Statistical Analysis Plan
WWARN Ivermectin Exposure in Small Children Study Group
Version 1.0
09.03.20

WorldWide Antimalarial Resistance Network (WWARN)

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Version History

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V 0.1		
V 1.0	**Incorporated comments**	**9 March 2020**

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www.wwarn.org

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1. Introduction and Rationale

Ivermectin is a widely used antiparasitic drug. It is approved for the treatment of onchocerciasis [1], lymphatic filariasis [2], strongyloidiasis [1] and scabies [3]. Billions of people have been treated with ivermectin during mass drug administrations (MDAs) for onchocerciasis and lymphatic filariasis. Recent evidence demonstrates that ivermectin MDAs can reduce scabies burden [4] and malaria parasite transmission [5]. When used in MDA for onchocerciasis, the population coverage achieved during drug distribution is a key factor for efficacy [6], a similar effect is expected for malaria [7] and scabies. The safety and effectiveness of ivermectin in children weighing less than 15 kg has not been established [1]. This means that children less than 15 kg are not treated during MDAs, since this group comprises roughly 20-30% of populations in malaria and scabies endemic areas [4,5] this directly limits the proportion of people that can be treated during MDA, therefore challenging the MDA impact.

For malaria, ivermectin kills the *Anopheles* mosquito vector thereby reducing *Plasmodium* transmission [5]. Thus, having a portion of the human population not treated during ivermectin MDAs will reduce insecticide delivery to the blood feeding Anopheles populations, diminishing MDA value. In Africa, children younger than five years are frequently bitten by Anopheles mosquitos as evidenced by high rates of new malaria infections in this population. Thus, untreated children less than 15 kilograms serve as an important reservoir of Plasmodium and facilitate onwards transmission to mosquitoes.

For scabies, ivermectin kills the causative mite agent, ***Sarcoptes scabei***. Children five years and under may have high prevalence of scabies compared to older age groups [8]. Since children less than 15 kg are not indicated for treatment with oral ivermectin due to a lack of safety evidence, topical creams such as permethrin or benzyl benzoate are used. However, topical creams are not always effective due to many reasons, including lack of compliance and adherence to application protocol when performed outside the clinical setting. Topical permethrin had lower scabies clearance rates than oral ivermectin in a recent MDA study in Fiji [4]. Non-ivermectin-treated children less than 15 kg could serve as a reservoir for scabies re-infection for the rest of the community during ivermectin MDAs, again reducing MDA impact.
In France, oral ivermectin can be used for scabies treatment in children less than 15 kg if primary topical permethrin and benzyl benzoate treatments fail and the child is asthmatic so cannot be treated with esdepallethrin [9]. Oral ivermectin has been used off-label in numerous clinical investigations and settings to treat children less than 15 kg for scabies, head lice, cutaneous larval migrans, strongyloidiasis, onchocerciasis, gnathostomiasis, and baylisascaris. To achieve these important goals, we aim to pool individual patient data of all known ivermectin exposures in children less than 15 kilograms, and assess any adverse events. The proposed work will provide evidence to inform the use of ivermectin in children less than 15 kilograms.

2. Aim of the study

The objective of this study is to compile all known ivermectin exposures in children less than 15 kilograms and assess adverse events following ivermectin exposure in this population.

3. Eligibility criteria for inclusion in pooled analysis

3.1 Inclusion criteria for data analyzed for safety

Any systematic reviews, clinical trials, observational studies, case-control studies, case series, case reports, and pharmacovigilance database entries that specifically report adverse outcomes after ivermectin exposure in children less than 15 kilograms will be included. Minimum individual patient data required is weight, assessment of adverse events associated with ivermectin and dosing regimen.

3.2 Desirable criteria (not required for inclusion)

The following information is desirable and will be extracted if available:

- Height and age
- Gender
- Ivermectin manufacturer and trade name
- Country where ivermectin treatment occurred
- Disease treated with ivermectin
- Concomitant medications and diseases treated

3.3 Study exclusion criteria

None

3.4 Patient exclusion criteria

None

4. Methodologies

4.1 Data pooling

The data sets uploaded to the WWARN repository will be standardized into CDISC format using the WWARN Data Management and Statistical Analysis Plans[1] (DMSAP v1.11) for clinical data and pooled into a single database of quality-assured individual patient data. Information on study design (randomized trial, single arm trial, prospective observational study) and methodology of assessing adverse events will also be recorded. Data will remain the property of the individual donor(s) and publication will be in accordance with an agreed publication.

5. Safety Endpoints

5.1 Primary

Presence of any AE after administration of ivermectin will be considered as a primary outcome.

We will also characterize the incidence, type, and study drug relationship of reported AEs and serious adverse events (SAEs)

5.2 Definition of Endpoints

AEs will be defined as the appearance or worsening of any undesirable sign, symptom, or medical condition after starting the study drug, even if the event was not considered related to the study drug, according to the ICH E2A guidelines [8].

SAEs will be defined as any untoward medical occurance that at any dose: results in death; is life-threatening; requires inpatient hospitalization or results in prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is a medically important event or reaction [8]. Standardised dictionaries will be integrated into the database, allowing all events to be coded to the relevant dictionary, thereby facilitating data retrieval and reporting. All SAEs will be classified by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) level.

Grading and causality classification of adverse events, as made by the on-site principal investigator or physician in each study will be pooled and analysed.

For the AE analysis, only events known to occur after the administration of ivermectin will be considered (i.e. treatment-emergent AEs). If day of onset is missing, or time of onset in relation to the ivermectin dose is not recorded we will contact the investigator for clarification.
All studies will be included in the analysis, irrespective of the reporting schedule, as we will assume that any AE with an onset between the follow-up visits will be reported at the next visit
Association with ivermectin will be analysed as a binary variable: not related / possibly related. In studies with 1-5 ratings, AEs rated as 3, 4, 5 (possibly, probably, definitely related to ivermectin) will be considered as possibly related. If the association is not assessed specifically for ivermectin, but to drugs, it will be assumed to be also relevant to ivermectin.

6. Covariates Examined

- Dose of ivermectin administered
- Weight
- Gender
- Age
- Indictaion
- Study design

7. Outline of Statistical Analysis

7.1 Specific objectives of the analysis

- To characterize the incidence, type, and study drug relationship of reported AEs and SAEs

7.2 Statistical analysis

Data Description

1. Table of methodology used in studies related to AE collection (duration, what grade AE reported, methods of elicitation used etc)

2. Descriptives and baseline characteristics
    a. A summary (study profile) of the relevant studies uploaded to the WWARN repository will be presented to highlight potential selection bias
    b. A summary of key study characteristics will be outlined
    c. The baseline characteristics of patients in the eligible studies will be summarized by study and overall

Analysis of Adverse Events

1. Distribution of time to onset of any AE after ivermectin administration will be examined
2. Table of all AEs will be created. Frequencies will be presented for observational studies and clinical trials. For case-control studies only number of recorded events will be provided.
   Columns in table: AE name, n observed, N tested, n case-reports
3. Table of all SAEs will be created. Frequencies will be presented for observational studies and clinical trials. For case-control studies only number of recorded events will be provided.
   Columns in table: SAE name, n observed, N tested, n case-reports
4. Table of all (S)AEs possibly related to ivermectin will be created. Frequencies will be presented for observational studies and clinical trials. For case-control studies only number of recorded events will be provided.

Columns in table: AE name, n observed, N tested, n case-reports

5. Tables 2-4 by the elicitation method, indication, time of onset will be created, data permitting

8. Statistical Methodology

8.1. Descriptive statistics

Descriptive statistics will use median and range for continuous measurements and frequencies and proportions for categorical parameters.

8.2. Analysis of adverse events

Analyses of AEs will be based on descriptive summaries of frequency, severity and relatedness to ivermectin, by AE type. Data permitting, for each type of AE, proportions of patients affected will be calculated, overall and by study, indication excluding case reports. Overall AE proportions will be calculated using fixed effects logistic regression model.

9. Tools

All statistical analyses will be carried out using *Stata 15.1* (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA). Using alternative statistical software does not require amendment of this SAP.

10.Study group governance, coordination and membership

The Study Group comprises participating investigators who contribute relevant data sets to the pooled analysis. Data sets remain the property of the investigator. The Study Group collectively makes decisions with respect to including additional studies, data analysis and plans for publication, in line with the WWARN Publication Policy. The Safety Study Group will identify one or two people to coordinate activities including data analysis, and drafting of publications and reports for group review. The policy regarding authorship will be widely discussed in the group. The manuscript preparation and writing committee will be composed of Kevin Kobylinski, Philippe Guerin and the WWARN statistician Kasia Stepniewska. They will be responsible for circulating drafts for comments to the study group members. The WWARN statistician(s) will be responsible for statistical analyses.

After upload to the WWARN Data Repository, data sets will be transformed, standardized and pooled according to the WWARN Clinical Data Management and Statistical Analysis Plans. The statistician appointed to the project developed this statistical analysis plan specifically for the pooled analysis, in close collaboration with Mahidol University, AFRIMS,and with Study Group members.

11.Timelines

Details about joining the Study Group were made available in Q2 2017 with an open invitation to potential participants.

12.Potential Policy Outcome

The data provided by this analysis will be used to inform policy makers and research on the relative risks ofivermectin use in children weighing less than 15kg for a range of diseases. Determination of a safe, effective therapeutic range of single-dose ivermectin, values that would define the lowest efficacious dose and the highest safe dose, and guide the establishment of appropriate dosing recommendations in field settings.

13.References

1. Merck & Co.: Stromectol. FDA approved Package insert 2009(link is external) (accessed June 2015).

2. Ministere des affaires sociales de la sante et des droits des femmes: STROMECTOL 3 mg, comprimé - Résumé des caractéristiques du produit.

3. Merck & Co.: Stromectrol. TGA-Australia approved Package insert 2014(link is external) (accessed July 2016).

4. Romani L, Whitfeld MJ, Koroivueta J, Kama M, Wand H, Tikoduadua L, Tuicakau M, Koroi A, Andrews R, Kaldor JM, Steer AC: Mass drug administration for scabies control in a population with endemic disease. N Engl J Med. 2015, 373:2305-2313.

5. Foy B, Alout H, Seaman JA, Rao S, Magalhaes T, Wade M, Parikh S, Soma DD, Sagna AB, Fournet F, Slater HC, Bougma R, Drabo F, Diabaté A, Coulidaty AGV, Rouamba N, Dabiré RK. Efficacy and risk of harms of repeat ivermectin mass drug administrations for control of malaria (RIMDAMAL): a cluster-randomised trial. *Lancet* **393**, 1517-1526 (2019).

6. Turner HC, Walker M, Churcher TS, Basanez MG: Modelling the impact of ivermectin on River Blindness and its burden of morbidity and mortality in African savannah: EpiOncho projections. Parasit Vectors 2014, 7:241.

7. Slater HC, Walker PG, Bousema T, Okell LC, Ghani AC: The potential impact of adding ivermectin to a mass treatment intervention to reduce malaria transmission: a modelling study. J Infect Dis 2014, 210:1972-1980

8. Karimkhani C, Colombara D, Drucker A, Norton S, Hay R, Engelman D, et al. The global burden of scabies: a cross-sectional analysis from the Global Burden of Disease Study 2015. Lancet Infect Diseases. 2017;17(12):1247-54.

9. Berthe-Aucejo A, Prot-Labarthe S, Pull L, Lorrot M, Touratier S, Trout H, Bourdon O, Dehen L, Bourrat E. Treatment of scabies and Ascabiol® supply disruption: What about the pediatric population?Archives de pédiatre 2014, 21: 670-675.