Technical consultation on determining non-inferiority of vector control products within an established class

Report of a virtual meeting, 31 August–2 September 2021
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ABBREVIATIONS

AI  active ingredient
FIC  first-in-class
GLP  good laboratory practice
ITN  insecticide-treated net
MFO  mixed function oxidase
PBO  piperonyl butoxide
PQT/VCP Prequalification Team for Vector Control Products
SIC  second-in-class
WHO  World Health Organization
1. OPENING REMARKS AND WELCOME

Opening the meeting, Dr Pedro Alonso, Director of the Global Malaria Programme of the World Health Organization (WHO), underscored the importance of determining the non-inferiority of vector control products and providing reassurance that second-in-class (SIC) products perform at least as well as the first-in-class (FIC) products originally recommended by WHO on the basis of epidemiological impact data. At its biannual meeting in April 2021, the Malaria Policy Advisory Group had highlighted the need for continued investigation into the potential value of non-inferiority studies.

Dr Alonso thanked all those serving as members and participants in the technical consultation for their support of WHO’s work.

1.1 Declarations of Interest

Prior to the meeting, Dr Jan Kolaczinski, Head of the Vector Control and Insecticide Resistance Unit of the Global Malaria Programme, assessed the Declarations of Interest submitted by members of the technical consultation. Based on the assessment, it was decided that none of the declarations constituted conflicts of interest in this context and that the experts concerned could participate in the meeting, subject to the public disclosure of their interests. The statement of Declarations of Interest (see Annex 1) was read out at the meeting.

1.2. Proceedings of the meeting

The technical consultation was convened virtually from 31 August to 2 September 2021. The agenda is included as Annex 2 and the list of participants as Annex 3. The open sessions of the meeting (days 1 and 2) were open to all meeting attendees. During the open sessions, results of the trials in question were presented and deliberated, as was secondary analysis based on these trial results. The secondary analysis was performed with the aim of responding to specific questions regarding the design and analysis of non-inferiority trials that would benefit from additional clarity and/or guidance from WHO. The final day of the meeting was a closed session, attended only by members and the WHO Secretariat.

2. BACKGROUND, OBJECTIVES AND EXPECTED OUTCOMES

The WHO vector control evaluation process transitioned from the WHO Pesticide Evaluation Scheme (WHOPES) to the Prequalification Team for Vector Control Products (PQT/VCP) in 2017. The evaluation process has continued to evolve, with the latest guidance published in late 2020 in the form of a document entitled Norms, standards and processes underpinning development of a WHO recommendation on vector control (1). This document outlines the two parallel pathways of the process. The first is designed to assess new, FIC interventions, and guide the generation of epidemiological impact evidence to enable such assessment. Such evidence informs the development of WHO recommendations, published in relevant disease guidelines. The second is designed to confirm the safety, quality and entomological efficacy of all vector control products, irrespective of whether they are FIC or SIC, with the aim of supporting WHO prequalification and an associated listing.
SIC interventions are not required to demonstrate epidemiological impact, and hence it remains unclear whether their impact in the field against the target disease(s) is at least equivalent to that of the FIC product that established the intervention class. The Malaria Policy Advisory Group therefore requested WHO to investigate whether assessments of non-inferiority of SIC products based on entomological end-points could provide some form of reassurance that impact under field conditions is likely to be as good as that of the product for which epidemiological impact data are available.

In late 2018, WHO published a notice of intent on the potential introduction of non-inferiority assessment as part of the vector control evaluation process and posted a draft protocol for public consultation (2). This study protocol was designed to generate data to inform an assessment of the potential value of non-inferiority trials as part of the vector control evaluation process. Based on public feedback, the study protocol was finalized in early 2019 and trials were conducted thereafter.

The goal of the current meeting was to evaluate the data generated by these two trials and to formulate a recommendation to WHO on the next steps regarding the use of non-inferiority assessments in the vector control evaluation process. The recommendations contained within this report were then to be presented to the Malaria Policy Advisory Group for their decision in October 2021. The objectives of the non-inferiority consultation were:

• to determine whether there is value in the use of non-inferiority assessments based on the datasets generated for pyrethroid-piperonyl butoxide (PBO) nets;
• to identify the advantages, disadvantages and potential challenges associated with the use of a non-inferiority study design and with the interpretation of data generated by such studies;
• where appropriate, to make specific suggestions on how the identified challenges could be addressed and on improvements to the current protocol/methods, as well as on research gaps; and
• to suggest ways in which non-inferiority data could be made public, if the method were to be adopted as standard practice.

Particular points for discussion that were identified prior to the meeting are listed below. A summary of the discussions around each of these points is presented in Section 4 of this report.

• In the case of pyrethroid-PBO nets, should mosquito mortality and/or mosquito blood-feeding inhibition be adopted as study end-points?
• Should these end-points be measured and evaluated using unwashed (new) nets, nets that have been washed 20 times (as per standard WHO requirements), or a combined measure using washed and unwashed nets?
• What type of statistics are best used to assess outcomes against the established non-inferiority margin: odds ratio, relative risk, absolute differences in risk, or a combination/sequence of these measures?
• What should be the criteria and/or process to pool data derived from different study sites?
3. PRESENTATIONS OF DATA ON PYRETHROID-PBO NETS

3.1. PQT/VCP review and analysis of the chemistry and manufacturing of pyrethroid-PBO nets

PQT/VCP provided an update on the status of the product review and some key findings from the analysis. The prequalified products reviewed included six insecticide-treated nets (ITNs) containing a pyrethroid co-formulated with the synergist PBO. These products were also included as part of the non-inferiority experimental hut trials. Interceptor G2 and Royal Guard were also included in the product review, along with relevant submissions currently under assessment (DuraNet Plus 2.0).

The product review was initiated in March 2020 with the purpose of complementing other ongoing efforts in the sector to investigate/research the performance of these specific ITNs. One example is the non-inferiority pilot.

The first phase of the PQT/VCP review of these products focused on the formulation chemistry and manufacturing processes used in the development of these vector control tools. An ITN is a complex product that combines a specific chemical formulation with a delivery mechanism (net), which is then subjected to harsh conditions and relatively uncontrolled processes from the time of manufacture through to distribution to communities and long-term use in the field. Formulation chemistry, manufacturing processes and information on the materials used in the product manufacture are key elements informing the performance of ITNs. Understanding the chemistry and manufacturing information provides the baseline data/information necessary to define the products and address any issues, such as perceived product failure, quality control issues, chemical and physical durability, etc. Historically, the WHO assessment of chemistry and manufacturing data and information has been limited to the evaluation of data to establish product specifications.

The product review involved an assessment of all relevant data submitted previously to WHO, e.g. WHO Pesticide Evaluation Scheme reports, and the additional data requested in the data call-in letter sent by PQT/VCP to manufacturers in March 2020.

The assessment focused on the description of the manufacturing process, identifying the steps that are critical to the product manufacture and assessing the details provided with respect to the chemical formulation (including active ingredient [AI] sources), masterbatch formulations and process of applying the chemical formulation to the net material. Details of the processes in place, data requested and assessment findings are available on the PQT/VCP website.1

The next step in the product review will be to link the information gleaned from this assessment to bioefficacy data requirements and combine these into data

1 https://extranet.who.int/pqweb/vector-control-products
requirements that provide a better understanding of the mechanisms involved and the product performance, both from a chemical and physical perspective.

This product review will inform a number of ongoing projects involving ITNs, namely the development of ITN guidelines, revised data requirements, testing methods, quality assurance/quality control, specification development, post-marketing surveillance, inspections, enhanced use of products in the field, clarity on appropriate transport and storage conditions, differentiation of product shelf-life and intended useful life, and the non-inferiority pilot.

3.2. Presentations of non-inferiority trial data from experimental hut trials

The assessment of pyrethroid-PBO nets in two experimental hut trials included a number of net products (the same products were evaluated in both studies). The nets were assessed in two sites: Mbe, Côte d’Ivoire and Ifakara, the United Republic of Tanzania. The study protocol guiding both studies was published in 2019 (Table 1) (3).

Table 1: Summary of the products, and their respective role within each of the two pilot studies evaluated in this technical consultation

<table>
<thead>
<tr>
<th>ROLE IN COMPARISON</th>
<th>NET NAME</th>
<th>MANUFACTURER</th>
<th>CHEMISTRY</th>
<th>TRIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated control</td>
<td></td>
<td></td>
<td>Côte d’Ivoire and United Republic of Tanzania</td>
<td></td>
</tr>
<tr>
<td>Pyrethroid control</td>
<td>Olyset®</td>
<td>Sumitomo</td>
<td>Permethrin</td>
<td>United Republic of Tanzania only</td>
</tr>
<tr>
<td>Pyrethroid PBO – A</td>
<td>Olyset® Plus</td>
<td>Sumitomo</td>
<td>Permethrin + PBO</td>
<td>Côte d’Ivoire and United Republic of Tanzania</td>
</tr>
<tr>
<td>Pyrethroid PBO – B</td>
<td>Tsara Boost®</td>
<td>Moon Netting</td>
<td>Deltamethrin + PBO</td>
<td>Côte d’Ivoire and United Republic of Tanzania</td>
</tr>
<tr>
<td>Pyrethroid PBO – C</td>
<td>PermaNet® 3.0</td>
<td>Vestergaard</td>
<td>Deltamethrin + PBO</td>
<td>Côte d’Ivoire and United Republic of Tanzania</td>
</tr>
<tr>
<td>Pyrethroid PBO – D</td>
<td>Veeralin®</td>
<td>VKA Polymers</td>
<td>Alphacypermethrin + PBO</td>
<td>Côte d’Ivoire and United Republic of Tanzania</td>
</tr>
</tbody>
</table>

Sarah Moore presented the non-inferiority trial conducted in the United Republic of Tanzania. Having outlined the study design, she detailed the specific approach taken to allow nets to regenerate after washing, how nets were stored, and the verification of net efficacy using the cone bioassay and tunnel test prior to the start of the study.

The experimental hut trials tested the non-inferiority of each candidate PBO net relative to the FIC, Olyset Plus. The six treatment arms were evaluated over 36 nights in 24 huts. Unwashed and washed nets of each arm were paired and allocated to two hut pairs, and volunteers were also paired. Two huts per net condition were used. Measures were taken throughout the study to reduce bias, which included concealment, randomization (random allocation then sequential rotation of
treatments), investigator bias (by using a predefined analysis plan), and study conduct (two huts per treatment arm, and study oversight by an independent quality assurance team). Data were entered weekly, with double data entry to ensure consistency.

The study investigated two primary end-points: the proportion of mosquitoes dead after 24 hours, and the proportion that were blood-fed. Secondary end-points investigated in the study included induced exophily, deterrence, personal protection, and blood-fed and alive (combined measure of feeding and mortality). A priori estimates of statistical power were met by obtaining more than 20 mosquitoes per hut per night. The dominant species was *Anopheles arabiensis*, which was the focus of these analyses, but *An. funestus* also contributed a small proportion. An analysis combining both species was later presented (see Section 4 of this report).

For the mortality end-point, all of the candidate PBO nets were shown to be non-inferior to Olyset Plus, for both the washed and unwashed time points. Odds ratios were in the direction of higher mortality for candidate nets. With regard to blood-feeding inhibition, all treated nets reduced blood-feeding rates to less than 6% compared to the rate for the untreated net of 20%. However, none of the candidate nets were shown to be non-inferior to Olyset Plus; all confidence intervals crossed the non-inferiority margin. The large confidence intervals resulted from the small number of blood-fed mosquitoes collected (itself a sign of efficacy), which made it more difficult to attain success. However, relative to the untreated net, an over 70% reduction in blood-feeding occurred in both the pyrethroid-only arm and the pyrethroid-PBO arms.

Overall, the trial demonstrated that it was possible to complete non-inferiority assessments of multiple nets in an experimental hut trial in 36 nights by using 24 experimental huts. Results of the trial showed evidence of non-inferiority of the candidate PBO nets to the FIC and enhanced mosquito mortality in all PBO arms, both unwashed and 20-times washed. Therefore, the results support the conclusion of public health value based on epidemiological data on PBO nets from randomized controlled trials.

**Raphael N’Guessan** presented the equivalent results from the non-inferiority trial conducted in Mbe, Côte d’Ivoire. The study site represents a large rice-growing area, which is productive throughout most of the year. The main malaria vector in the area is *An. coluzzii*. These populations are highly resistant to pyrethroids, DDT, organophosphates and carbamates, with intensity of resistance to deltamethrin showing 160-fold resistance.

The study investigated the same two primary end-points as the trial in the United Republic of Tanzania, yielding estimates of the proportion of mosquitoes dead after 24 hours and the proportion that were blood-fed. The study had 11 treatment arms, tested within a simple Latin square design, which required 11 weeks to perform one full rotation. Due to an observed low number of mosquitoes during the first rotation, the blinded data were sent to Imperial College for assessment of statistical power. With only approximately six mosquitoes per hut per night observed after the first rotation, it was determined that another full rotation was needed to have enough statistical power for the study. Following the completion of the two rotations, mean numbers of mosquitoes rose to just above 10. Blood-feeding inhibition levels by PBO nets varied from 46% to 74%. Resistance of *An. coluzzii* in the Mbe area impacted the overall power of all PBO-based nets to kill mosquitoes (<22% mortality).
Supplementary assays were completed, including cylinder tests of the constituent AIs in the ITNs with and without PBO, as well as the WHO cone bioassay before and after the hut trials. The cylinder assay confirmed that there was significant resistance to pyrethroids at the Mbe site, with PBO only restoring pyrethroid activity from 6–9% to 22–34% mortality of mosquitoes.

Similar to the study in the United Republic of Tanzania, results demonstrated that none of the candidate nets were shown to be non-inferior to Olyset Plus on the blood-feeding inhibition end-point. Only after 20 washes was Veeralin deemed non-inferior to the active comparator, Olyset Plus. By contrast, mosquito mortality induced by the unwashed candidate nets was comparable, and all were deemed non-inferior. For washed nets, only Veeralin was non-inferior; inconclusive results were obtained for the other candidate nets.

4. LESSONS LEARNED FROM NON-INFERIORITY TRIALS AND DISCUSSION ON THE POTENTIAL UTILITY OF THE METHOD

4.1. Overview of lessons learned from non-inferiority trials

Joseph Challenger presented a secondary analysis of the data obtained from the trials in both the United Republic of Tanzania and Côte d’Ivoire. Outcomes considered in these studies were whether mosquitoes were killed, blood fed, or deterred from hut (see Fig. 1). The analysis was conducted to gain a broader understanding of the variability in the observations, statistical power achieved, and overall implications for the adoption of non-inferiority studies for vector control interventions, using PBO nets as the first example. The analysis considered the following factors:

- Number of mosquitoes entering the huts over the course of the trial
- Trial duration (number of data points per arm)
- Magnitude of sources of variation present (between-hut variation)
- The non-inferiority margin selected.

Data related to unwashed nets, washed nets, and both estimates combined, were analysed for the four treatment arms. The analyses showed consistent trends (with minimal aberration) in the point estimates of the results for each net type, indicating that washed nets had a lower efficacy (expectedly). This finding was consistent across studies, despite the different numbers of mosquitoes collected.

A meta-analysis of 10 trials was performed to try to understand the sources of variation. Sources of variation included the huts and sleepers rotating between the huts each night. Additionally, non-specified variance (i.e. variation that cannot be accounted for by any of the variables in the model) was also considered. This source of variation was the greatest.
The study in the United Republic of Tanzania employed 24 huts to conduct four simultaneous 6x6 Latin squares. The study achieved 90% statistical power to be able to detect non-inferiority (should it exist), with a mean of more than 20 mosquitoes collected per hut per night. For the study in Côte d’Ivoire, the study required two rotations of the Latin square, given that there were fewer mosquitoes entering the huts in this study (<10 per hut per night). The second rotation enabled the study to sustain 89% power to detect non-inferiority.

Higher mortality was noted in the Tanzanian dataset than in the Ivorian dataset. This could be attributed to a different representation of species, different resistance profiles between the sites and/or differences in hut design. Combining the data from both sites, all candidate arms of the trials were deemed non-inferior with respect to mortality.

Overall, the study in Côte d’Ivoire saw higher blood-feeding than the one in the United Republic of Tanzania. When looking at blood-feeding inhibition as the end-point, combined data from the two sites showed that no candidate could be identified as being non-inferior to the active comparator. Indeed, due to Olyset Plus’s high efficacy in relation to blood-feeding inhibition, the active comparator generally had lower blood-feeding compared to all candidate nets.

It was observed that because of the wide confidence intervals for the odds ratios in relation to mortality and blood-feeding inhibition, some studies could have been underpowered to detect true differences. A simulation was conducted to illustrate how changing several variables (one/two rotations, non-inferiority margin from 0.6 to 0.8, mean number of mosquitoes ranging from five to 20 and variance in observational error) can cause the power to fluctuate from 0.14 to 1.0 (see Fig. 2). The simulation illustrates how minor changes to these variables will quickly result in a study dropping from having an acceptable level of statistical power, to having power below that required to generate statistically significant results.
It was emphasized that power assessment of an experimental hut trial can be repeated during the first few weeks of the trial in order to make an on-the-spot decision as to whether more time is needed to assess the efficacy of the treatment arms. Making the decision to prolong the trial while it is underway may reduce costs overall and simplify the analyses, compared to having to initiate another trial (starting over, rewashing nets, etc.) and needing to control for this as a variable in the final analysis of the intervention. Such an analysis can be performed effectively while the trial is still being conducted, without unblinding the trial.

**Figure 2: Simulation of resulting power estimates in experimental hut trials when multiple factors are allowed to vary, including the non-inferiority margin, variance in observational error, number of rotations, and mean number of mosquitoes captured per hut per night**

![Simulation of resulting power estimates](image)

Source: Joseph Challenger, Imperial College London.

*Numerical values for the power estimates will further depend on experiment-specific factors such as the trial design and the magnitude of mosquito mortality observed.*

Tom Churcher gave an overview of the potential implications of non-inferiority assessments and gave suggestions on how these should be considered, so as to stimulate discussion within the group. Discussion touched on how the implementation of non-inferiority assessment would impact changes in process, bearing in mind that the protocol of the two trials was indeed a provisional protocol. The two trials were intended to be the foundation for discussion, leading potentially to the refinement of the protocol for non-inferiority assessments, as no specific discussion on the requirement for adopting a non-inferiority approach as standard WHO practice took place during protocol development.
It was highlighted that over the last 30 years, observations of mortality in trials have decreased (4) likely as a result of increased prevalence of insecticide resistance in mosquito populations. By contrast, similar changes in blood-feeding inhibition have not been observed over this time; this observation is possibly impacted by the long-term practice of making artificial holes in the netting in order to assess mosquito feeding capacity. It therefore does not reflect the personal protection one receives from a new net and is unlikely to accurately reflect the durability of a net overall.

The question was then raised of which end-points should be used to measure the efficacy of nets. To illustrate the potential for variation in this measure, a comparison of the data from the two trials in question was presented. Both studies demonstrated data that were consistent in direction, but the magnitude of the reduced impact following 20 washes differed among nets.

Given the high bar set by Olyset Plus in terms of personal protection from blood-feeding, candidate SIC nets were challenged to demonstrate non-inferiority against the active comparator. It becomes difficult to certify the non-inferiority of an intervention against a high-performing FIC intervention when odds ratios are used, and small differences observed are indeed unlikely to have a significant epidemiological impact. Alternatively, one could employ the relative risk or absolute differences in risk, or even set a post-estimate threshold that cannot be exceeded to be deemed non-inferior. Programmatically, the personal protection offered by the candidate SIC nets was actually very good, and there would be little difference in terms of operational importance whether one is selected over another.

There was discussion of variation in study sites, in terms of East and West African geography and associated species composition and epidemiology, and how one should interpret the results of discordant trials in terms of net efficacy when it comes to making procurement decisions. Differences in species between sites could also influence results. Breaking down the data, one could consider species-specific effects that could explain site-specific variation, but, in doing so, one would also lose statistical power. The question was raised of whether trials should be repeated in the event of negative outcomes or whether an overall positive result could be identified following pooling, and how this might influence any potential requirements for repeating studies. Repeating studies while trying to reach the desired outcome could be viewed as cherry-picking results.

In preparing for the trial, obtaining the active comparator for assessment may not always be possible. The FIC intervention might be hard to source for reasons of availability or more likely competition, if the manufacturer is unwilling to see its product tested against other products. Alternative options for using SIC active comparators were offered, and the benefits and challenges of each option were noted. The major issue is that if one is free to choose the active comparator, it will be beneficial to always select the lowest performing comparator, thus making it easier to determine non-inferiority.

Two factors influencing the likelihood of determining non-inferiority were also raised. The first was related to the number of mosquitoes captured per hut per night, because smaller numbers increased the confidence intervals of the odds ratios, making it harder to clearly designate a candidate net as being non-inferior. Related to this point, the second issue raised was that of mosquito deterrence from huts. Where the presence of a net actually deters a mosquito from entering a hut, the nightly capture rate will be lower, making it more difficult to have high enough numbers to reduce the confidence intervals. This latter point warrants further investigation of how deterrence can be more effectively measured in future experimental hut trials.
With the necessity of having sufficient numbers of mosquitoes to reach statistical power requirements, it was suggested that a study be continued until a minimum threshold of mosquitoes has been reached. As presented above, interim calculations were indeed performed in the Côte d’Ivoire study while the data were still blinded, which allowed the duration of the study to be extended to increase the sample size. Such routine interim calculations could avoid issues of insufficient power in assessing non-inferiority.

4.2. Open discussion on the utility of non-inferiority trials to differentiate vector control products

The chair guided the meeting participants through a discussion on the multiple issues that had been raised in previous sessions, seeking viewpoints from all parties.

Study end-points

The discussion of end-points raised numerous views, some of them mixed. Several important points included the pertinence of two end-points for the vectorial capacity equation, in that, the higher mortality of vectors has a greater impact on $R_0$ than blood-feeding; therefore, mortality should be a priority. Given that the primary mode of action of PBO is to increase killing, the assessment of the non-inferiority of pyrethroid-PBO nets should not exclude this end-point. Practically, it is simpler to power studies to address a single end-point, bearing in mind that secondary end-points are not invisible and that these can have additional weight when procurers are selecting their products.

Alternative approaches suggested to the group included an "either/or" approach, in which a product could be deemed non-inferior to the active comparator in either blood-feeding inhibition or mortality. Further to this, it was suggested that, as pyrethroids affect blood-feeding inhibition, the mortality end-point should be compared to other PBO nets, whereas the impact on blood-feeding of a pyrethroid-PBO net should be compared to a pyrethroid-only net. Finally, it was also suggested that a combined measure of mortality and blood-feeding could be devised (weighted or otherwise), thereby allowing a single measure and easier calculations of sample size.

At the same time, the point was made that it is mosquito biting that has a direct relevant impact on public health because without biting, transmission cannot occur. It was also noted that adherence to net usage by the public is strengthened by the personal desire for protection against bites.

Active comparators: If the FIC is not available, what do we do?

When there is more than one net in an intervention class, it will be necessary to determine which net(s) can be used to determine non-inferiority moving forward. The risk is that if the active comparator changes each time, for each consecutive assessment, the bar changes (normally being lowered). Therefore, it is better to have the same comparator used across the board. However, the accessibility of the nets could be a challenge. All manufacturers are encouraged to make their nets available for testing, rather than obstructing the potential for more products to become available on the market, which is in the global interest. FIC nets clearly offer the ultimate comparator, as they are the nets that have demonstrated epidemiological evidence against the target disease. If this FIC net is not available, an SIC net that has epidemiological evidence associated with it should be the next best option. For example, PermaNet 3.0 also has epidemiological data associated with it, so it would be the next best option.
Using best in class nets is also an option in the case that an SIC net has actually outperformed the FIC. However, if the best in class was actually superior to the FIC, it would be (perhaps unfairly) hard for suppliers to demonstrate non-inferiority if they were unable to get hold of the FIC. Therefore, it was suggested that the most similar net to the FIC should be an option for the alternative.

**Pooling of data**

Discussion was held about when it is acceptable and practical to pool data in relation to species data, data related to washed and unwashed nets, and data from different trial sites.

**Species.** For species data, given the different compositions of species at sites, profiles of resistance and mechanisms, there was a push to avoid pooling data. Current recommendations are to test the dominant vector, but this may pose problems when molecular characterization is necessary and in places where there are numerous dominant vectors. Therefore, an overall estimate of efficacy by pooling species data also holds value.

**Sites.** For study site data, numerous participants shared the view that, given the differences between sites, one should always view the data from a trial by itself as a standalone result, before any consideration is given to pooling data. This is especially true when trials show opposing trends between sites. Alternatively, those in favour of pooling argued that pooling allows one to more easily generalize results as to the efficacy of the net. Discussion followed that any pooling of data could be performed in a formal meta-analysis, and weighted means were considered so that smaller trials would contribute appropriate weight.

Another point raised was on the issue of site selection, as it is also key that the site should have pre-exposure assay data available; the Côte d’Ivoire site had strong recent indications of mixed function oxidase (MFO)-driven resistance before the trial started – based on overexpressed CYP6P3. Considering such information in site selection could aid in the determination of efficacy.

**Washed and unwashed nets.** For washed and unwashed data, participants again felt that each measurement in and of itself provided valuable information and so should not be automatically combined, despite the increased power that this would provide for the trial. Nevertheless, considering the lifespan of a net, having an overall estimate of how it performs at the start and at the end of its life was deemed more representative of how it might perform in the field. The decision of whether to report pooled or individual data for the unwashed/washed nets will influence power calculations.

Prequalification Team data assessments currently use only the performance of nets following 20 washes, and so such consistency between requests for data should be considered.

**Odds ratios for non-inferiority criteria**

The issue of non-inferiority assessments using odds ratios was raised in light of the high benchmark for blood-feeding inhibition set by Olyset Plus, although this applies to any non-inferiority assessment in which the reference arm is very high or very low. When the standard set by the FIC arm is high (whether it be for mortality, blood-feeding or another end-point), the probability of the SIC candidate passing will be influenced; as such, use of the odds ratio may not be ideal. Alternative statistics
discussed by the group as being potentially acceptable were prevalence ratios or setting a standard cut-off that the SIC candidates must pass.

**Regeneration time of nets following washing**

The difference in regeneration time between nets was considered an important factor in planning an experimental hut trial using washed nets. The compositions of nets differ with respect to both the AIs and the chemistry. As such, it is important to ensure that one allows sufficient regeneration time to maximize the efficacy of the nets after each wash.

Blood-feeding and mortality estimates may also be altered because the migration of each chemical back to the surface of the netting may differ. It was also discussed whether the rate of regeneration within a net may change over time as a result of depleted reservoirs within the material; in effect, migration time could increase as the net ages (or if it is washed more).

Where adoption of any non-inferiority assessment occurs, the testing protocol should ensure that instructions are provided (perhaps this should be the responsibility of manufacturers) to ensure that the investigators testing the nets employ the correct regeneration time for each net. Applying a strict seven-day regeneration time for all nets means that it would take six months to one year to do a study; however, if there are no nets that take seven days to regenerate included in the study, there should be no need to require this seven-day regeneration time. This may encourage manufacturers to consider how to optimize the migration of chemicals back to the surface to reduce regeneration time.

**Usefulness of the process on non-inferiority**

Overall, it was deemed that non-inferiority assessments have value. End-users felt that it was a straightforward assessment using existing methods and a priori consideration of power estimates is valuable to ensure high-quality data. It was mentioned that the protocol would benefit from being adapted to ensure guidance on powering trials well. The weight of evidence for other end-points should also be considered.

Further to this point, guidance could be included in the protocol or more generally using an online platform (such as MTM), or regular training on appropriate statistics could be offered to make sure that all investigators are able to analyse the trials appropriately. This would also help build capacity at the sites. Otherwise, collaborations could be sought.

**Capacity-building**

Should there be a WHO requirement for all SIC nets to undergo non-inferiority assessment (and perhaps expanded to other intervention classes beyond nets), there would be a need to ensure that the infrastructure was adequate. General capacity-building at the level of hut construction and maintenance was discussed, with the recognition that more huts would enable larger trials (whether this means more arms to a trial, or fewer rotations with a smaller number of arms) and more rapid results. The added benefit of this is that shorter trials are also less subject to temporal fluctuations in mosquito density or species composition over a season.

Statistical support, whether it be in the form of supporting collaborations or online platforms, to support the automation of appropriate statistical approaches was
also discussed. Regular training or workshops could be developed and offered to investigators, designed with specific curriculum relevant to their trials.

5. CONCLUSIONS AND RECOMMENDATIONS IN THE CLOSED SESSION

The closed sessions of the meeting involved only the designated members of the technical consultation, exclusive of all industry observers and temporary advisers. The members reviewed and deliberated on the points from the previous days’ discussions and agreed on the following formal recommendations on the value of non-inferiority assessments for SIC products within an established intervention class.

5.1. Major recommendations

Value of non-inferiority studies

- Non-inferiority studies have value in determining whether SIC products should be covered by a WHO recommendation formulated for an FIC product. The approach should be adopted as a general procedure across vector control interventions, not limited to pyrethroid-PBO nets.

- To implement the approach routinely, however, the non-inferiority protocol will need updating to reflect the specific points outlined below

End-points

- Mortality is to be used as the primary end-point for pyrethroid-PBO nets and for other products whose primary entomological mode of action is the killing of mosquitoes. Mortality results should be used to make the ultimate decision regarding non-inferiority of a product and its inclusion under a WHO recommendation for an intervention.

- For this and other intervention classes with similar entomological modes of action, blood-feeding is to be included as a secondary end-point to assist in informing programmatic and procurement decisions. For the secondary end-point, there is no requirement for the use of a non-inferiority margin or for non-inferiority analysis. The investigators should report the percentage of blood-fed mosquitoes for each net, with a confidence interval and p-value. A comparison to a standard reference product (in this case a pyrethroid-only net) should also be presented. This information will enable the reader to interpret these results in the context of the non-inferiority results for the primary end-point.

- For intervention classes with other entomological modes of action, such as sterilization, other end-points should be used to inform a non-inferiority assessment. WHO should provide guidance to manufacturers/researchers on what end-points are relevant to evaluate the non-inferiority of products in other classes.

- For ITNs, unwashed and 20-times washed nets should be tested. The results of both should be reported, with the primary non-inferiority analysis performed on the combined results of both time points.

- The primary end-point should be calculated based on data for the dominant vector species (or species complex) only. A secondary analysis should be performed on data pooling all species.
**Number of trials**

- A minimum of two independent trials are needed, ideally from different geographical regions. Data from each trial should be analysed separately.

- To be classified as non-inferior, the candidate product must be deemed non-inferior in at least two trials. If results from one of the two initial trials are inconclusive or if one of the trials demonstrates inferiority, a third trial should be conducted to inform a final decision regarding the inclusion/exclusion of a product within an intervention class. If a candidate product does not demonstrate non-inferiority in two out of three trials it will be deemed to not meet the non-inferiority criterion compared to the FIC product and should not be considered as covered by a WHO recommendation for the applicable intervention class.

**Non-inferiority margin**

Analyses of non-inferiority for the primary end-point should be calculated using odds ratios of the proportion of mosquitoes killed. In the case of pyrethroid-PBO nets, the candidate net should be compared to the FIC net (or a suitable alternative [see below]), using a non-inferiority margin of 0.7 for the odds ratio, reported with the corresponding 95% confidence interval.

**Selection of active comparator**

- Primary option: the FIC product, if it can be sourced (e.g., Olyset Plus for evaluation of pyrethroid-PBO net products).

- Second-best option: any SIC product for which epidemiological evidence is available (e.g., PermaNet 3.0 for evaluation of pyrethroid-PBO net products).

- Third-best option: a product that has shown superiority to the FIC in the primary end-point. If superiority is shown by any SIC product, it would be acceptable as an active comparator

- Fourth-best option: In the event that no SIC product has shown superiority to the FIC product, the best performing product among the SIC products should serve as the comparator.

- The study report must provide a justification for why a specific comparator product was used in the trials.

**Statistics**

- To ensure valuable return on investment, statistics support will need to be sought for development of the detailed study protocol and for data analysis.

- Statistical analysis of the data must be done using a logistic regression model with fixed effects for the brand of net, hut, sleeper, night and number of washes.

- A priori power calculations are required.

- It is strongly recommended to conduct at least one blinded interim analysis to assess if the assumptions underlying the power calculations are verified. If the assumptions are not verified, the planned size of the study may need to be adjusted. A suitable point for an interim analysis would generally be after one full rotation of products and sleepers. Investigators planning to conduct an interim analysis should include reference to this in their study protocol.

- Simulations using mathematical modelling may be used to support study design.
• It is recommended that WHO develop a course on non-inferiority evaluation in the context of vector control evaluation. The course should be made available as an online resource to support investigators in the design and analysis of these types of trials.

• Lastly, WHO should promote training in appropriate statistics for the analysis of data from this type of experimental design.

**Non-inferiority and prequalification assessments**

• WHO should clearly define the process to be used for non-inferiority assessments and who within WHO will be responsible for overseeing it. Alignment/complementarity with the data requirements and data generation for the WHO prequalification process is needed.

5.2. Minor recommendations

**General**

The protocol will need to be adapted for interventions with different entomological modes of action (e.g. change in end-points used to determine non-inferiority).

**Registration of trials**

To avoid the cherry-picking of positive trial results, all trials should be registered in a registry prior to starting.

• **Proposal.** Tests can only be done at good laboratory practice (GLP)-accredited sites or, in the interim, performed according to GLP standards at sites undergoing certification. Sites are responsible for registering studies in their own registry in an attempt to avoid failure to report negative trial outcomes. Other mechanisms to provide such transparency should be explored, analogous to the requirement for registration of clinical trials.

• **Selection of test sites.** Sites should be appropriate for the question being asked. Site selection should be justified based on a baseline assessment of class-relevant parameters (e.g., P450 resistance mechanisms in the case of pyrethroid-PBO nets). These should be articulated in the registry a priori and in the report. For all vector control interventions, the mosquito species composition and its insecticide resistance profile are the minimum requirements to be reported; however, these details may need to be supplemented with class-specific background information, as indicated in the example above.

**Infrastructure and capacity-building**

Investment in infrastructure and training according to GLP is needed to expand site capacity in order to ensure that non-inferiority (and other) entomological studies are conducted on time and to a high standard.

• If the non-inferiority process is adopted, investment in more sites, more huts at existing sites and maintenance of sites will be necessary to support the process (not just for PBO assessments, but for other nets and other interventions as appropriate).

**Data availability and sharing**

• Data should be made available in sufficient detail to enable independent verification of the results reported.
• It is also recommended that WHO develop or expand an existing online platform to facilitate non-inferiority trial data entry and secondary analysis by third parties.

• WHO should investigate this in more detail (including potential legal issues).

**Regeneration time of nets between washes**

• Manufacturers need to generate this evidence as part of the data package for WHO evaluation of a vector control intervention and submit the results as part of that package.

• Regeneration time for each product should be determined at a GLP-accredited laboratory and provided as a standard for non-inferiority studies. Regeneration times already generated for the pyrethroid-PBO nets evaluated to inform the present deliberations should be used for future studies, where relevant.

• The washing interval should correspond to the regeneration time for the net in question, not a standardized seven days.

### 5.3. Research gaps

**Measurement of end-points**

• Understand how deterrence, currently measured based on the number of mosquitoes entering intervention experimental huts relative to untreated net control huts, should be measured and interpreted and how the phenomenon influences the assessment of ITNs’ effectiveness.

• Performance of pyrethroid-PBO nets in West Africa: Pyrethroid-PBO nets showed relatively poorer performance in the West African trial. The synergistic effect of PBO was also much lower in bioassays. The available evidence of the improved epidemiological effect of pyrethroid-PBO nets has so far been generated only in East Africa. There are concerns that these nets may have a different outcome in West Africa, considering the historically higher levels of pyrethroid resistance and poor synergistic effect of PBO in the region. A randomized controlled trial may need to be performed in West Africa to assess the impact of these nets in the region.

### 5.4. Final conclusions

Based on the above criteria, all of the pyrethroid-PBO net products evaluated in the two non-inferiority trials – namely PermaNet 3.0, Tsara Boost and Veeralin – are considered to have met the requirement of demonstrating non-inferiority to Olyset Plus.

It is recommended that WHO consider all of these products as part of the same intervention class and thus as covered by the conditional recommendation for pyrethroid-PBO nets published in the consolidated guidelines for malaria (5).²

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² See also the WHO guidelines for malaria on the online MAGICapp platform at [https://app.magicapp.org/#/guideline/5438](https://app.magicapp.org/#/guideline/5438).
6. REFERENCES


ANNEX 1. DECLARATIONS OF INTEREST

The Malaria Vector Control and Insecticide Resistance Unit of the Global Malaria Programme held a technical consultation, from 31 August to 2 September 2021, on assessing the value of determining non-inferiority of vector control products within an established class. The meeting was a follow-up to an Evidence Review Group on the same topic, held by WHO from 5 to 6 July 2018 at the request of the Malaria Policy Advisory Group. The detailed deliberations of the earlier meeting, including a study protocol to guide data collection to inform further discussion on non-inferiority determination in the area of vector control, can be consulted in the Evidence Review Group meeting report (1) and the data requirements and protocol document (2).

As part of the consultation conducted in 2018, WHO published a notice of intent (3) to introduce partners to the Organization’s exploratory work in this area and the potential for non-inferiority determination to be adopted as standard practice in the area of vector control evaluation.

The current meeting was convened as a follow-up to the work in 2018 to review non-inferiority datasets from two field studies on pyrethroid-PBO nets, and to formulate recommendations to WHO on whether and how to proceed. The recommendations formulated at the technical consultation will be presented to the Malaria Policy Advisory Group at its October 2021 meeting.

This technical consultation consisted of four categories of invitees, namely: (i) “members”, including the Chair, who formulated the recommendations to WHO and were each required to complete a Declaration of Interest and Confidentiality Undertaking form; (ii) participants, which in this case were the investigators who conducted the research studies or researchers who conducted additional analyses of these data; (iii) observers, such as industry partners and donors; and (iv) WHO staff. All invitees were able to attend the open sessions of the meeting, while only members and WHO staff were allowed to participate in the closed session.

Declarations of Interest

All members completed and submitted their DOI and Confidentiality Undertaking forms. The review of the completed DOI forms identified one member as having a potential conflict of interest. The interest and its management by the Global Malaria Programme are outlined below.

Dr Corine Ngufor is employed by the Centre de Recherche Entomologique de Cotonou, Benin, and the London School of Hygiene and Tropical Medicine. She declared receiving research support for testing of vector control products from Shobikaa Impex Private Limited, which ended in 2018, and from Moon Netting and Tainjin Yrkool International, both of which ended in 2020.

Conclusion: Given that no active research support was declared or otherwise identified by WHO and that past support was not related to the topic of discussion at the current meeting, the declared potential conflict of interest was judged to not present an actual conflict with respect to the content of the current meeting.
References


## ANNEX 2. MEETING AGENDA

### DAY 1 – TUESDAY, 31 AUGUST 2021

**Open Session (Members, Participants, Observers and WHO Staff)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>14:00</td>
<td>Opening remarks and welcome</td>
<td>Dr Pedro Alonso</td>
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<tr>
<td>14:10</td>
<td>Declarations of Interest</td>
<td>Dr Jan Kolaczinski</td>
</tr>
<tr>
<td>14:15</td>
<td>Background, objectives and expected outcomes</td>
<td>Dr Jan Kolaczinski</td>
</tr>
</tbody>
</table>

**PART I: PRESENTATION DATA ON PYRETHROID-PBO ITNS**

**Open Session (Members, Participants, Observers, and WHO Staff)**

<table>
<thead>
<tr>
<th>Time</th>
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<tbody>
<tr>
<td>14:25</td>
<td>PQT/VCP review and analysis of the chemistry and manufacturing of pyrethroid-PBO nets</td>
<td>Dr Marion Law</td>
</tr>
<tr>
<td>15:00</td>
<td>Presentation of non-inferiority trial data from the United Republic of Tanzania</td>
<td>Dr Sarah Moore</td>
</tr>
<tr>
<td>16:00</td>
<td>Presentation of non-inferiority trial data from Côte d’Ivoire</td>
<td>Dr Raphael N’Guessan</td>
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</table>

### DAY 2 – WEDNESDAY, 1 SEPTEMBER 2021

**Open Session (Members, Participants, Observers and WHO Staff)**

**PART II: LESSONS LEARNED FROM NON-INFERIORITY TRIALS AND DISCUSSION ON THE POTENTIAL UTILITY OF THE METHOD**

<table>
<thead>
<tr>
<th>Time</th>
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<tbody>
<tr>
<td>14:00</td>
<td>Combined estimate of data from both Côte d’Ivoire and the United Republic of Tanzania and possible hypotheses for differences should they appear</td>
<td>Dr Thomas Churcher</td>
</tr>
<tr>
<td>15:00</td>
<td>Overview of lessons learned from non-inferiority trials</td>
<td>Dr Joseph Challenger</td>
</tr>
<tr>
<td>16:00</td>
<td>Discussion on the utility of non-inferiority trials to differentiate vector control products within the same intervention class</td>
<td>Chair</td>
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### DAY 3 – THURSDAY, 2 SEPTEMBER 2021

**Closed Session (Members and WHO Staff)**

**PART III: CONCLUSIONS AND RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>15:00</td>
<td>Finalization of meeting conclusions and formulation of recommendations to WHO</td>
<td>Chair</td>
</tr>
</tbody>
</table>
ANNEX 3. LIST OF PARTICIPANTS

MEMBERS

John Bradley
London School of Hygiene and Tropical Medicine
London, United Kingdom of Great Britain and Northern Ireland

John Gimnig
Centers for Disease Control and Prevention
Atlanta, United States of America

Immo Kleinschmidt
London School of Hygiene and Tropical Medicine
London, United Kingdom

Pie Müller
Swiss Tropical and Public Health Institute
Basel, Switzerland

Corine Ngufor
Centre de Recherche Entomologique de Cotonou
Benin

Robert Reiner
Institute for Health Metrics and Evaluation
Seattle, USA

Peter Smith
London School of Hygiene and Tropical Medicine
London, United Kingdom

Charles Wondji
Liverpool School of Tropical Medicine
Liverpool, United Kingdom (Chair)

PARTICIPANTS

Joseph Challenger
Imperial College London
London, United Kingdom

Thomas Churcher
Imperial College London
London, United Kingdom

Sarah Moore
Ifakara Health Institute
Ifakara, United Republic of Tanzania

Raphael N’guessan
Institut Pierre Richet (IPR)
Abidjan, Côte d’Ivoire

Amanda Ross
Swiss Tropical and Public Health Institute
Basel, Switzerland

Mark Rowland
London School of Hygiene and Tropical Medicine
London, United Kingdom

OBERVERS

Caroline Derousseaux
Vestergaard Sàrl
Lausanne, Switzerland

Melinda Hadi
Vestergaard Sàrl
Lausanne, Switzerland

John Invest
Sumitomo Chemical Co., Ltd.
London, United Kingdom

Takao Ishiwatari
Sumitomo Chemical Co., Ltd.
Tokyo, Japan

Kate Kolaczinski
The Global Fund to Fight AIDS, Tuberculosis and Malaria
Geneva, Switzerland

John Lucas
Sumitomo Chemical Co., Ltd.
London, United Kingdom

Anand Samiappan
VKA Polymers Pvt. Ltd.
Tamil Nadu, India

Ole Skovmand
Intelligent Insect Control, Adviser to Moon Netting
Castelnau le Lez, France

Minoru Takano
Sumitomo Chemical Co., Ltd.
Tokyo, Japan

Hayato Teshima
Sumitomo Chemical Co., Ltd.
Tokyo, Japan
Barnabas Zogo  
Sumitomo Chemical Co., Ltd.  
London, United Kingdom

SECRETARIAT

Pedro Alonso  
Director, Global Malaria Programme

Lauren Carrington  
Technical Officer, Vector Control and Insecticide Resistance  
Global Malaria Programme

Jan Kolaczinski  
Unit Head, Vector Control and Insecticide Resistance  
Global Malaria Programme

Marion Law  
Technical Officer, Prequalification Team for Vector Control Products, Regulation and Prequalification

Dominic Schuler, Technical Officer, Prequalification Team for Vector Control Products, Regulation and Prequalification

Jennifer Stevenson  
Technical Officer Vector Control and Insecticide Resistance  
Global Malaria Programme

Raman Velayudhan  
Unit Head, Veterinary Public Health, Vector Control and Environment  
Department of Control of Neglected Tropical Diseases

Rajpal Yadav  
Scientist, Veterinary Public Health, Vector Control and Environment  
Department of Control of Neglected Tropical Diseases
For further information please contact:

Global Malaria Programme
World Health Organization
20, avenue Appia
CH-1211 Geneva 27
Switzerland
Email: GMPinfo@who.int