Global **Malaria** Programme

Determining non-inferiority of insecticide-treated nets and indoor residual spray products within an established product class

Evidence Review Group meeting report
5–6 July 2018 Geneva, Switzerland

World Health Organization

Global **Malaria** Programme

Determining non-inferiority of insecticide-treated nets and indoor residual spray products within an established product class

Evidence Review Group meeting report
5–6 July 2018 Geneva, Switzerland

World Health Organization

Suggested citation. Determining non-inferiority of insecticide-treated nets and indoor residual spray products within an established product class – Evidence Review Group meeting report. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

This publication contains the report of the meeting of the Evidence review group on determining non-inferiority of insecticide-treated net and indoor residual spraying products within an established class and does not necessarily represent the decisions or policies of WHO.

WHO/CDS/GMP/2018.21

TABLE OF CONTENTS

BACKGROUND

As of 1 January 2017, WHO started to implement a new process for evaluating vector control products so as to better meet the needs of countries endemic for or at risk of vector-borne diseases. The aim of the new process is to provide enhanced assurance regarding product safety, quality and efficacy. Guidance to ensure these enhancements is evolving.

One area that urgently requires additional evaluation and guidance on how to conduct such evaluation is ensuring that a policy recommendation based on epidemiological evidence demonstrating the public health value of a 'first-in-class' product can with reasonable certainty be applied to 'second-in-class' products, which are not required to demonstrate epidemiological impact. This case is exemplified by mosquito nets treated with a pyrethroid insecticide and the synergist piperonyl butoxide (PBO).

Pyrethroid-PBO nets were given an interim endorsement as a new product class in 2017 *(1)* based on epidemiological data demonstrating the efficacy of one product, generated through one cluster randomized trial conducted with Olyset®Plus (manufactured by Sumitomo Chemicals Co. Ltd) *(2)*. At the time, four other net products containing PBO had been assessed and recommended by the WHO Pesticide Evaluation Scheme (WHOPES) as pyrethroid nets. In the transition from WHOPES to the new WHO evaluation system, these recommendations were converted to a prequalification listing. However, the four nets differ from Olyset® Plus in terms of their design/specifications. Key differences include: the location of the PBO (i.e., all net panels or just the top panel); the PBO loading dose; the type and content of pyrethroid; and the regeneration time and wash resistance of the PBO. Therefore, it remains unclear whether these second-in-class products should be covered by the policy recommendation that was developed based on the epidemiological data generated by the first-in-class product (in this case Olyset®Plus). Guidance is needed to support generation of data to provide clarity in this area.

An Evidence Review Group (ERG) was held in September 2017 to determine the data requirements and methods to support the evaluation of new vector control products *(3)*. A discussion was initiated on the further assessment of pyrethroid-PBO nets and other key areas that require better evidence to inform WHO guidance to Member States. Following the presentation of the ERG deliberations to the Malaria Policy Advisory Committee (MPAC), one of the recommendations to WHO was that vector control products with the same biochemical mode of action[1] and entomological effect[2] as a product in a class covered by a WHO policy recommendation should be required to:

- Meet current testing criteria for the product class based on laboratory studies[3], small-scale field trials[4] and large-scale field trials[5] with entomological endpoints. Current guidance for each intervention type (insecticide-treated nets [ITNs], indoor residual spraying [IRS],

[1] A biochemical mode of action describes the manner in which pesticides interfere with the biochemistry of animals and plants.

[2] Entomological effect refers to a product's effect on a disease vector in terms of killing, inhibiting feeding, deterring, and reducing fertility or susceptibility to infection. Products with different biochemical modes of action may have similar entomological effects on target insects; for example, indoor residual spraying (IRS) formulations with pyrethroids and carbamates differ in their biochemical modes of action, yet are considered to have a similar impact on the target insect in areas of insecticide susceptibility.

[3] Formerly referred to as WHOPES Phase I evaluation

[4] Formerly referred to as WHOPES Phase II evaluation

[5] Formerly referred to as WHOPES Phase III evaluation

larviciding, etc.) should be consulted and updated to include details on the determination of non-inferiority.[6]

- Demonstrate non-inferiority to a first-in-class product in the product class, or another suitable comparator as identified by WHO, by means of entomological field trials (e.g., experimental hut trial studies in the case of ITN and IRS products).
- For pyrethroid-PBO nets, define a set of criteria for the bioavailability of PBO on the net over time, including not only that PBO is retained in the net, but also that it is replenished on the surface of the fibre after washing or during use.

The MPAC-endorsed recommendations specifically requested that WHO conduct further in-depth work on the assessment of non-inferiority of products within a class. While the ERG convened in 2017 acknowledged that entomological field studies – in particular experimental hut trials – are likely to provide a suitable approach for determining non-inferiority for some vector control interventions such as ITN and IRS products, it was recommended that the design of such trials be reviewed and additional guidance developed to support the implementation of standardized, rigorous study design and analysis. To support this process, an in-depth assessment of existing experimental trial data from different settings, along with a well-defined statistical methodology for analysing new and existing experimental trial data, was recommended. Specific guidance on the determination of non-inferiority should then be developed and incorporated into current WHO testing guidance.

WHO therefore convened an ERG on 5–6 July 2018 in Geneva, Switzerland to address these needs and to develop a methodology for determining the non-inferiority of candidate second-in-class products belonging to the ITN and IRS intervention types, with specific consideration given to an appropriate methodology for assessing the non-inferiority of pyrethroid-PBO nets.

OBJECTIVES OF THE ERG

The main objective of the ERG meeting was to develop a methodology for determining the non-inferiority of candidate second-in-class[7] ITN and IRS products. For ITNs, the methodology needed to be suitable for assessing pyrethroid-PBO nets, as this is an area of priority, but ideally it should also be applicable for comparing other ITN products within their respective product classes.

SPECIFIC ACTIVITIES OF THE ERG

The identified activities for the ERG were as follows:

1. Review existing data on laboratory and experimental hut studies conducted on pyrethroid-PBO nets in order to understand the:

[6] A vector product under evaluation shows non-inferiority when the confidence bound of the difference in the effect measure between the comparator product and the new product does not overlap the specified non-inferiority margin. The effect measure may be based on entomological effect and/or protective efficacy against infection and/or disease in humans. The non-inferiority margin is pre-specified based on the difference in the clinical (or entomological) effect that would be considered not to be of material importance in terms of public health benefit.

[7] Second-in-class refers to all products other than the first-in-class products for which epidemiological data were generated to assess their public health value.

a. Evaluation methodologies used to date and the variation in results between products;

b. Data available and the performance of the products evaluated against key performance indicators through the former WHOPES process, with WHO to provide an overview of the available data for this purpose;

c. Guidance given to date by the Global Malaria Programme (GMP) and WHO Prequalification (PQ) on these products, with WHO to provide an overview of the available data and current guidance for this purpose.

2. Review draft methodologies proposed for the assessment of non-inferiority of: i) pyrethroid-PBO nets, drawing on data from earlier experimental hut studies; and ii) candidate second-in-class IRS products, based on recent experience with the evaluation of SumiShield® WG.

3. Discuss and refine the methodologies as needed to support the generation of high-quality data to inform the development of WHO guidance on the deployment of second-in-class products.

SPECIFIC OUTPUTS OF THE ERG

The anticipated outputs from the ERG meeting were:

1. A study protocol specifically developed for determining the non-inferiority of pyrethroid-PBO nets;

2. Generic study protocol for determining the non-inferiority of ITNs (based on output 1, but highlighting potential areas of divergence, if applicable);

3. Generic study protocol for determining the non-inferiority of IRS products.

PROCEEDINGS OF THE ERG MEETING

An ERG was convened by WHO GMP in July 2018. The meeting involved 11 ERG members and seven temporary advisors. The agenda is provided in Annex 1, while the list of meeting participants is provided in Annex 2. The meeting included open and closed session formats. The open session was attended by members of the ERG, temporary advisors and the WHO Secretariat. The closed session was attended by ERG members and the WHO Secretariat only.

Opening and orientation to the topic (open session)

The meeting was opened and attendees were welcomed by Dr Deusdedit Mubangizi, Coordinator of the Prequalification Team in the WHO Department of Essential Medicines and Health Products. Dr Mubangizi noted the urgent need for a variety of new tools in vector control, as well as clear guidance on which to use under what circumstances. He reiterated the importance of ensuring that products are safe, of good quality, and efficacious, with new products in a class required to be at least as efficacious as established tools. Dr Mubangizi concluded that the ERG should focus on providing researchers involved in the evaluation of vector control products with guidance that is appropriate and useful to enable the testing of candidate products to inform a prequalifications assessment.

Prior to the meeting, declarations of interest provided by ERG members were assessed by Dr Jan Kolaczinski, Coordinator of the Entomology and Vector Control Unit of GMP and an Ethics Officer from the Office of Compliance, Risk Management and Ethics. Based on the review, it was decided

that none of the declarations constituted conflicts of interest in this context and that the considered experts could participate in the meeting, subject to the public disclosure of their interests. The Statement of Declarations of Interests was read aloud at the meeting and is provided here in Annex 3.

Dr Kolaczinski then explained the background, objectives and expected outcomes of the meeting, as set out above. Dr Kolaczinski noted that the key audience for the protocol would be researchers supporting the evaluation of vector control products. He reiterated that the outputs are expected to inform the ongoing revision of broader testing guidance for vector control products in order to ensure a standardized approach to the evaluation of new and existing tools. It was indicated that MPAC would be provided with an update on the outcome of the ERG meeting, and be presented with the findings from the first non-inferiority evaluations once these are available so as to advise WHO on whether this method fulfils its intended purpose.

Dr Kolaczinski provided a summary of the current gaps in the evidence base for pyrethroid-PBO nets, as follows: Pyrethroid-PBO nets were given an interim endorsement as a new vector control product class in 2017 *(1)* based on epidemiological data from one cluster randomized trial conducted at a site in United Republic of Tanzania with Olyset® Plus, manufactured by Sumitomo Chemicals Co. Ltd *(2).* As noted in the WHO recommendation, "*Further evidence on pyrethroid-PBO nets is required to support the refinement of WHO guidance regarding conditions for the deployment of products in this class*". MPAC requested the Vector Control Advisory Group (VCAG) to examine the data from a second randomized controlled trial being undertaken in Uganda. In addition, it remains to be confirmed whether the higher efficacy of the pyrethroid-PBO net product (compared to a pyrethroid-only long-lasting insecticidal net [LLIN]) observed in Tanzania over 21 months persists over the full period for which an LLIN is expected to retain its biological activity (i.e., 3 years).

Candidate second-in-class products are not required to generate epidemiological data to prove their efficacy. Instead, entomological laboratory and field studies – in particular experimental hut trials – should be used for evaluation. The four other pyrethroid-PBO nets that have been converted from a WHOPES recommendation to a PQ listing, namely PermaNet® 3.0, DawaPlus® 3.0, DawaPlus® 4.0 and Veeralin® LN, however, differ from Olyset® Plus and from each other in terms of their design and specifications. Key differences between these products include the location of the PBO (i.e., all net panels or just the top panel), the PBO loading dose, and the type and content of pyrethroid. Moreover, the regeneration time and wash resistance of the net's PBO component have not yet been systematically established. Regeneration time has been assessed mainly for pyrethroids, with wash intervals of nets used in experimental hut evaluations based primarily on the regeneration time of the pyrethroid component alone and not considering the PBO component. Only some of the laboratory and experimental hut studies have used appropriate strains of resistant mosquitoes for testing. As outlined in the recommendations from the 2017 ERG meeting *(2)* and summarized below, a number of evidence gaps on pyrethroid-PBO nets remain.

The generation of appropriate evidence for candidate second-in-class pyrethroid-PBO nets requires clarity on methods to:

- Determine the appropriate approach for demonstrating non-inferiority using experimental hut trials, including selection of test sites, hut types, study design, sample size, as well as data analysis;
- Determine the appropriate approach for laboratory testing, including selection of mosquito strains, and measurement of regeneration time (considering this may be different for pyrethroid and PBO components) and wash interval;
- Determine the appropriate testing methodology for confirming wash resistance by product, including whether to test in the laboratory or experimental hut studies and whether to use

nets washed 20 times to simulate actual aging or whether to use nets following 3 years of field use.

ERG members were requested to focus on these key critical methodological considerations when providing inputs on the draft protocol that was circulated ahead of the meeting.

Cochrane systematic review of experimental hut data on pyrethroid-PBO nets

Ms Kath Gleave, Ms Natalie Lissenden and Mr Leslie Choi from the Liverpool School of Tropical Medicine presented an unpublished Cochrane systematic review of experimental hut data on pyrethroid-PBO nets. The objective was to compare the effects of pyrethroid-PBO nets currently in production with their non-PBO equivalent in relation to malaria infection (prevalence or incidence) and entomological outcomes. The review focused on trials conducted in areas with *Anopheles gambiae* and *An. funestus* mosquitoes. Data were considered for nets treated with pyrethroid and PBO that had received an interim or full WHOPES recommendation – and have since been converted to a WHO PQ listing. The primary epidemiological outcomes considered were parasite infection prevalence and confirmed clinical malaria, and the primary entomological outcomes were mosquito mortality and blood-feeding success. The protocol for the review is available online via the Cochrane website *(4)*. At the time of the meeting, the Cochrane review was undergoing peer review and as such the findings cannot be made public in this meeting report.

Explanation and investigations of non-inferiority

Dr Thomas Churcher presented on the definition of non-inferiority and considerations for its measurement in relation to vector control products. An outline of the aim of a non-inferiority trial was provided, that is, to demonstrate that a candidate second-in-class product is no worse than the comparator by more than a pre-specified amount (the non-inferiority [NI] margin), as summarized in Fig. 1.

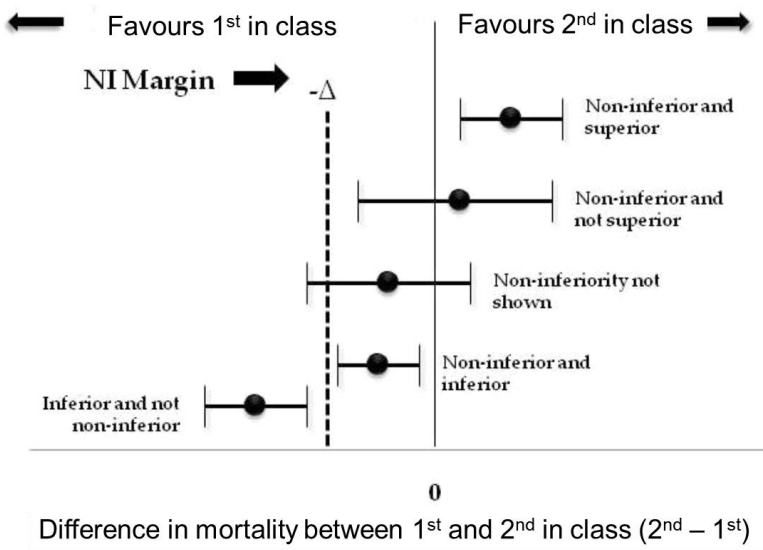

Fig. 1. Possible outcomes of a non-inferiority trial. Modified from Schumi and Wittes, 2011 *(5)*, where NI is non-inferiority

It was explained that the null hypothesis of a non-inferiority trial (as opposed to a superiority trial) is that the candidate product is inferior to the comparator. The trial will then attempt to generate evidence against this null hypothesis, i.e., to demonstrate that the test product is no worse than the comparator by more than a pre-specified amount, for example, the largest difference in mosquito

mortality that would be acceptable between a first-in-class and a candidate second-in-class product. This amount is known as the non-inferiority margin, Δ. For a non-inferiority margin of –Δ, the lower confidence bound on the difference in effect between the two products is greater than this amount, i.e., closer to zero than -Δ (Fig. 1). Robust sample size calculations are an essential component of non-inferiority trial design. Sufficiently large sample sizes are needed to provide evidence that the efficacy of a candidate second-in-class product is within the boundaries of acceptability. Power calculations, therefore, are needed to ensure that the sample size is large enough for two products with the same efficacy to be defined as non-inferior with a probability greater than e.g. 80% (i.e., the 95% confidence interval estimates do not exceed the non-inferiority margin).

Dr Churcher noted that conducting small-scale field trials using experimental hut studies is a highly informative approach, with multiple endpoints typically measured. These types of studies, however, are subject to a large degree of variation due to the relative proximity of huts to breeding sites, the attractiveness of volunteer sleepers and seasonality, and may also differ according to mosquito behaviour and resistance to insecticides. Example data (published and unpublished) from experimental hut trials were presented to demonstrate this variation. Generalized linear models may be an appropriate method to analyse such data**.**

Non-inferiority margins were discussed in detail, with numerous illustrations presented drawing on actual or theoretical data. The public health consequences of different non-inferiority margins were discussed, in particular in reference to the uncertainty around how malaria would increase with inferior ITNs, considering that products with inadequate insecticide may still provide personal protection. The mathematical models of transmission dynamics used to estimate malaria burden in Africa, parameterized with experimental hut trial data, may provide a feasible approach for translating trial results into likely public health impact. However, this approach is weakened by heavy reliance on numerous assumptions in such models, including translation of entomological efficacy into epidemiological effect, lack of data on the impact on malaria incidence (as opposed to prevalence of infection), and extrapolation from one trial to a whole continent.

To support the development of the protocol, estimates of possible non-inferiority margins were generated through simulations considering: i) a single primary endpoint; ii) the test statistic; and iii) the size of the non-inferiority margin. Based on the outcomes and discussions, it was clear that a balance is required between the feasibility of conducting hut trials given required sample sizes, and the potential detriment to public health should an insufficiently powered trial fail to detect that a candidate product is indeed inferior to the standard of care. There was discussion around whether non-inferiority margins should be based on relative risks, absolute differences in risk, or odds ratios. Agreement was reached to use an odds ratio of 0.7 on mosquito mortality as the non-inferiority margin, i.e., the proportion of mosquitoes dying must be high enough so that the 95% confidence interval estimate of the candidate second-in-class product (relative to the active comparator) is greater than 0.7. It was agreed that further simulations should be run using the agreed odds ratio in order to illustrate the implications of such a non-inferiority margin on the study design.

Review of a draft study protocol for non-inferiority determination

A draft protocol document circulated to the ERG members and technical advisors prior to the meeting was then reviewed in detail, with proposed edits and comments captured to inform revisions. The document outlines data requirements and a study protocol for determining non-inferiority of ITN and IRS products within an established WHO policy class. The aim of the protocol is to evaluate whether the entomological efficacy of a second-in-class candidate ITN or IRS product is no worse than that of the first-in-class product by more than a non-inferiority margin, using experimental hut trials. Extensive discussions were held on the content of the protocol. The revised version of this protocol has been published separately alongside the meeting report. The following emerged as major considerations and decision points, and the protocol should be referred to for more detailed discussions of each point:

- **Primary outcome measures:** Mosquito mortality and blood-feeding inhibition should both be considered as the primary outcome measures for assessing the non-inferiority of ITNs. Studies should be powered to detect non-inferiority on the smallest effect size (which is likely to be mosquito mortality in most cases) so that both endpoints can be evaluated. Mosquito mortality should be the primary outcome measure for assessing the non-inferiority of IRS products.
- **Sample size considerations:** A key consideration for study feasibility is the required sample size, as there is a clear need to ensure sufficient power and limit the probability of inferior products being erroneously declared non-inferior by no more than 5% (as is standard for rejecting the null hypothesis in trials, including non-inferiority trials). This needs to be weighed against the duration of study required to generate the required sample size (especially considering that malaria transmission and associated mosquito densities are seasonal). Further simulations are required to inform sample size calculations. These will need to be conducted specifically for each study setting and draw on recent data on the number of mosquitoes entering experimental huts and on expected mosquito mortality with the first-in-class product.
- **Analytic technique:** Comparing the relative effectiveness of a candidate second-in-class product to that of a first-in-class product requires a method that can account for uncertainty in the estimate for both the first-in-class comparator and the candidate second-in-class product. It is essential that data be analysed according to the design of the experiment and take into account variation between huts, sleepers and timepoints. An adjusted logistic regression model that estimates odds ratios and 95% confidence intervals, and that allows for within-cluster correlation of responses, was proposed as the analytical method of choice, although it was recognized that other analytical methods could be used depending on the endpoints under investigation. It is most likely that professional statistical support will be needed. This should be sought in the study design stage of the trial.
- **Latin square design:** Clarity on the proposed approach to study design is required, as this can be a source of confusion. It was suggested to incorporate an annex with diagrams of an appropriate randomized approach, or links to online resources that give appropriate examples.
- **Study arms:** For ITNs, a 7-arm study was proposed that includes:
    1. Untreated net unwashed (negative control);
    2. Standard ITN unwashed (standard comparator);
    3. Standard ITN washed 20 times (standard comparator);
    4. First-in-class ITN unwashed (active comparator);
    5. First-in-class ITN washed 20 times (active comparator);
    6. Candidate second-in-class ITN unwashed (test item);
    7. Candidate second-in-class ITN washed 20 times (test item).

  For IRS, the appropriate study arms will depend on whether there is only one or multiple first-in-class products under evaluation, and whether these are of the same or different insecticide classes. It is a minimum requirement to include an active comparator that is the standard of care in the area where the test is conducted in addition to a negative control. It was recommended that at least four huts be used per treatment arm in IRS trials in order to improve precision of the endpoints measured. Clear justification for the selection of the arms should be included in the protocol.
- **Naturally aged ITNs:** For ITNs, a decision on whether to include the candidate product in the product class should be made using data from unwashed nets and nets washed 20 times. The product's inclusion within the policy class should be re-examined once experimental hut trial data become available for products aged for 3 years under user conditions.

- **Site selection:** Details must be included on the minimum essential data required to adequately characterize the local vector populations at potential or actual experimental hut sites in order to inform site selection and data analyses.
- **Criteria to "pass" the non-inferiority test:** It was proposed that the candidate ITN or IRS products must satisfy two criteria with regard to their primary endpoint(s) in order to be considered non-inferior: 1) It is non-inferior relative to the first-in-class product (i.e., on both mosquito mortality and blood-feeding inhibition for ITNs and mortality alone for IRS); and 2) it performs significantly better than the current standard of care (only if the product claims to be better than the current standard comparator, for example, a pyrethroid-only LLIN or IRS).
- **Other general comments:** The draft protocol will be expanded to include clear explanations of the rationale for the various protocol specifications, as significant investments of both time and money will be required to generate the stipulated data. Some restructuring will be needed to distinguish between requirements for ITN and IRS product assessments, and to outline the components required for assessment. Some of the descriptive content should be moved to the annex or, if available in other documents, should simply be cited rather than including unnecessary detail in the body of the protocol. It is anticipated that researchers will develop detailed site-specific protocols and analysis plans based on the WHO protocol.
- **Additional information:** The meeting proposed the inclusion of a checklist for reporting requirements for entomological data (similar to the CONSORT guidelines for clinical trials *(6)*). All raw data generated from a trial should be provided to WHO.
- **Process for revision:** The importance of early guidance by WHO on study design and conduct to ensure the generation of appropriate data was acknowledged. However, given the numerous unknowns in designing and analysing data from non-inferiority studies at this stage, the importance of feedback mechanisms was reiterated in order to review data and revise testing guidance as necessary.

FOLLOW-ON ACTIONS

The draft protocol was revised on the basis of the meeting discussions and decisions, and circulated in its revised version to ERG members for review. GMP will provide a brief update on the ERG meeting to MPAC in October 2018. Once data from comparative effectiveness trials of pyrethroid-PBO nets are available, GMP will reconvene the ERG to review the study outcomes and protocol in the light of this evidence. Based on this assessment, WHO GMP will provide an in-depth update to MPAC – most likely in late 2019 or early 2020, with a view to determining the value of non-inferiority studies in the context of WHO's policy-making process, in particular with regard to extending a policy based on epidemiological evidence generated for first-in-class products to second-in-class ones.

REFERENCES

1. Conditions for deployment of mosquito nets treated with a pyrethroid and piperonyl butoxide. Geneva: World Health Organization; 2017 (http://www.who.int/malaria/publications/atoz/use-of-pbo-treated-llins/en/, accessed 10 July 2018).
2. Protopopoff N, Mosha JF, Lukole E, Charlwood JD, Wright A, Mwalimu CD, et al. Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomised controlled, two-by-two factorial design trial. Lancet. 2018;391(10130):1577–88.(https://www.ncbi.nlm.nih.gov/pubmed/29655496, accessed 10 July 2018).
3. Data requirements and methods to support the evaluation of new vector control products. Geneva: World Health Organization; 2017 (http://www.who.int/malaria/publications/atoz/requirements-vector-control-products/en/, accessed 10 July 2018).
4. Gleave K, Lissenden N, Richardson M, Ranson H. Piperonyl butoxide (PBO) combined with pyrethroids in long-lasting insecticidal nets (LLINs) to prevent malaria in Africa [Protocol]. Cochrane Infectious Diseases Group; 2017 (http://www.cochrane.org/CD012776/INFECTN_piperonyl-butoxide-pbo-combined-pyrethroids-long-lasting-insecticidal-nets-llins-prevent-malaria, accessed 10 July 2018).
5. Schumi J, Wittes JT. Through the looking glass: understanding non-inferiority. Trials. 2011;12:106.
6. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG, CONSORT Group. Reporting of noninferiority and equivalence trials: extension of CONSORT 2010 statement. JAMA. 2012;308:2594–604.

ABBREVIATIONS

ERG	Evidence Review Group
GMP	Global Malaria Programme
IRS	Indoor residual spraying
ITN	Insecticide-treated net
LLIN	Long-lasting insecticidal net
MPAC	Malaria Policy Advisory Committee
NI	Non-inferiority
PBO	Piperonyl butoxide
SOP	Standard Operating Procedure
VCAG	Vector Control Advisory Group
WHO	World Health Organization
WHOPES	WHO Pesticide Evaluation Scheme

ANNEX 1. AGENDA

Thursday 5 July 2018		
Open Session (ERG Members, Temporary Advisors & WHO Staff)		
09.00 – 09.10	Opening remarks and welcome	Dr Deus Mubangizi
09.10 – 09.20	Declaration of interest	Dr Jan Kolaczinski
09.20 – 09.30	Background, objectives and expected outcomes	Dr Jan Kolaczinski
Part I: Proposed methods for determination of non-inferiority of ITN and IRS products		
Open Session (ERG Members, Temporary Advisors & WHO Staff)		
9.30 – 10.00	Gaps in evidence on pyrethroid-PBO nets	Dr Jan Kolaczinski
10:00 – 10.45	Cochrane systematic review of experimental hut data on pyrethroid-PBO nets	Ms Kath Gleave / Ms Natalie Lissenden / Mr Leslie Choi
11:15 – 12.30	(1) How is non-inferiority typically measured? (2) Quantifying the variability in experimental hut trials (3) Estimating acceptable non-inferiority margins through simulation.	Dr Thomas Churcher
13:30 – 14.15	Draft study protocol for non-inferiority determination of ITNs	Dr Thomas Churcher
14.15 – 15.00	Discussion on study protocol for ITNs	Chair
15.30 – 16.15	Discussion on entomological work to be conducted in the context of the non-inferiority study	Chair
16.15 – 17.00	Final discussion on study protocol for ITNs	Chair
17:00 – 17.30	Conclusions from day 1 (End of Open Session)	Chair
Friday 6 July 2018		
Part I: Proposed methods for determination of non-inferiority of ITN and IRS products (continued from day 1)		
9:00 – 9.45	Presentation of draft study protocol for non-inferiority determination of IRS products	Dr Sarah Moore / Dr Thomas Churcher
9:45 – 10:30	Discussion on study protocol for IRS products	Chair
Closed Session (ERG Members & WHO Staff)		
Part II: Finalization of study protocols		
11.00 – 12:30	Finalization of study protocol for non-inferiority determination of insecticide-treated net products	Chair
13.30 – 14.30	Finalization of study protocol for non-inferiority determination of insecticide-treated net products	Chair
14.30 – 15.30	Finalization of meeting conclusions and recommendations	Chair
16.00 – 16.30	Meeting closure	Dr Jan Kolaczinski

ANNEX 2. LIST OF PARTICIPANTS

Chair

Prof Steven LINDSAY
Department of Biosciences
Durham University
Durham
UNITED KINGDOM

ERG Members

Dr John BRADLEY
Department of Infectious Disease Epidemiology
London School of Hygiene and Tropical Medicine
London
UNITED KINGDOM

Dr John GIMNIG
Entomology Branch
Division of Parasitic Diseases and Malaria
Centers for Disease Control and Prevention
Atlanta, Georgia
USA

Prof Immo KLEINSCHMIDT
Department of Infectious Disease Epidemiology
London School of Hygiene and Tropical Medicine
London
UNITED KINGDOM

Dr Raphael N'GUESSAN
Institut Pierre Richet (IPR)
Abidjan
CÔTE D'IVOIRE

Dr Corine NGUFOR
Centre de Recherche Entomologique de Cotonou
BENIN

Dr Pie MÜLLER
Swiss Tropical and Public Health Institute
Basel
SWITZERLAND

Dr Richard OXBOROUGH
Abt Associates
Massachusetts
USA

Dr Robert REINER
Institute for Health Metrics and Evaluation
Seattle, Washington
USA

Dr Amanda ROSS
Swiss Tropical and Public Health Institute
Basel
SWITZERLAND

Prof Peter SMITH
London School of Hygiene and Tropical Medicine
London
UNITED KINGDOM

Temporary Advisers

Dr Leslie CHOI
Cochrane Infectious Disease Group
Liverpool
UNITED KINGDOM

Dr Thomas CHURCHER
School of Public Health
Imperial College London
London
UNITED KINGDOM

Dr Katherine GLEAVE
Liverpool School of Tropical Medicine
Liverpool
UNITED KINGDOM

Dr Natalie LISSENDEN
Liverpool School of Tropical Medicine
Liverpool
UNITED KINGDOM

Dr Sarah MOORE
Ifakara Health Institute
Ifakara
TANZANIA

Prof Mark ROWLAND
London School of Hygiene and Tropical Medicine
London
UNITED KINGDOM

Dr Joseph WAGMAN
PATH
Washington D.C.
USA

WHO Secretariat

Mrs Anna BOWMAN
VCAG Manager
Entomology and Vector Control
Global Malaria Programme
WHO Headquarters, Geneva

Dr Anna DREXLER
Technical Officer
Vector and Ecology Management
Department of Control of Neglected Tropical Diseases
WHO Headquarters, Geneva

Dr Tessa KNOX
Technical Officer
Entomology and Vector Control
Global Malaria Programme
WHO Headquarters, Geneva

Dr Jan KOLACZINSKI
Coordinator
Entomology and Vector Control
Global Malaria Programme
WHO Headquarters, Geneva

Dr Marion LAW
Prequalification Team
Department of Essential Medicines and Health Products
WHO Headquarters, Geneva

Dr Deusdedit MUBANGIZI
Coordinator
Prequalification Team
Department of Essential Medicines and Health Products
WHO Headquarters, Geneva

Dr Rajpal YADAV
Scientist
Department of Control of Neglected Tropical Diseases
Vector Ecology and Management Unit
WHO Headquarters, Geneva

ANNEX 3. DECLARATIONS OF INTEREST

All members of the ERG completed and submitted Declaration of Interest (DOI) and Confidentiality Undertaking forms. On review of the completed DOIs, the following experts declared interests that required further consideration and discussion with the WHO Office of Compliance, Risk Management and Ethics (CRE).

- Dr Raphael N'Guessan is employed by the Institut Pierre Richet, Côte d'Ivoire and the London School of Hygiene and Tropical Medicine in the UK. He has previously received research support from: BASF, Germany; Bayer Crop Science, Germany; IVCC, UK; and WHOPES for the evaluation of new pesticide products. All of these grants came to an end either in 2017 or before.
- Dr Corine Ngufor is employed by the Centre de Recherche Entomologique de Cotonou, Benin, and the London School of Hygiene and Tropical Medicine. She has received research support from Disease Control Technologies, USA, and Sumitomo Chemical, Japan, both of which came to an end earlier this year.
- Dr Amanda Ross is employed by the Swiss Tropical and Public Health Institute (TPH), Switzerland. She has not received any direct funding to support work related to this ERG, but declared that she has provided statistical support to other units within the Swiss TPH that received support from companies for work on IRS and mosquito net products.

The WHO Secretariat assessed the conflicts of interest declared by the experts. Upon review, it was decided that the declarations did not constitute conflicts of interest in this context and that the considered experts could participate in the meeting, subject to the public disclosure of their interests.