

Proposed ERG on determining non-inferiority of insecticide-treated net and indoor residual spraying products within an established class

Terms of Reference of the Evidence Review Group meeting
to be held on 5–6 July 2018

Background

As of 1 January 2017, the WHO process for evaluating vector control products has been revised to better meet the needs of countries endemic for, or at risk of, vector-borne diseases. Under the revised evaluation system, WHO will provide enhanced assurance regarding the quality and effectiveness of products. This includes those products that fall within an established intervention class, but that differ in design (specifications) from the first-in-class product that established the class and for which epidemiological data are available. One key area where additional evaluation is urgently required is mosquito nets treated with a pyrethroid insecticide and the synergist piperonyl-butoxide (PBO). Pyrethroid-PBO nets were given an interim endorsement as a new class in 2017¹ based on epidemiological data from one cluster randomized trial conducted with Olyset Plus (produced by Sumitomo Chemicals Co. Ltd). However, four other net products containing PBO were previously assessed and recommended by WHOPES as pyrethroid nets; all of these differ from Olyset Plus in terms of their design/specifications. Key differences between these products include the location of the PBO (all net panels or just the top panel), the PBO loading dose, the type and content of pyrethroid, and the wash-fastness and bioavailability of the PBO.

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. 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 WHO² was that vector control products with the same biochemical mode of action and entomological effect as a product in a class covered by WHO policy should be required to:

- Meet current testing criteria for the product class based on laboratory and small-scale field trials³ and large-scale field trials⁴ with entomological endpoints. Current

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-lins/en/>).

2 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/>).

3 Formerly referred to as WHOPES Phase II evaluation

4 Formerly referred to as WHOPES Phase III evaluation

guidance for each intervention type (LLINs, IRS, larvicide, etc.) should be consulted and updated to include details on the determination of non-inferiority.⁵

- Demonstrate non-inferiority to at least one existing product in the product class by means of small-scale field trials (i.e. experimental hut studies in the case of LLINs and IRS products). This comparator should represent current best practice used by the national programme in the region of the trial.
- For pyrethroid-PBO nets, define a set of criteria for PBO persistence over time, including not only that PBO is retained in the net but that it is also replenished.

The MPAC-endorsed recommendations specifically requested WHO to conduct further in-depth work on the assessment of non-inferiority of products within a class. While the ERG acknowledged that entomological field studies, in particular experimental hut trials, are likely to provide a suitable approach for determining non-inferiority, it was recommended that the design of such trials be reviewed and additional guidance developed to support the implementation of a standardized and rigorous study design and analysis. To support this process, an in-depth assessment of existing experimental trial data from different settings, along with a comparison of statistical methods for analysing new and existing experimental trial data, was recommended. Based on these analyses, it was recommended that specific guidance on the assessment of non-inferiority be developed and incorporated into current WHO testing guidelines.

WHO is therefore convening an ERG to address these needs and to develop a methodology for determining non-inferiority of second-in-class products belonging to the insecticide-treated net (ITN) and indoor residual spraying (IRS) intervention types, with specific consideration given to an appropriate methodology for assessing non-inferiority of pyrethroid-PBO nets. The development of such guidance will draw on recent experience in evaluating pyrethroid-PBO nets and, in the case of IRS, a neonicotinoid IRS product.

Objectives of the ERG

1. To develop a methodology for assessing non-inferiority of second-in-class⁶ ITN and IRS products. For ITNs, the methodology needs to be suitable for assessing pyrethroid-PBO nets, but ideally applicable to comparing other ITN products within their respective classes.

Specific activities to be conducted by the ERG

1. Review existing data on laboratory and experimental hut studies conducted on pyrethroid-PBO nets, in order to:
 - a. familiarize themselves with the evaluation methodologies used to date and the variation in results between products;

⁵ A vector product under evaluation shows non-inferiority when it demonstrates an equal or better entomological effect and/or protective efficacy against infection and/or disease in humans than the comparator product. Non-inferiority relies on a measurement of effect whereby the difference should be only a small amount, called delta. Delta is pre-specified based on the desired clinical (or entomological) effect. Specifying a smaller delta for a non-inferiority trial can test whether a new product's performance is similar to that of a comparator product (i.e. effect is <delta), but demonstrating statistical significance may require larger sample sizes.

⁶ Second-in-class refers to all products other than the first-in-class product for which epidemiological data were generated to assess its public health value.

- b. familiarize themselves with the data available and the performance of the products evaluated against key performance indicators through the former WHOPEs process. WHO will provide an overview of the available data for this purpose;
 - c. familiarize themselves with the guidance given to date by GMP and PQ on these products. WHO will 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 developed with the aid of mathematical modelling drawing on data from earlier experimental hut studies, and ii) second-in-class IRS products, based on recent experience with the evaluation of SumiShield WG.
3. Refine the study 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 to be provided by the ERG

1. Study protocol specifically developed for determining non-inferiority of pyrethroid-PBO nets;
2. Generic study protocol for determining non-inferiority of ITNs (based on output 1, but highlighting potential areas of divergence, if applicable);
3. Generic study protocol for determining non-inferiority of IRS products.

All ERG outputs will be reviewed by the MPAC.