumefantrine and dihydroartemisinin-piperaquine) are used in Burkina Faso as first line antimalarials (Lines 141-144). If this is correct, it means the country is already using multiple first line ACTs. Then why do they want to conduct this study while three ACTs are already in use? 4. The study design is not well justified. What were the reasons for choosing this and not other types of study designs? How were the different drugs assigned to the different groups of the population and why? What are the questions to be addressed? 5. What are the inclusion and exclusion criteria for patients to be included in each treatment arm? 6. ACTs are not recommended for the treatment of malaria in the first trimester but the study proposes to use artemether-lumefantrine in pregnant women without stating if those in the first trimester will be excluded from the study. This needs to be stated and the type of antimalarials to be prescribed to pregnant women in the first trimester should also be mentioned. 7. The study proposes to assess and determine the feasibility, acceptability and costs of triple first line ACTs but the data collection methods does not clearly show how the feasibility and acceptability will be assessed. Clarity of the type of data and how such data will be collected to determine feasibility and acceptability should be stated in the methods. 8. Authors should state the reasons for including different target populations in the study (such as households) and the type of information to be collected and the purpose or use of such data. 9. Since the study population is under DSS, it is not clear of what extra information will be collected from households apart from that which is collected routinely in the DSS. The reasons for collecting such information should also be stated. 10. A draft data analysis plan should be included in the protocol. Why should the plan be written later? Discussion: I would suggest the discussion to be focused on the research questions and how they will be addressed. Potential limitations should also be stated.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: José Manuel Ramos Rincón

Institution and Country: Universidad Miguel Hernández de Elche

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

The manuscript presents the protocol of s quasi-experimental study aims at assessing the feasibility, the acceptability and the cost of MFT strategy deploying three ACTs targeting three segments of the population for managing uncomplicated malaria in health district of Kaya, Burkina Faso

Recommendation: acceptation
The protocol is well written and meets all the standards of a quasi-experimental study protocol.
The manuscript could be approved in the current version

We thank the first reviewer for his positive feedback on the proposed manuscript.

Reviewer: 2

Reviewer Name: Aung Pyae Phyo

Institution and Country: Myanmar Oxford Clinical Research Unit, Myanmar

Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below

Major comments

1. In page-8, the choice of ACT is Pyronaridine-Artesunate (Pyr-AS) for children under five, Artemether-Lumefantrin (AL) for pregnant women and Dihydroartesinin-Piperaquine (DHA-PQ) for individuals equal or more than 5 years. Can the author specify the rationale for the choice of ACT which is not in line with the National Guideline where the first-line ACT are Artesunate-Amodiaquine, Artemether Lumefantrine and Dihydroartemisinin-Piperaquine. (Page 7, line 140)
Again the choice of ACT is not reflecting the protocol title "Multiple first-lines ACTs" since Pyronaridine-Artesunate is not the first line ACT in Burkina Faso.

Response: At the time of designing this current protocol, Pyronaridine-Artesunate was not yet approved in the national guideline for the management of uncomplicated malaria case. However, this ACT was prequalified by the World Health Organisation, registered and marketed in Burkina Faso. In addition, Pyr-As was efficacious and well tolerated as well as currently marketed ACTs such as (Dihydroartemisinin-Piperaquin, Artemether-Lumefantrin, Amodiaquin-Artesunate) as demonstrated by WANECAM trial conducted in West Africa including Burkina Faso[1,2]. With regards to these data,

[1] Sagara I, Beavogui AH, Zongo I *et al*. Safety and efficacy of re-treatments with pyronaridine-artesunate in African patients with malaria: a substudy of the WANECAM randomised trial. Lancet Infect Dis. 2016 Feb;16(2):189-98. doi: 10.1016/S1473-3099(15)00318-7. Epub 2015 Oct 23. PMID: 26601738

[2] West African Network for Clinical Trials of Antimalarial Drugs (WANECAM). Pyronaridine-artesunate or dihydroartemisinin-piperaquine versus current first-line therapies for repeated treatment of uncomplicated malaria: a randomised, multicentre, open-

the National Malaria Control Programme of Burkina is planning to review the national guidelines. We have anticipated by including this drug in this pilot study and to assess whether three ACTs could be appropriately managed at the same time, in parallel at health facility level in the context of multiple first-line therapies. The rationale for the choice of the three ACTs has been addressed at the Discussion section of the revised manuscript.

2. In page 9, Objective section said, to assess the feasibility, acceptability, costs and "effects" of multiple first-lines ACTs. But author didn't describe tools/variables to measure the effect of multiple first-lines ACTs. How will the effect be evaluated? Effect on malaria prevalence or mortality?

Response: We will assess the effects of the strategy on malaria morbidity and mortality. The related indicators, methods of assessment, time point for assessment, targeted population and data collection tools have been described in the Supplementary table 1.

In page 11, the author roughly stated that "exhaustive assessment of malaria-related morbidity and mortality will be conducted through the updates of the HDSS and comparing data from the year before the project with those generated during the year of deployment of the pilot MFT programme". Please clearly specify variables and exact time period to be compared.
And will the current sample size allow to compare the statistically significant effect of the multiple first-line ACTs?
Again this objective is not in line with the protocol title where it said "to assess the feasibility, acceptability and costs of multiple first-lines". The protocol title doesn't mention to assess the "effect" of multiple first-lines ACTs.

Response: First of all, we would like to mention that this is a before and after study design with multiple outcomes to be assessed as clearly defined in the Supplementary table 1 (Outcome, related indicators, numerator/denominator, methods of assessment, time point for assessment, targeted population and data collection tools). We agree with the reviewer that the term “effect” could have been added, reflected in the protocol title. But, it would be difficult to make a detailed description of all the outcomes of interest in title of the article without exceeding the word limit. The assessment of the effect of this pilot study on malaria morbidity and mortality will be assessed exhaustively at health facility level and at community level using respectively routine data collected at health facility level and using HDSS updates at community level without any formal sample sizes. Data will be captured over 12 calendar months before and during the deployment of this multiple first-line therapies. The sample size computed and mentioned in the proposed manuscript protocol is intended to assess the effect of

label, longitudinal, controlled, phase 3b/4 trial. Lancet. 2018 Apr 7;391(10128):1378-1390. doi: 10.1016/S0140-6736(18)30291-5. Epub 2018 Mar 29. PMID: 29606364

the study on the treatment seeking behaviors and cost-of-illness (febrile episode/malaria) related parameters.

3. In assessing the acceptability interviews and FGDs, will there be any question addressing the safety and tolerability of ACTs especially Pyronaridine-Artesunate which could be one of the pivotal factors in treatment policy decision.

Response: We confirm that perceptions on safety and tolerability will be part of the topics that will be explored during the qualitative surveys.

Minor comments

1. Please add more updated data about population and malaria prevalence/incidence if available later than 2016. (Page 7)

Response: Suggestion is well taken. We have updated these data in the manuscript with the most recent data available (2018).

2. Please add anticipated study period (Start-End).

Response: The anticipated study start and end dates are respectively 2019 and 2021. These date have been added in the revised manuscript, marked copy (Lines 170 - 171).

3. Specific objective (Page 9) said "To train and sensitise the key stakeholders of the MFT programme". Please elaborate the term "sensitise" and tools to evaluate this objective.

Response: The term “sensitise” here mean to keep a continuous communication with the stakeholders regarding the potential benefits of the study so that to improve their compliance with the study protocol.

This is an operational objective and not an evaluation objective. The sensitisation is mainly performed through the monitoring visits at the health facilities level.

4. Please add ethics approval validity. It was approved in 2018 (N°2018-8-113).

Response: According to the ethical committee procedures, the approval has a lifespan of one year and therefore must be renewed every year. The initial approval was obtained on 2018. These elements have been added in the revised protocol, marked copy (Lines 382 – 384).

5. Please mention how the interviewers or FGD facilitator will be trained/selected. Also state how the IDI/FGD participants will be selected?

Response: The selection of IDI/FGD participants has been described in the table 1 (Sampling strategy for qualitative surveys). Kindly, refer to this table.
The selection/training process of the interviewers/facilitators for FGD/IDI is declined in the institutional standard operating procedures for qualitative surveys. As requested, the following summary has been included in the revised manuscript (Lines 295 – 301 in the revised manuscript, marked copy):
"The qualitative surveys will be conducted by social scientists (interviewers/facilitators) holding a Bachelor/Master degree in socio-anthropology under the coordination of a senior social scientist. They will be recruited through a call for application and then well-trained on the objectives of the study, the specific standard operating procedures, the data collection tools and the process of consent taking. The training sessions will be followed by pre-tests on the ground to address any misunderstanding of the interview guides, the process of data collection and to adapt the interview guides before the commencement of surveys."

Reviewer: 3

Reviewer Name: Solange Whegang Youdom

Institution and Country: University of Dschang, Department of Public Health, Faculty of medicine and pharmaceutical sciences, University of Dschang

Please state any competing interests or state 'None declared':
No competing interest

Please leave your comments for the authors below
The topic presented by the authors is very crucial in a context of ACT resistance. The deployment of multi-treatment effectively can contribute to the reduction of recrudescence and reinfection. Cost-effectiveness is also an important part to address.

1. Lines 139 to 144 should be in the background not the study site.
in these lines it is mentioned the first line drugs in Burkina Faso. In the context of this country, I will suggest the author to add more rationale in the background to explain whether these combinations have been tested through randomized controlled trials or not, and state whether they are effective in Burkina Faso.

Response: The lines 139 to 144 have been moved into the background section. In addition, this section has been more elaborated to show whether these combinations have been tested in Burkina Faso and to what extent they were effective, as follows (Lines 103 – 117 in the revised manuscript, marked copy):
"As per World Health Organisation (WHO) recommendation, all cases of clinical malaria in Burkina Faso should be biologically confirmed with a malaria rapid diagnostic test (mRDT) or microscopy, when available, before any treatment. As per National Malaria Control Programme guidelines, Amodiaquine-Artesunate or Artemether-Lumefantrine or Dihydroartemisinin-Piperaquine are the recommended first-line drugs for the treatment of uncomplicated malaria. The granules for oral

suspension of Pyronaridine-Artesunate prequalified by WHO, has been registered in Burkina Faso and is available at private pharmacies across the country. Several studies conducted in sub-Saharan Africa including Burkina Faso have demonstrated the safety and the efficacy of these four ACTs (AS-AQ, AL, DHA-PQ and Pyr-As) against uncomplicated malaria. Oral quinine is recommended for the management of uncomplicated malaria cases in pregnant woman as well as ACTs except the first trimester of pregnancy. Four ACTs (DHA-PQ, AL, AS-AQ and Artesunate-Mefloquine) shown to be safe and effective in pregnant women in sub-Saharan Africa including Burkina Faso as reported by the PREGACT Study group". [3] [4] [5] [6] [7] [8]

2. One of the best way to evaluate these three drugs could be through a randomized controlled trial, showing the gain in the efficacy with new ACT compared to existing ones. Is pyronaridine-artesunate already in use in Burkina Faso?

Response: To evaluate the efficacy and safety of ACTs compared to existing ones, we do agree that the randomized controlled trial is the best design. However, this study does not intend to evaluate the efficacy of ACTs. This study is an implementation study aiming to assessing the feasibility, acceptability and costs of three ACTs as first-line for uncomplicated malaria case management. Pyronaridine-artesunate has been registered and use in Burkina Faso for the management of uncomplicated malaria case. It has not yet been introduced in Malaria National Control Program guidelines as a recommended first line treatment but it is prescribed in private sector.

3. I would have suggested that, rather than using a quasi-experimental study over 22 months, why not using an experimental study with ASPY as a new combination, and make use of the WHO guideline?

[3] Sagara I, Beavogui AH, Zongo I, *et al*. Safety and efficacy of re-treatments with pyronaridine-artesunate in African patients with malaria: a substudy of the WANECAM randomised trial. Lancet Infect Dis. 2016 Feb;16(2):189-98. doi: 10.1016/S1473-3099(15)00318-7. Epub 2015 Oct 23.

[4] West African Network for Clinical Trials of Antimalarial Drugs (WANECAM). Pyronaridine-artesunate or dihydroartemisinin-piperaquine versus current first-line therapies for repeated treatment of uncomplicated malaria: a randomised, multicentre, open-label, longitudinal, controlled, phase 3b/4 trial. Lancet. 2018 Apr 7;391(10128):1378-1390. doi: 10.1016/S0140-6736(18)30291-5. Epub 2018 Mar 29.

[5] Duparc S, Borghini-Fuhrer I, Craft CJ, *et al*. Safety and efficacy of pyronaridine-artesunate in uncomplicated acute malaria: an integrated analysis of individual patient data from six randomized clinical trials. Malar J. 2013 Feb 21; 12:70. doi: 10.1186/1475-2875-12-70.

[6] Adjei A, Narh-Bana S, Amu A, *et al.* Treatment outcomes in a safety observational study of dihydroartemisinin/piperaquine (Eurartesim(®)) in the treatment of uncomplicated malaria at public health facilities in four African countries. Malar J. 2016 Jan 27; 15: 43. doi: 10.1186/s12936-016-1099-7.

[7] Bassat Q, Mulenga M, Tinto H, *et al.* Dihydroartemisinin-piperaquine and artemether-lumefantrine for treating uncomplicated malaria in African children: a randomised, non-inferiority trial. PLoS One. 2009 Nov 17;4(11): e7871. doi: 10.1371/journal.pone.0007871.

[8] PREGACT Study Group, Pekyi D, Ampromfi AA *et al*. Four Artemisinin-Based Treatments in African Pregnant Women with Malaria. N Engl J Med. 2016 Mar 10 ;374(10):913-27. doi: 10.1056/NEJMoa1508606.

Response: As mentioned in the previous response, this is not a comparative clinical trial to assess the efficacy and the safety of the three ACTs we have. This study is an implementation research which aims to pilote the multiple first-line therapies for uncomplicated malaria and assessing its feasibility, acceptability and costs in a health district in Burkina Faso. We agree that for health programme evaluation, we can use several study designs in epidemiology with their strengths and limitations such as cluster randomized trial, quasi-experimental study with before and after design, here and elsewhere design… Here we opted for the before and after quasi-experimental design with regards to practical reasons including ethical issues and the resources available.

4. Study outcomes (line 219)

It is mentioned that study outcomes are reported on Table 1, but the first table is Table 2, this should be checked. Add a paragraph in how the study will be handle with Covid19 going on.

Response: We checked and it is rather the Supplementary table 1 titled "Outcomes to be measured during the monitoring and evaluation phase".

We do agree that the COVID19 pandemic is affecting some of our activities on ground and requires us to review our daily living behaviour. However, the time the protocol was developed and approved for the first time, the COVID-19 was not yet occurred. Moreover, this is an observational study and we do not claim to change any practice and behaviour at health facility level. We just ensure that the study implementation complies with Burkina Faso Ministry of health COVID-19 preventive measures and COVID-19 control guidelines.

5. How will the outcome listed be linked with the multi-treatment effectiveness?

Response: As emphasized above, we are not conducting a comparative clinical trial aimed at assessing the safety and effectiveness of the ACTs of interest for this pilot study. The primary focus on this project is not on how the drugs performed; rather how the health workforce is able to handle efficiently multiple ACTs. Besides that, we are also interested to assess the effect of this multi first line treatment strategy on the treatment seeking behaviour for febrile episode/malaria (using household survey before and after the deployment of the multiple first-line therapies), the effect of this strategy on the incidence of malaria at health facility level (using a linear regression model) and the effect of the study on mortality associated with febrile episodes/malaria using data collected before and after through a demographic surveillance system. More information could be found in the supplementary table 1.

6. The study was registered and the funding details provided; a Consort summary/ or a diagram regarding how the sample size will be obtained could have been better to summarize the sampling strategies.

Response: We aim to use mixed-methods (desk reviews, qualitative surveys and quantitative surveys) to assess the study outcomes. The sampling strategy of the qualitative surveys before and after the simultaneous deployment of three ACTs are summarised in the table 1. For the quantitative approach data will be collected both at community and health facility levels. The collection of data at health facility level and through the DSS will be exhaustive and the sample size for the household surveys (at community level) have been provided on the lines 225 – 236 in the initial manuscript submitted (lines 252 – 263 in the revised manuscript - marked copy).

7. My suggestions to improve the abstract is to add the current ACT treatment in Burkina Faso for malaria, and state whether they had been found non effective in any study. This statement will complete the main results from theoretical model.

Response: We have already mentioned the ACTs that will be used in this pilot study i.e. Artemether-Lumefantrine, Dihydroartemisinin-Piperaquine and Pyronaridine-Artesunate. The safety and efficacy of these ACTs have been demonstrated in clinical trials conducted in sub- Saharan Africa including Burkina Faso and the introduction section of the proposed manuscript has been revised accordingly. We would like in this study to test whether a simultaneous deployment of these three drugs as multiple first – line treatments is feasible and acceptable at primary health centres in a health district of Burkina Faso.

8. Regarding your analysis plan, I will suggest that you draft the plan before starting collecting the data as well the table shells and figures to go fast, not to wait before having the data base. I suggest that the authors make it clear whether they will use theoretical models on the data base to validate the background hypothesis, or not.

Response: We appreciate the suggestions and will work towards them; although we do not feel that analysis plan need to be in place before the start of the data collection. This will be developed in details alongside with the study conduct but firmly will be finalized before the data base lock and the actual analysis. However, a summary of the data analysis plan has been added in the revised protocol manuscript, marked copy (Lines 348 – 359).

9. There are several objectives listed but no timeline and it becomes difficult to assess whether they will fit in the proposed duration of the work (22 months). 22 months seems very long. The author would need to clarify this. They would need to add some expected results if any and the timeline.

Response: We confirm that the proposed duration of this study is 22 months including 6 months for the formative phase (Phase 1), 12 months for the simultaneous deployment of ACTs (Phase 2), and 4 months for the monitoring and evaluation phase (Phase 3).

All the objectives have been translated into study outcomes. We describe in the Supplementary table 1 how these outcomes will be assessed and the time-points for the assessment as well. For more information, kindly have a look on the Supplementary table 1.

Minor revisions are to be made by the authors, and I recommend the protocol to be accepted by the editors.

Comments: Once again, we would like to thank the reviewer for her contribution to improve this proposed paper. We went through again it, incorporate the revisions and correct typographical errors.

Reviewer: 4

Reviewer Name: Deus Ishengoma

Institution and Country: National Institute for Medical Research (NIMR), Tanzania

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

General comment: The proposed protocol addresses an important subject in malaria case management due to the current threat of artemisinin resistance and ACT treatment failure, even in Africa as recently reported in Rwanda. Despite presentation of clear outcomes, the study design and methods are not well presented. The paper will require a major review before it can meet the required standards for publication.

Specific comments: The following issues need to be clearly addressed.

Abstract:

Authors should briefly state what they will do to attain the goals of the study. The current version presents the objectives and outcomes but not the methodological details of the study.

Response: Thank you for notifying your concerns about the methodology of the study to be used to attain the goals of the study. However, we think we have clearly mentioned in the methods and analysis section of the abstract, that we will be conducting a quasi-experimental study through four overlapping phases: formative phase, MFT deployment phase, monitoring and evaluation phase and post-evaluation phase. In addition, we have given detailed information on the four phases in the body of the proposed manuscript. Moreover, we added in the Methods and analysis part of the abstract that we will be using a mixed-methods design (desk reviews, quantitative and qualitative methods) to collect required data needed to assess the study outcomes.

Introduction:

1. A thorough assessment and presentation of the current status and issues related to multiple first line ACTs or triple combination therapy should be presented. Recently, the subject has been well discussed and some papers published. These should reviewed and cited.

Response: We would kindly like to remind that our work aims at assessing a multiple first-line therapies strategy and is not focused on the triple combination therapy for uncomplicated malaria which is currently addressed by several studies as you mentioned. In addition, to cope with the threat of the emergence of artemisinin-based combination therapies, we mentioned in the introduction that in addition to the concept of multiple first-line therapies for uncomplicated malaria, other approaches exist such as research and development of new generations of antimalarials and the concept of triple combination therapies which is now subject to several completed and ongoing clinical trials in sub Saharan Africa. Moreover, the concept of multiple first-line therapies has been mainly addressed by theoretical, mathematical models. To go further and generate field data on this concept, some studies are emerging and at the time of submitting this manuscript, there was no publication related to this yet.

2. Authors presented country data of 2016 which is over 4years old. I would suggest to present more recent data to show the current status of malaria in Burkina Faso.

Response: The suggestion is well taken. The data have been updated in the revised version of the manuscript.

Methods:

1. The study site is reported to be under DSS since 2007 but authors decided to present the data of 2016. Is the area still under DSS? If yes, why not incorporate the most recent data?

Response: We confirm that the study area is under a demographic surveillance system (DSS)[9]. However, this DSS was not focused on malaria related morbidity all year round, which is the disease of interest in this study. It was looking at mainly the movement of the population (immigration, emigration), some indicators of reproductive health, the causes of mortalities using verbal autopsies.

2. On lines 139 – 141, authors cite WHO guidelines for parasitological confirmation of malaria before treatment. However, it is not stated if the same guidelines have been adopted and used in Burkina Faso.

[9] Séni Kouanda, Aristide Bado, Maurice Yaméogo, et al. The Kaya HDSS, Burkina Faso: a platform for epidemiological studies and health programme evaluation. Int J Epidemiol . 2013 Jun;42(3): 741-9.doi: 10.1093/ije/dyt076.

Response: We could confirm that on lines 139 – 141 in the initial manuscript submitted, we stated that the WHO guidelines for parasitological confirmation of malaria before treatment are being used in Burkina Faso.

3. Authors stated that three ACTs (amodiaquine-artesunate, artemether-lumefantrine and dihydroartemisinin-piperaquine) are used in Burkina Faso as first line antimalarials (Lines 141-144). If this is correct, it means the country is already using multiple first line ACTs. Then why do they want to conduct this study while three ACTs are already in use?

Response: We confirm that three ACTs (amodiaquine-artesunate, artemether-lumefantrine and dihydroartemisinin-piperaquine) are used in Burkina Faso as first line antimalarials. However, this does not meet the real concept and the philosophy of multiple first line ACTs treatment strategy as described in the discussion section of this manuscript.[10,11] Indeed, we are assessing in this study since the critical element of segmentation of the population (who gets which drugs) is missing in the current treatment guidelines.

4. The study design is not well justified. What were the reasons for choosing this and not other types of study designs? How were the different drugs assigned to the different groups of the population and why? What are the questions to be addressed?

Response: First of all, we believed that we have extensively mentioned the study hypothesis both in the introduction of the abstract (Lines 32 – 34 in the initial manuscript submitted) and in the last sentence of the introduction of the article's body (Lines 115 – 116 in the initial manuscript submitted). We do agree that we did not mention the rationale of the population segmentation and of the drugs assignment to these segments as well. We have elaborated on this in the discussion section of the revised manuscript, marked copy (Lines 444 – 463). Moreover, we did not justify the study design because we assume that this proposed manuscript is not about the methodological aspects of study design. Several papers already have described the advantages and the limits for example of quasi-experimental study design versus cluster randomized trials in assessing health programmes and policies.

5. What are the inclusion and exclusion criteria for patients to be included in each treatment arm?

Response: We did not describe any formal inclusion and non-inclusion criteria in this manuscript. Indeed, this is an observational study and does not aim to change routine practices of health workers. However, these items are included in the training manuals of health workers as reminders. We have

[10] Boni MF, Smith DL, Laxminarayan R. Benefits of using multiple first-line therapies against malaria. Proc Natl Acad Sci USA. 16 sept 2008;105(37) :14216- 21.
[11] Boni MF, White NJ, Baird JK. The Community As the Patient in Malaria-Endemic Areas: Preempting Drug Resistance with Multiple First-Line Therapies. PLoS Med. mars 2016;13(3):e1001984.

added these elements in the revised version of the manuscript, marked copy, as follows (Line 183 – 191):

- For Pyronaridine-Artesunate in children under-five:
    - Inclusion criteria: age less than five years of age and weight equal and more than 5 kilogrammes,
    - Non-inclusion criteria: Know hypersensitivity to the drug.
- For Dihydroartemisinin-Piperaquine:
    - Inclusion criteria: age equal and more than five years,
    - Non-inclusion criteria: Know hypersensitivity to the drug.
- For Artemether-Lumefantrine:
    - Inclusion criteria: Pregnant women,
    - Non-inclusion criteria: first trimester of pregnancy and known hypersensitivity to this drug.

6. ACTs are not recommended for the treatment of malaria in the first trimester but the study proposes to use artemether-lumefantrine in pregnant women without stating if those in the first trimester will be excluded from the study. This needs to be stated and the type of antimalarials to be prescribed to pregnant women in the first trimester should also be mentioned.

Response: The comment has been addressed above by stating the inclusion and non-inclusion criteria for the three study ACTs.

7. The study proposes to assess and determine the feasibility, acceptability and costs of triple first line ACTs but the data collection methods does not clearly show how the feasibility and acceptability will be assessed. Clarity of the type of data and how such data will be collected to determine feasibility and acceptability should be stated in the methods.

Response: The feasibility, acceptability and costs are study outcomes. As mentioned on the lines 219 – 222 of the initial manuscript submitted. The details requested are provided in the Supplementary table1. Please, refer to outcomes 1, 2, 3 and 6 of the Supplementary table 1.

8. Authors should state the reasons for including different target populations in the study (such as households) and the type of information to be collected and the purpose or use of such data.

Response: The question is not clear to us. However, we would like to remind that the total population in the study area has been stratified into three (three target populations according to the different ACTs that will be made available at health facility level in the study area for uncomplicated malaria case management). The data collection at the community level are specific to these three strata and will enable us to assess some study outcomes. Kindly, refer to the Supplementary table 1 for the

study outcomes, indicators, methods of assessment, time point for assessment and target population for data collection.

9. Since the study population is under DSS, it is not clear of what extra information will be collected from households apart from that which is collected routinely in the DSS. The reasons for collecting such information should also be stated.

Response: In the framework of this study, the DSS will be used as a platform to the assess the effect of the simultaneous deployment of three ACTs on the malaria related mortality. The DSS allows the collection of this information on the entire study population. Household surveys will be performed in a sample study population where more detailed information such as the treatment seeking behavior for febrile episode/malaria, the episode treatment costing data… which could not be captured by the DSS at individual level. More details are given in the Supplementary table 1.

10. A draft data analysis plan should be included in the protocol. Why should the plan be written later?

Response: As you may have seen in the proposed manuscript, we have already addressed the qualitative data management and analysis plan. Moreover, regarding the number of study outcomes and the words limit required for the protocol manuscript in the author's instructions, it is difficult to go through quantitative data analysis in details. However, the different approaches that will be used in the analysis of quantitative data have been included in the revised version of the manuscript as well, as follows (Line 348 – 359 in the revised manuscript, marked copy):

"Basic descriptive univariate and bivariate analysis will be undertaken to describe socio-demographic and economic characteristics of the study populations, communities' knowledge, attitudes and practices regarding febrile episodes/malaria and access to effective malaria case management including diagnostic and treatment before and during the implementation of this study. Appropriate statistics including proportions, means, medians, interquartile ranges, standard deviations and confidence intervals will be computed. The effect of the MFT on treatment seeking behavior for febrile episode/ malaria and on the malaria incidence will be assessed using multivariate analysis including logistic regression and the approach of interrupted time series analysis respectively. The effect of the MFT on febrile episode/malaria related mortality will be assessed using the mortality rate ratios derived from data collected one calendar year before and one calendar year along the implementation of the study."

Discussion:
I would suggest the discussion to be focused on the research questions and how they will be addressed. Potential limitations should also be stated.
Response: The way the research question will be addressed has already been described in the

“Methods and analysis” section of this protocol manuscript. However, the discussion section of the manuscript has been revised as follows (Line 423 – 470 in the revised manuscript, marked copy):
“The MFT programme has not yet been implemented in a structured way in sub-Saharan Africa. This study will be among the first to generate evidence of the feasibility, acceptability and cost of MFT strategy.

The MFT is one of the potential strategy that could effectively mitigate the enormous threat in the fight against malaria which is the emergence and spread of artemisinin resistance. Indeed, the loss of artemisinin effectiveness would likely result in the loss of all ACTs. Therefore, there is urgent need to identify and to implement in sub-Saharan Africa a better way to optimise the use of these ACTs that could provide a much higher long-term barrier to the emergence and/or the spread of resistance and thus protecting them. Theoretical models showed that the simultaneous deployment of MFT for uncomplicated malaria is a promising strategy to extend the useful therapeutic life of the current ACTs by reducing drug pressure and slowing the spread of resistance without putting lives at risk. The development of feasible strategies for implementing MFT is therefore recommended. (17,18) Treating half of the population with one ACT and the other half with a different ACT would reduce the fitness of resistant parasites approximately as well as treating half as many patients. (19) Therefore, there is an advantage in deploying two or more ACTs. There are several scenarios for implementing MFT strategy depending on the target: i) the partition of the ACTs market by segments of the same population: pediatrics patients, pregnant women, adult’s patients, ii) the distribution of one ACT for home-based care and use a different ACT in the clinic, iii) the mosaic distribution of ACTs i.e. an alternating distribution of different ACTs in the same population over a given period of time… (20)

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

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

VERSION 2 – REVIEW

REVIEWER	Dr Aung Pyae Phyo Myanar Oxford Clinical Research Unit
REVIEW RETURNED	06-Oct-2020

GENERAL COMMENTS	The authors have addressed all the suggestions and comments from the reviewers. The revised manuscript could be approved.

REVIEWER	Solange Whegang Youdom University of Dschang, Department of Public Health, Faculty of medicine and pharmaceutical sciences, University of Dschang
REVIEW RETURNED	08-Dec-2020

GENERAL COMMENTS	The authors have revised deeply the protocol, and this version is better than the first one.