PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Seasonal Malaria Vaccination: protocol of a Phase III trial of seasonal vaccination with the RTS,S/AS01E vaccine, seasonal malaria chemoprevention and the combination of vaccination and chemoprevention
AUTHORS	Chandramohan, Daniel; Slater, Karen; Dicko, Alassane; Zongo, Issaka; Sagara, Issaka; Cairns, Matthew; Kuepfer, Irene; Diarra, Modibo; Tapily, Amadou; Issiaka, Djibrilla; Sanogo, Koualy; Mahamar, Almahamoudou; Sompougdou, Frederic; Yerbanga, Serge; Thera, Ismaila; Milligan, Paul; Tinto, Halidou; Ofori-Anyinam, Opokua; Ouedraogo, Jean-Bosco; Greenwood, B.

VERSION 1 – REVIEW

REVIEWER	Lorenz von Seidlein Mahidol-Oxford Tropical Medicine Research Unit (MORU) Faculty of Tropical Medicine Mahidol University 420/6 Rajvithi Road Bangkok 10400 Thailand
REVIEW RETURNED	27-Nov-2019

GENERAL COMMENTS	Review Seasonal Malaria Vaccination: protocol of a Phase III trial of seasonal vaccination with the RTS,S/AS01 vaccine, seasonal malaria chemoprevention and the combination of vaccination and chemoprevention There is considerable interest in the results of SMC/RTS,S project. The trial builds on an already successful malaria intervention, seasonal malaria chemoprophylaxis and adds a malaria vaccine which afford short term protection. Combining these two intervention holds promise to achieve nearly complete, individual protection. The protocol under review will be of considerable interest for copycats if the study turns out to be as successful and sceptics if the results disappoint. In any case the publication will be highly welcomed. The protocol is proficiently well written. The authors decided to provide an easily readable and comprehensible overview. Readers looking for detail such as tables with trial procedures, study visits, AE criteria etc which would help even better comprehension (and replication) will be disappointed. Perhaps the authors could consider providing a little bit more detail? The trial is well designed making using of the best available trial methodology , an RCT. The study arms and endpoints are well considered and pragmatic. The study only enrols young children. The reasons for this decision are probably related to regulatory

	requirements of the vaccine producer but this is not stated and could be explained? This age restriction is a major limitation in the study design as it will require follow-up trials to evaluate the potential benefits of the combined intervention SMC+RTS,S in older age groups irrespective of the impact of the current study. This limitation could perhaps be mentioned in the manuscript? The protocol includes sections on the assessment of antimalarial resistance. It may be helpful to state the underlying research question/null hypothesis? Are the investigators interested whether the addition of a vaccine can contain the spread of resistance and if so what are the sample size implications? Is the trial powered to explore such a question adequately? Minor suggestions: P7 L57 Pharmaceuticals not “Guilin Pharamceuticals” P10 L42 “The trial has 80% power to exclude, at the 2.5% significance level, a relative difference in the incidence of clinical episodes of malaria between the RTS,S/AS01 and SMC alone groups of 20% over the three-year study period, if the two interventions were equally effective.” I think there is a word missing? consider rephasing? P12 L35 “at the end each malaria transmission season.” Should read “at the end of each malaria transmission season.”

REVIEWER	Thomas Smith Swiss Tropical and Public Health Institute Basel Switzerland
REVIEW RETURNED	12-Dec-2019

GENERAL COMMENTS	This is a very professionally assembled trial protocol. I do not think it requires any revision.

REVIEWER	Laura Steinhardt US Centers for Disease Control and Prevention, USA
REVIEW RETURNED	04-Jan-2020

GENERAL COMMENTS	This is an important trial whose results will have great relevance to SMC-eligible countries in West Africa. The protocol manuscript is succinct and well organized, but there are some additional key details (e.g., how study staff will ensure that enrolled children do not receive routine SMC in the study area) that would present a more complete trial description; in addition, the sample size section is somewhat confusing. Overall, there are some grammatical and typographical errors throughout the manuscript, which could benefit from a thorough proofreading and careful editing. The tense also switches back and forth a bit between present and past tense, and it would be helpful to be consistent. Abstract: In the first sentence the authors say that SMC does not provide complete protection; can you please be more specific clarify against what? For example, clinical malaria, parasitemia, severe malaria? Second sentence: The RTS,S/AS01 malaria vaccine provides high level of protection against malaria shortly after vaccinations. Should this be either “a high level of protection or simply “high level protection”?

	Third sentence: This trial aims to determine whether seasonal vaccination with RTS,S/AS01 vaccine could an alternative" the word 'be' is missing. Methods and Analysis: SPAQ is abbreviated previously as SP+AQ. Please be consistent. For the modified ITT analysis, the authors note this is children who received the first dose of the vaccine. Is this the RTS,S vaccine in groups 1 and 3 or the rabies vaccine in group 2, or both? Please clarify. Strength of the study: instead of saying a strength is adequate sample size to test the study hypotheses (which all studies should have), perhaps you can highlight that there is adequate power, given the relatively large sample size, to test a non-inferiority hypothesis, which requires larger sample sizes. Introduction: 2nd paragraph: The follow sentence is a bit long and might be better as two or more separate sentences: "Many countries in the Sahel and sub-Sahel region of West Africa have now incorporated SMC into their national malaria control programme achieving high levels of coverage [10] but malaria continues to be a major cause of mortality and morbidity in these countries and additional control tools are needed." Methods Study setting: There is an extra ")" at the end of the second sentence. Third sentence: ITN needs to be spelled out on first reference. Extra space between artemether -lumefantrine. Interventions: "All treatments were given under observation." Please clarify whether only the first dose of SMC/placebo was given under observation or whether the second and third doses were also given under observation. Implementation of interventions: Is SMC implemented routinely in both study areas? If so, how will study staff ensure that children enrolled in the trial do not receive routinely implemented SMC? Study outcomes: Under study outcomes, the "m" at the end of falciparum needs to be italicized. mm Sample size: Superiority: This section is a little confusing. With a superiority trial, it's typical to mention the assumed efficacy/proportion/rate/etc. in each arm, or in one arm along with the absolute or relative difference the study is powered for. It is unclear what the 30% and 25% efficacy in this paragraph refer to: does the 30% refer to the 30% efficacy that SMC+RTS,S would have over either intervention alone? Please clarify. Follow-up and measurement of outcomes Since the primary outcome of clinical malaria will be detected by passive surveillance, can the authors provide more details on the

	health services available and care-seeking patterns in the study communities? For example, what proportion of malaria cases are estimated to be seen in the study clinics? Will there be incentives (e.g., transportation reimbursement) for caregivers to bring their children there when ill? Laboratory methods In the 'Detection of polymorphisms in the csp gene' section, the authors might want to remind readers that this is to look at the "sieve effect" or RTS,S on malaria parasites. Data management Do electronic CRFs apply to study health centers and community health workers diagnosing malaria? Thus, all relevant health centers and CHWs will collect data for enrolled children on tablets or similar? If not, how will data management work for capture of the primary endpoint? Analysis plan You state twice that ATP analyses will be done. Trial management The left-hand quotation mark before negligent harm needs fixing. FUNDING The first sentence has a repeated fragment ("The trial is being funded by the UK Joint Global Health Trials"); please delete.

REVIEWER	Jeremy Keenan UCSF USA
REVIEW RETURNED	04-Jan-2020

GENERAL COMMENTS	A well-written protocol. A few comments below. A general comment: please check the SPIRIT statement to make sure the protocol is complete. P3, line 24: it might be easier to understand this on first read if the groups were named in some way (eg: "Children in the vaccine group received…children in the SMC group received…children in the combined vaccine-SMC group received…" P3, line 36: a random subset of children? P3, line 46: provide full name of London School P4, line 34: this sentence is confusing to me; it implies that children are visited 4 times but drug given only 3 times. I don't think this is what is meant though? P6, line 26: I think this is the first reference to ITNs? If so please give the words before abbreviation P6, line 31: 1068 per 1000: what is the unit? From the reference appears to be person-years. I am not sure what is technically correct phrasing here but I'll just mention that at first read it confused me because it suggested greater than 100% of kids had an episode. I presume it means that kids were allowed to have more than 1 event and were not right-censored after having an

	event (I guess normally when I think of incidence I think of disease as being a saturating event and that a person cannot contribute multiple events, though this may not be correct!) (Could it be instead said that children experienced a mean of XX parasite-confirmed malaria episodes over the transmission season?) P6, line 47: presumably the inclusion criteria is by self-report? Was the carte de sante checked to confirm the age or was this caregiver-report? Perhaps just mention that all of this was self-report (which would clarify for example that no hospital/clinic records were checked for HIV or allergies etc.) P7, line 22: normally more information would be given about randomization (eg method of sequence generation, any restriction/stratification, allocation concealment mechanism, implementation of sequence). Please see the SPIRIT statement. P9, line 40: please define CSP P10, line 24: the lower limit of confidence of what? Of the treatment efficacy? P10: I had a hard time following the sample size calculations. The text seems unnecessary complicated and I wouldn't really know where to start with trying to replicate this. P12, line 5: "randomly selected" P14, line 21: what is the timing of enrollment, randomization, and interventions? Perhaps a schematic diagram giving the participant timeline would be helpful (as suggested in SPIRIT statement) P14, line 21: Perhaps state here "modified intention to treat." Also perhaps give a little rationale for this. I am not sure the modified intention-to-treat is clear to me, because the timing is not clear to me. When was randomization performed? If the first vaccination dose is required in order to be included in the analysis, why was the randomization not done immediately before the first vaccine dose? (Why give participants the chance to become lost to follow-up between randomization and vaccination?) Also, will a secondary analysis be performed that gives the true intention-to-treat analysis? P16, line 27: first part seems to be redundant

REVIEWER	Kevin Marsh University of Oxford
REVIEW RETURNED	09-Jan-2020

GENERAL COMMENTS	This is an extremely important trial. The protocol comprehensive and clearly written.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Lorenz von Seidlein

Institution and Country:
Mahidol-Oxford Tropical Medicine Research Unit (MORU)
Faculty of Tropical Medicine
Mahidol University
420/6 Rajvithi Road
Bangkok 10400
Thailand
Please state any competing interests or state 'None declared': none to delare

Please leave your comments for the authors below
Review Seasonal Malaria Vaccination: protocol of a Phase III trial of seasonal vaccination with the RTS,S/AS01 vaccine, seasonal malaria chemoprevention and the combination of vaccination and chemoprevention

There is considerable interest in the results of SMC/RTS,S project. The trial builds on an already successful malaria intervention, seasonal malaria chemoprophylaxis and adds a malaria vaccine which afford short term protection. Combining these two intervention holds promise to achieve nearly complete, individual protection. The protocol under review will be of considerable interest for copycats if the study turns out to be as successful and sceptics if the results disappoint. In any case the publication will be highly welcomed.
The protocol is proficiently well written. The authors decided to provide an easily readable and comprehensible overview. Readers looking for detail such as tables with trial procedures, study visits, AE criteria etc which would help even better comprehension (and replication) will be disappointed. Perhaps the authors could consider providing a little bit more detail?

We could not expand these section due to the word limit.

The trial is well designed making using of the best available trial methodology , an RCT. The study arms and endpoints are well considered and pragmatic. The study only enrols young children. The reasons for this decision are probably related to regulatory requirements of the vaccine producer but this is not stated and could be explained? This age restriction is a major limitation in the study design as it will require follow-up trials to evaluate the potential benefits of the combined intervention SMC+RTS,S in older age groups irrespective of the impact of the current study. This limitation could perhaps be mentioned in the manuscript?

The trial is restricted to <5 year old children because SMC is recommended to this age group although in few setting SMC is given to children up to 10 years of age. Currently available evidence suggests that the three priming doses of RTSS vaccine works better in the 5 to 17 month old children. Thus including older children within this study is not possible. To evaluate the role of RTSS vaccine in >5 year old children a different study design is needed. First we need to know the safety of >2 annual booster doses of RTSS vaccine. We plan to evaluate the safety and efficacy booster doses 4 and 5 as an extension of this study if funding could be secured.

The protocol includes sections on the assessment of antimalarial resistance. It may be helpful to state the underlying research question/null hypothesis? Are the investigators interested whether the addition of a vaccine can contain the spread of resistance and if so what are the sample size implications? Is the trial powered to explore such a question adequately?

The assessment of the antimalarial resistance is to understand the efficacy of SMC and the vaccine in the present level of resistance to SP in the study area. We did not hypothesise an effect of the RTSS vaccine on drug resistance and therefore we did not do a formal sample size calculation for the assessment of SP resistance.

Minor suggestions:
P7 L57 Pharmaceuticals not "Guilin Pharamceuticals" *done*
P10 L42 "The trial has 80% power to exclude, at the 2.5% significance level, a relative difference in the incidence of clinical episodes of malaria between the RTS,S/AS01 and SMC alone groups of 20%

over the three-year study period, if the two interventions were equally effective." I think there is a word missing? consider rephasing?

We have rephrased this sentence

P12 L35 "at the end each malaria transmission season." Should read "at the end of each malaria transmission season." *done*

Reviewer: 2

Reviewer Name: Thomas Smith
Institution and Country:
Swiss Tropical and Public Health Institute
Basel
Switzerland
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
This is a very professionally assembled trial protocol. I do not think it requires any revision.

Reviewer: 3

Reviewer Name: Laura Steinhardt
Institution and Country: US Centers for Disease Control and Prevention, USA
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
This is an important trial whose results will have great relevance to SMC-eligible countries in West Africa. The protocol manuscript is succinct and well organized, but there are some additional key details (e.g., how study staff will ensure that enrolled children do not receive routine SMC in the study area) that would present a more complete trial description;

We have added the following sentence: a member of the study team went with the team that administered SMC to prevent the risk of study children receiving SMC from the routine delivery system.

in addition, the sample size section is somewhat confusing. Overall, there are some grammatical and typographical errors throughout the manuscript, which could benefit from a thorough proofreading and careful editing. The tense also switches back and forth a bit between present and past tense, and it would be helpful to be consistent.

We have proof read and corrected the typos. The mixing of present and past tense is unavoidable because the had already started and is still on going.

Abstract:
In the first sentence the authors say that SMC does not provide complete protection; can you please be more specific clarify against what? For example, clinical malaria, parasitemia, severe malaria?
Specified

Second sentence: The RTS,S/AS01 malaria vaccine provides high level of protection against malaria shortly after vaccinations. Should this be either "a high level of protection or simply "high level protection"?
done
Third sentence: This trial aims to determine whether seasonal vaccination with RTS,S/AS01 vaccine could an alternative" the word 'be' is missing.

done
Methods and Analysis: SPAQ is abbreviated previously as SP+AQ. Please be consistent.
Due to word limits the + sign was not included. Now we have added the + sign between SP and AQ
For the modified ITT analysis, the authors note this is children who received the first dose of the vaccine. Is this the RTS,S vaccine in groups 1 and 3 or the rabies vaccine in group 2, or both? Please clarify.
specified: malaria
Strength of the study: instead of saying a strength is adequate sample size to test the study hypotheses (which all studies should have), perhaps you can highlight that there is adequate power, given the relatively large sample size, to test a non-inferiority hypothesis, which requires larger sample sizes.
done
Introduction:
2nd paragraph: The follow sentence is a bit long and might be better as two or more separate sentences: "Many countries in the Sahel and sub-Sahel region of West Africa have now incorporated SMC into their national malaria control programme achieving high levels of coverage [10] but malaria continues to be a major cause of mortality and morbidity in these countries and additional control tools are needed."

We think this sentence is not too complex.
Methods
Study setting:
There is an extra ")" at the end of the second sentence. *corrected*
Third sentence: ITN needs to be spelled out on first reference. *done*
Extra space between artemether -lumefantrine. *done*

Interventions:
"All treatments were given under observation." Please clarify whether only the first dose of SMC/placebo was given under observation or whether the second and third doses were also given under observation.
clarified
Implementation of interventions:
Is SMC implemented routinely in both study areas? If so, how will study staff ensure that children enrolled in the trial do not receive routinely implemented SMC?
clarified
Study outcomes:
Under study outcomes, the "m" at the end of falciparum needs to be italicized. mm
corrected
Sample size:
Superiority: This section is a little confusing. With a superiority trial, it's typical to mention the assumed efficacy/proportion/rate/etc. in each arm, or in one arm along with the absolute or relative difference the study is powered for. It is unclear what the 30% and 25% efficacy in this paragraph refer to: does the 30% refer to the 30% efficacy that SMC+RTS,S would have over either intervention alone? Please clarify.

The study is powered to i) assess the statistical evidence against the null hypothesis of no difference between the combined group and either used alone, and ii) estimate the efficacy of the combined group with a relatively high degree of precision. This latter aspect is important because it is necessary to show that adding RTS,S/AS01 to SMC has clinically significant benefit. We have modified the text to explain this point.

Follow-up and measurement of outcomes
Since the primary outcome of clinical malaria will be detected by passive surveillance, can the authors provide more details on the health services available and care-seeking patterns in the study communities? For example, what proportion of malaria cases are estimated to be seen in the study clinics? Will there be incentives (e.g., transportation reimbursement) for caregivers to bring their children there when ill?

All treatment was free for study children. There are no private health care providers other than the

MoH clinics in the study area. Thus we assume most of the cases that needed treatment were seen by our CHWs or health centres.

Laboratory methods
In the 'Detection of polymorphisms in the csp gene' section, the authors might want to remind readers that this is to look at the "sieve effect" or RTS,S on malaria parasites.
We have clarified that is to look for the selection effect of RTS,S vaccine on malaria parasites

Data management
Do electronic CRFs apply to study health centers and community health workers diagnosing malaria? Thus, all relevant health centers and CHWs will collect data for enrolled children on tablets or similar? If not, how will data management work for capture of the primary endpoint?

All study health centres and hospitals had Tablet PCs loaded with electronic CRFs. The community health workers referred all suspected malaria cases to the study health facilities. The CHWs did not collect data on morbidity. This is not clarified in the protocol.

Analysis plan
You state twice that ATP analyses will be done. *corrected*

Trial management
The left-hand quotation mark before negligent harm needs fixing. *corrected*
FUNDING
The first sentence has a repeated fragment ("The trial is being funded by the UK Joint Global Health Trials"); please delete. *done*

Reviewer: 4

Reviewer Name: Jeremy Keenan
Institution and Country:
UCSF
USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
A well-written protocol. A few comments below.

A general comment: please check the SPIRIT statement to make sure the protocol is complete.

P3, line 24: it might be easier to understand this on first read if the groups were named in some way (eg: "Children in the vaccine group received…children in the SMC group received…children in the combined vaccine-SMC group received…"

Due to word count restriction it not possible to do this. We believe the description of the groups is understandable as it is described now.

P3, line 36: a random subset of children? *Yes. It is specified as randomly selected subset of children*

P3, line 46: provide full name of London School *done*

P4, line 34: this sentence is confusing to me; it implies that children are visited 4 times but drug given only 3 times. I don't think this is what is meant though? *Corrected*

P6, line 26: I think this is the first reference to ITNs? If so please give the words before abbreviation *done*

P6, line 31: 1068 per 1000: what is the unit? From the reference appears to be person-years. I am not

sure what is technically correct phrasing here but I'll just mention that at first read it confused me because it suggested greater than 100% of kids had an episode. I presume it means that kids were allowed to have more than 1 event and were not right-censored after having an event (I guess normally when I think of incidence I think of disease as being a saturating event and that a person cannot contribute multiple events, though this may not be correct!) (Could it be instead said that children experienced a mean of XX parasite-confirmed malaria episodes over the transmission season?)

The unit is now added. 1068 per 1000 child years at risk. As malaria is a short duration illness multiples episodes per child are possible. This is not the incidence of the first or the only malaria episode of malaria per child. It is the incidence of all episodes of malaria during the person-time at risk accrued during the study.

P6, line 47: presumably the inclusion criteria is by self-report? Was the carte de sante checked to confirm the age or was this caregiver-report? Perhaps just mention that all of this was self-report (which would clarify for example that no hospital/clinic records were checked for HIV or allergies etc.) *clarified as self-reported or obtained from health records*

P7, line 22: normally more information would be given about randomization (eg method of sequence generation, any restriction/stratification, allocation concealment mechanism, implementation of sequence). Please see the SPIRIT statement.
The process of concealment is added in this section

P9, line 40: please define CSP
done
P10, line 24: the lower limit of confidence of what? Of the treatment efficacy?
lower limit of protective efficacy is now clarified

P10: I had a hard time following the sample size calculations. The text seems unnecessary complicated and I wouldn't really know where to start with trying to replicate this.

This is a complex trial because there are two arms, and two types of comparisons: a superiority comparison of the combined group relative to either alone (to determine if both interventions are markedly superior to either SMC or RTS,S/AS01 alone) and a non-inferiority comparison of SMC and RTS,S/AS01 alone (to determine whether vaccination alone is comparable to SMC, which is the current standard of care). We have tried to simplify this section, but it is necessary to give a sufficient level of detail that this rationale is clear.

P12, line 5: "randomly selected*" It is correct*

P14, line 21: what is the timing of enrollment, randomization, and interventions? Perhaps a schematic diagram giving the participant timeline would be helpful (as suggested in SPIRIT statement)
A schematic diagram added.

P14, line 21: Perhaps state here "modified intention to treat." Also perhaps give a little rationale for this. I am not sure the modified intention-to-treat is clear to me, because the timing is not clear to me. When was randomization performed? If the first vaccination dose is required in order to be included in the analysis, why was the randomization not done immediately before the first vaccine dose? (Why give participants the chance to become lost to follow-up between randomization and vaccination?) Also, will a secondary analysis be performed that gives the true intention-to-treat analysis?

All children potentially eligible were enumerated at the census in 2017. Informed consent was obtained from the care givers of the children who were deemed to be eligible. All children for whom consent was obtained were randomised one month before the date of vaccination in order to print photo ID cards, and to print vaccine envelope labels. This was necessary to ensure that vaccination could be done quickly and accurately for all study children, as well as ensuring that capture of

morbidity episodes during the study were accurately recorded. Photo ID is particularly important for the capture of morbidity episodes in households in which more than one child was a participant. As there was a one month time lag between the randomisation and the vaccination, some children did not come for the vaccination and were never enrolled in the study. Therefore the "modified intention to treat" analysis includes only children who received the first dose of the vaccines. It is not possible to perform a 'true intention to treat' as suggested because some of the children who did not receive the first dose of vaccine left the study area, and thus there is no capture of their morbidity episodes.

P16, line 27: first part seems to be redundant
corrected

Reviewer: 5

Reviewer Name: Kevin Marsh
Institution and Country: University of Oxford
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
This is an extremely important trial. The protocol comprehensive and clearly written.

VERSION 2 – REVIEW

REVIEWER	Lorenz von Seidlein Mahidol-Oxford Tropical Medicine Research Unit (MORU) Faculty of Tropical Medicine Mahidol University 420/6 Rajvithi Road Bangkok 10400 Thailand
REVIEW RETURNED	19-Feb-2020

GENERAL COMMENTS	My queries have been adequately addressed.

REVIEWER	Laura Steinhardt Centers for Disease Control and Prevention, USA
REVIEW RETURNED	09-Mar-2020

GENERAL COMMENTS	Methods Randomisation Tablets should not be capitalized if in the middle of a sentence. It is a bit strange to call the person who randomized the child using the prepared randomization lists the "chief vaccine administrators" or "chief vaccinators" when in fact, they did not administer the vaccines. Is there a reason why the term study pharmacist or similar was not used? Figures 2 and 3 are missing from the revised version. Implementation of the interventions The following sentence could change 'person' to study staff: "Loading of syringes … to blind the person administering the vaccine was done by a study staff who also took no further part in the trial" In the added text in the second-to-last paragraph, the word member is misspelled. Also, was SMC introduced in the study area in both Mali and Burkina Faso in 2018? Please clarify.

	Study outcomes How is malaria infection (symptomatic or asymptomatic parasitemia) in (3) different from malaria parasitaemia (including gametocytaemia in (4)? Please clarify or use the same term. Follow-up and measurement of outcomes The tense in the added sentence is in the past tense, but the very similar sentence directly preceding is the present tense. I suggest changing to present tense for consistency. Analysis plan Since the authors state in the fourth paragraph that in general, primary analyses will be by modified ITT and ATIP analyses will also be undertaken, these statements are not needed at the end of the previous paragraph.

REVIEWER	Jeremy Keenan UCSF USA
REVIEW RETURNED	24-Apr-2020

GENERAL COMMENTS	Sample size calculation: I will leave this to the biostatisticians so no changes needed from my end, but it is still a little confusing to me. (Specifically for the superiority analysis of the combined intervention vs. SMC or vaccination alone: I'm not accustomed about discussing the lower bound of a 95% confidence interval for a superiority analysis but rather an "effect size.") Primary comparison: this is also best left to the biostatisticians but it is not clear to me what the primary analysis is. There are several main comparisons described in the sample size section (I think it is the following, although this is not so clear to me: [A] superiority 1: any difference between the 3 treatment groups, [B] superiority 2: combined vaccine/SMC group vs either vaccine or SMC used alone (apparently with an aggregated group formed from the vaccine-only group and SMC-only group, and not 2 separate pairwise comparisons, though this is not explicitly stated), [C] non-inferiority between vaccine-only group vs SMC-only group). The "Analysis plan" section is not quite clear about the total number of p-values/confidence intervals that will be considered as part of the "primary analysis." Did the DSMC allow the investigators a significance level of 0.05 for each of the comparisons? Or will they have to spend it in some way? Or will they designate one of these as the primary comparison and the others as secondary? In addition, were any interim analyses planned/conducted (and if so, how was the alpha spent)? Modified ITT: I would just point out that the term "modified intention to treat analysis" is really only defined in the abstract but not in the main text. This seems like such a pillar of the analysis of a clinical trial that it would warrant at least 1 sentence in the main body of text to (A) define what the authors mean by it, and (B) give a rationale for why they are doing this. The authors described their rationale in the response to reviewers but didn't add anything in the paper text.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Lorenz von Seidlein
Institution and Country:
Mahidol-Oxford Tropical Medicine Research Unit (MORU)
Faculty of Tropical Medicine
Mahidol University
420/6 Rajvithi Road
Bangkok 10400
Thailand
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
My queries have been adequately addressed.

Reviewer: 3

Reviewer Name: Laura Steinhardt
Institution and Country: Centers for Disease Control and Prevention, USA
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
Methods
Randomisation
Tablets should not be capitalized if in the middle of a sentence.

Done

It is a bit strange to call the person who randomized the child using the prepared randomization lists the "chief vaccine administrators" or "chief vaccinators" when in fact, they did not administer the vaccines. Is there a reason why the term study pharmacist or similar was not used?

We have now changed the term chief vaccinator to chief pharmacist

Figures 2 and 3 are missing from the revised version.

These figures have been added

Implementation of the interventions
The following sentence could change 'person' to study staff: "Loading of syringes … to blind the person administering the vaccine was done by a study staff who also took no further part in the trial"

We have changed the term "person" to study staff"

In the added text in the second-to-last paragraph, the word member is misspelled. Also, was SMC introduced in the study area in both Mali and Burkina Faso in 2018? Please clarify.

The typo of member is corrected. It is clarified that SMC was introduced in Mali and Burkina Faso study areas

Study outcomes
How is malaria infection (symptomatic or asymptomatic parasitemia) in (3) different from malaria parasitaemia (including gametocytaemia in (4)? Please clarify or use the same term.

Both outcome 3 and 4 refer to measuring malaria parasitaemia (symptomatic and asymptomatic) but for outcome 3 parasitaemia is measured in a subset of children participating in the active surveillance component of the trial and for outcome 4 it is measured among the entire cohort at the end of transmission season. This is now clarified.

Follow-up and measurement of outcomes
The tense in the added sentence is in the past tense, but the very similar sentence directly preceding is the present tense. I suggest changing to present tense for consistency.

Done

Analysis plan
Since the authors state in the fourth paragraph that in general, primary analyses will be by modified ITT and ATIP analyses will also be undertaken, these statements are not needed at the end of the previous paragraph.

We agree and we have deleted the last sentence.

Reviewer: 4

Reviewer Name: Jeremy Keenan
Institution and Country:
UCSF
USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Sample size calculation: I will leave this to the biostatisticians so no changes needed from my end, but it is still a little confusing to me. (Specifically for the superiority analysis of the combined intervention vs. SMC or vaccination alone: I'm not accustomed about discussing the lower bound of a 95% confidence interval for a superiority analysis but rather an "effect size.")

The reviewer is correct in that the usual emphasis of a superiority comparison is the effect size, i.e. what treatment effect can be distinguished from no effect (and with what power and what confidence). However, for RTS,S to be a useful addition to SMC, the minimum additional efficacy would need to be substantially greater than 0, because it would not be worth adding vaccination to an SMC programme if the additional efficacy was small. For this reason, we focus the sample size description on the minimum efficacy that can be established.

We have added the following text to explain this:

'The study is powered to i) assess the statistical evidence against the null hypothesis of no difference between the combined group and either the SMC alone or RTS,S alone group, and ii) estimate the

efficacy of the combined group relative to the single intervention groups with a relatively high degree of precision. This latter aspect is important because if the combined intervention is to be used in practice, it is necessary to show that adding RTS,S/AS01 to SMC has a clinically significant benefit.

Primary comparison: this is also best left to the biostatisticians but it is not clear to me what the primary analysis is. There are several main comparisons described in the sample size section (I think it is the following, although this is not so clear to me: [A] superiority 1: any difference between the 3 treatment groups, [B] superiority 2: combined vaccine/SMC group vs either vaccine or SMC used alone (apparently with an aggregated group formed from the vaccine-only group and SMC-only group, and not 2 separate pairwise comparisons, though this is not explicitly stated), [C] non-inferiority between vaccine-only group vs SMC-only group). The "Analysis plan" section is not quite clear about the total number of p-values/confidence intervals that will be considered as part of the "primary analysis." Did the DSMC allow the investigators a significance level of 0.05 for each of the comparisons? Or will they have to spend it in some way? Or will they designate one of these as the primary comparison and the others as secondary? In addition, were any interim analyses planned/conducted (and if so, how was the alpha spent)?

This trial seeks to make two comparisons, of equal priority:

1. Whether seasonal vaccination with RTS,S/AS01 is non-inferior to four monthly courses of seasonal malaria chemoprevention (SMC) with sulphadoxine-pyrimethamine plus amodiaquine (SP+AQ) in preventing clinical malaria and other adverse outcomes.

2. Whether the combination of these two interventions (i.e. seasonal vaccination with RTS,S/AS01 and SMC with SP+AQ) is superior to RTS,S/AS01 alone or SMC alone in preventing clinical malaria and other adverse outcomes.

The reviewer is correct that the hypothesis testing procedure will follow the process outlined above (i.e. test first if there is any evidence of a difference between any of the treatment groups, before then performing pair-wise comparisons between the study arms). We have added the following text to explain this:

Hypothesis testing will follow the closed testing procedure, whereby there is initially a test of the null hypothesis that the incidence in the three groups is the same. If this is rejected at the 5% level, pairwise comparisons will be done also using a 5% significance level. Pairwise comparisons can be considered statistically significant only if the overall null hypothesis is rejected. This preserves the overall type I error rate at 5%. There were no formal interim analyses planned or conducted.

Modified ITT: I would just point out that the term "modified intention to treat analysis" is really only defined in the abstract but not in the main text. This seems like such a pillar of the analysis of a clinical trial that it would warrant at least 1 sentence in the main body of text to (A) define what the authors mean by it, and (B) give a rationale for why they are doing this. The authors described their rationale in the response to reviewers but didn't add anything in the paper text.

We have added the following sentence to clarify this issue:

'The primary analysis will be by modified intention to treat (mITT). The mITT population will include all children who were screened and who received the first dose of RTS,S/AS01 or control vaccine, irrespective of the number of doses of subsequent vaccines or SMC/SMC placebo received.'

VERSION 3 – REVIEW

REVIEWER	Jeremy Keenan UCSF USA
REVIEW RETURNED	28-May-2020

GENERAL COMMENTS	The authors have adequately addressed my concerns.