

**Data Management and Statistical Analysis Plan (DMSAP)
Version 1.0**

Pharmacology Module
WorldWide Antimalarial Resistance Network (WWARN)



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WorldWide Antimalarial Resistance Network (WWARN)

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Scope

A key aim of WWARN is to monitor geospatial and temporal trends in antimalarial drug resistance. To accurately define antimalarial drug resistance, by differentiating true resistance from inadequate drug exposure, antimalarial drug concentration data need to be collated at an individual patient level so that standardized methodologies and definitions can be applied.

The purpose of the **Pharmacology Data Management and Statistical Analytical Plan (DMSAP)** is to present a clear and transparent methodology by which WWARN handles and analyses pharmacology data. Documenting the entire process by which data is uploaded, transformed, analysed and presented ensures reproducibility.

2. Introduction

Achieving adequate antimalarial drug concentrations in the blood is pivotal to curing malaria. The Pharmacology Module is working to accurately define antimalarial drug resistance, by differentiating true resistance from inadequate drug exposure. It also hopes to contribute to reducing resistance by informing optimal antimalarial dosing in key target populations.

Informing optimal antimalarial selection and dosing, requires the global cooperation of researchers active in antimalarial pharmacology to:

- Adequately define therapeutic drug concentrations; and
- Facilitate a better understanding of the patient, dosing and disease factors that change antimalarial exposure enough to compromise the antimalarial efficacy.

The Pharmacology Module is working towards these goals as follows.

- Facilitating the inclusion of results from antimalarial pharmacology studies carried out by research groups, Non-Governmental Organisations (NGOs) or National Malaria Control Programmes (NMCPs) in a **Data Repository**.
- Creating **standardised** processes to facilitate the collation of diverse datasets from antimalarial pharmacology studies taking place around the world.
- Optimising **analytical tools** to accommodate this diversity and increase comparability of results between heterogeneous studies.

2.2 WWARN's process of data collation

WWARN aims to facilitate two processes: to give researchers the tools to collect, clean and analyse their own data, and to transform pharmacology data from a diverse range of studies into a common format that can be derived from almost all database structures, so that data from different studies can be pooled and analysed collectively in a standardised manner.

To achieve these goals, a series of steps are followed.

- I. Upload individual anonymised patient data from a study that includes antimalarial concentration data, hereafter referred to as a “pharmacology study”
- II. Transform uploaded data to a common format
- III. Search for and list unexpected/missing data
- IV. Data analysis, applying uniform analytical methodology and reporting drug concentrations and any association with therapeutic efficacy. These are provided as a report to the data submitter. If the data submitter agrees, the data may be presented on the WWARN Explorer, an interactive online tool which allows users to perform custom queries of more than a hundred studies and visualise the results using dynamic mapping.

3. Dataset submission process

The Pharmacology Module accepts datasets from antimalarial pharmacology studies that have been obtained in accordance with any laws and ethical approvals applicable in the country of origin.

3.1 Variables

The dataset and/or accompanying documents (e.g. protocols, publications, data dictionary) must contain the following information:

- I. Unique patient identifier
- II. Treatment received, dose (mg/kg) and day/date and time of each dose administered
- III. Drug/metabolite measured
- IV. Drug concentration(s) and day/date and/or time measured

V. Age and weight of the patients

If these essential variables are not provided or immediately apparent, additional information may be required prior to data processing. In these situations, WWARN Data Managers will contact the data submitter for clarification.

The full pharmacology data dictionary is available in Annex A.

3.2 Online submission system

Datasets are submitted using the WWARN online submission system. Data contributors must accept the Terms of Submission [available at <http://www.wwarn.org/data/usage>] during the submission process.

The data submission steps are:

- I. **Register a study:** contributors enter their study title. Each study is assigned a unique identifier. Contributors tick one or more boxes to indicate the type of data submitted (clinical, molecular, in vitro and/or pharmacology).
- II. **Permissions:** each study may have any number of administrators, assigned by the data submitter who created the study title and accepted the Terms of Submission. An administrator can access the study, upload files and edit supplied information.
- III. **Files:** contributors are asked to submit data files and supporting documentation including a data dictionary, protocols and publications.
- IV. **Publications:** contributors can provide the Pub Med ID, citation or DOI for publications relating to the submitted data.
- V. **Acknowledgements:** the names of acknowledged individuals and institutions will appear in the study details displayed in WWARN Explorer.
- VI. **Study site questionnaire (SSQ):** data submitters are asked to provide information on the study site and study design. They may enter this information themselves or upload files with relevant protocols and publications (see III. and IV.) which will be used by Data Managers to extract the relevant data.

4. Data extraction to a standardised format

Submitted data are extracted and transformed into a standardised format, allowing single study analysis, the generation of a study report and, visualisation of summary study information on WWARN Explorer. The transformed data is stored in a Data Repository for future pooling with other datasets and meta-analyses, provided specific approval is given by the data contributor.

4.1 WWARN Pharmacology Dictionary

The WWARN pharmacology dictionary contains the variables required for generating the WWARN pharmacology outputs. (See Annex A)

4.2 Database structure

The WWARN pharmacology dictionary is arranged in five tables linked by a unique patient identifier. The tables, with examples of component variables, are:

- I. **Subject** e.g. patient age, weight, gender
- II. **Treatment** e.g. generic name, manufacturer, dose (in mg) and day/date and time of each dose administered
- III. **Concentration** e.g. name of antimalarial drug (and /or metabolite) measured, sample matrix, units of measure, concentration result, day, date and time that the sample was taken (see Table 1 below)
- IV. **Endpoints** e.g. treatment outcome (See Clinical DMSAP; <http://www.wwarn.org/research/clinical/methodology>)
- V. **Study outcome** e.g. subject status at the end of follow-up (ACPR, treatment failure or lost to follow-up), PCR if available, (re-infection or recrudescence) and day/date of outcome

Submitted data are stored in the Data Repository within these five tables. Data within the clinical, molecular and *in vitro* tables could be linked to associated pharmacology data using the study and patient identifiers.

Each line in a table is one event with patient ID and event date. The Subject Table shows one line per patient. The Concentration Table may show one line per patient for a single concentration; if the drug/metabolite concentration has been measured on more than one occasion, more than one line per patient is present. The sample Concentration Table shown in Table 1 has a line for each time point that the drug/metabolite concentration was measured.

sid	pid	cdate	ctime	matrix	units	concentration
SEACAT241	2	31-Oct-08	7:38	plasma	ng/ml	0
SEACAT241	2	31-Oct-08	14:00	plasma	ng/ml	4000
SEACAT241	2	31-Oct-08	16:00	plasma	ng/ml	3490
SEACAT241	2	31-Oct-08	22:00	plasma	ng/ml	8730
SEACAT241	2	01-Nov-08	8:01	plasma	ng/ml	5280
SEACAT241	2	01-Nov-08	14:00	plasma	ng/ml	12200
SEACAT241	2	01-Nov-08	20:00	plasma	ng/ml	7310
SEACAT241	2	02-Nov-08	2:00	plasma	ng/ml	13200
SEACAT241	2	02-Nov-08	8:01	plasma	ng/ml	10300
SEACAT241	2	02-Nov-08	14:00	plasma	ng/ml	10300
SEACAT241	2	02-Nov-08	19:59	plasma	ng/ml	8940
SEACAT241	2	02-Nov-08	23:00	plasma	ng/ml	15200
SEACAT241	2	03-Nov-08	0:00	plasma	ng/ml	16700
SEACAT241	3	31-Oct-08	7:42	plasma	ng/ml	0
SEACAT241	3	31-Oct-08	14:04	plasma	ng/ml	4170
SEACAT241	3	31-Oct-08	16:04	plasma	ng/ml	3310
SEACAT241	3	31-Oct-08	22:04	plasma	ng/ml	8670
SEACAT241	3	01-Nov-08	8:04	plasma	ng/ml	3870
SEACAT241	3	01-Nov-08	14:04	plasma	ng/ml	6710

Table 1: Example of WWARN antimalarial drug concentration table

4.3 Data transformation and extraction

Source data may be presented as flat files, with one line per patient, or multiple relational database tables. The extraction process transforms all source datasets into a common standard format. Variables from the source dataset, equivalent to variables in the WWARN Pharmacology Dictionary, are extracted and imported into one of the five tables. An audit trail records and saves the complete data extraction and transformation process (see Section 7. Methods). Once transformed, the data submitter or assigned administrators may download the derived dataset for offline analysis.

5. Data cleaning

Data are checked for **inconsistencies**, **unexpected values** and **missing values**. If identified, these values are fed back to the data contributor, along with the patient

identifier, for possible validation, explanation or correction from source documents. Resubmitted, validated, corrected or additional values will be used to update the Data Repository. If corrections cannot be made, the inconsistencies and unexpected results are transformed to missing values.

5.1 Missing values on essential variables

The following variables are checked for missing values and a query generated for the submitter.

- I. Generic treatment name, dose (mg/kg) and day/date and time of each dose administered
- II. Age and weight
- III. Concentration result, date and time
- IV. Study treatment outcome and day of treatment outcome assessment

6. Deviation definitions

See Clinical DM_SAP at <http://www.wwarn.org/research/clinical/methodology>.

7. Methods

7.1 Mapping data variables to the WWARN pharmacology data format

Table 2 shows the data variables required for the WWARN Explorer (<http://www.wwarn.org/resistance/explorer-intro>) Pharmacology outputs.

MAPPING PK DATASETS TO THE WWARN FORMAT				
STUDY TITLE:				
WWARN VARIABLE NAME	DATATYPE	EXPLANATION	DATASET VARIABLE NAME	DATATYPE
sid	String	Random WWARN generated ID		
pid	string	Unique patient identifier		
study	string	Name of country [year study started]		
site	string	Study site		

gender	string	M;F		
weight	num	in kilograms		
age	num	years		
Under5	num	Number of participants less than 5 years		
arm	string	Treatment Group allocated		
reasontrt	string	Malaria, IPT, HV		
day	num	Day from first dose of antimalarial administration		
date	date	Date sample taken		
time	time	Time sample taken		
abstime	num	If no day or date recorded		
protocoltime	num	If no day or date recorded		
drugmet	string	Name of drug or metabolite concentration measured		
matrix	string	Sample matrix		
units	string	Units of concentration measured		
concentration	num	Concentration of drug/metabolite measured		
regimen	string	Antimalarial regimen		
route	string	PO, IM, IV, PR		
target dose	num	Recommended dose mg/kg		
num tabs	num	Number of tabs		
dosemg/kg	num	Derived from dose (mg) / body weight (kg)		
LOQ	num	Level of quantification		
BLOQ	0/1	Concentrations recorded as below the level of quantification (see 7.6 below)		
Ploutcome	string	Treatment outcome as recorded by the PI		
Ploutcomeday	num	Last day of follow up		
Plgenotype	string	PCR result		

woutcomeday	num	Last day of follow up generated by WWARN clinical module		
woutcomeadj	num	Outcome generated by WWARN clinical module PCR adjusted		
woutcomeunadj	num	Outcome generated by WWARN clinical module unadjusted		
normratio	num	Target dose mg/kg / dose mg/kg		
calcconc	num	Calculated concentration, for BLOQ, a value of 50% of the LOQ will be allocated		
normcalcconc	num	Concentration* normratio		
D1date	date	Date of first dose of antimalarial administered		
D1time	time	Time of first dose of antimalarial administered		
group	string	Study group allocated to if applicable		

Table 2: Required data variables for output to WWARN Explorer

For each dataset a “Mapping PK datasets to the WWARN format” table will be generated, stored in the study folder and accessible on entering the Data Submission portal on the WWARN website, providing a reference showing how contributed data variables have been mapped to the WWARN format.

Variables from the source data will be extracted into a Microsoft (MS) Excel or csv file and saved in the appropriate study folder as “[WWARN id]_PK_DataExtract”.

For each study, a MS Access database will be created and saved, in the appropriate study folder, as “[WWARN id]_PKDB”.

The csv data file [WWARN id]_PK_DataExtract will be imported into [WWARN id]_PKDB as a new table.

A simple query, with as many of the essential variables as are available, will be run to create the standard WWARN pharmacology module table for output to WWARN Explorer.

7.2 Curation

MS Access queries will be used, as necessary, to map input variable labels to the WWARN variable name and a record of the query SQL kept for audit purposes.

Example 1: "Original data variable name = "inclnum" WWARN format "pid" -

Example 2 : SELECT "LUM_Uganda" AS sid, clinical.inclnum AS pid, clinical.[gender], clinical.[weight], (([d0]-[birth])/365.25 AS age, clinical.[danger], clinical.monoinf AS pfmonointection, clinical.[illness], clinical.[pregn], clinical.[arm], "" AS smoke, "" AS ethnic, "Uganda" AS country, "1" AS malaria FROM clinical WHERE (((clinical.[PK])=1));

7.3 Generating new variables

Data relating to the study is derived from the relevant publication or SSQ and a record for each subject generated in the MS Access database.

For example, if the sample matrix has been recorded in the SSQ as "capillary plasma", a new variable will be generated in a new column: ["matrix:"capillary plasma"] inserted in the design view of an MS Access query.

```
SELECT concentrations_LUMUganda.[sid], concentrations_LUMUganda.[pid],
concentrations_LUMUganda.[day], concentrations_LUMUganda.[date],
concentrations_LUMUganda.[time], "" AS abstime,
concentrations_LUMUganda.[protocolttime], concentrations_LUMUganda.[matrix],
AS "capillary plasma" concentrations_LUMUganda.[concentration],
concentrations_LUMUganda.[units], [concentration]*1000 AS concentration1,
"ng/ml" AS units1
FROM concentrations_LUMUganda
WHERE ((([concentration]*1000) Is Not Null));
```

7.4 Variables not recorded in the dataset, publication or SSQ

A WWARN Data Manager will request any missing variables needed for the WWARN Explorer pharmacology output. If the data is not known or was not recorded at the time of the study, the missing variable will be populated with "" or "."

7.5 Generating age categories

The following age categories will be used in the summary outputs visible on Explorer:

<1 year agecat 1

1-4 years agecat 2

5-12 years agecat 3

>12 years agecat 4

7.6 Below the limit of quantification (BLOQ)

The method used to standardise concentrations reported as “BLOQ” or “missing” in data contributed for the WWARN Explorer is described below:

- I. The defined variable for “BLOQ” is 1,0
- II. Concentrations recorded as zero or values less than the reported level of quantification (LOQ) will be allocated a value of 1; concentrations above the reported LOQ will be allocated a value of 0
- III. Missing values will be treated as missing “”
- IV. A new variable will be generated “calcconc” (calculated concentration); for values above the LOQ there will be no adjustment; for values below the LOQ a value of 50% of the LOQ will be allocated.
- V. All concentrations recorded with a numeric value will be included in the box /scatter plots; a table reporting the n (%) of values BLOQ for each group will be inserted into the box graphs.

7.7 Units of measurement

All units of measurement will be converted to a standard unit for each drug (see Table 3). Concentrations recorded as Mmol will be converted to ng/ml or µg/ml.

Drug/metabolite	Abbreviation	Units
Amodiaquine	AQ	ng/ml
Artemether	AM	ng/ml
Artemisinin	ART	ng/ml
Artesunate	AS	ng/ml
Atovaquone	ATQ	µg/ml
Carboxymefloquine	MQm	ng/ml
Carboxyprimaquone	CPQ	ng/ml
Clindamycin	CL	µg/ml

Chloroquine	CQ	ng/ml
Cycloguanil	CG	ng/ml
Dihydroartemisinin	DHA	ng/ml
Desethyl-amodiaquine	AQm	ng/ml
Desbutyl-lumefantrine	LUMm	ng/ml
Doxycycline	DOX	µg/ml
Lumefantrine	LUM	ng/ml
Mefloquine	MQ	ng/ml
Naphroquine	NQ	µg/ml
Piperaquine	PQP	ng/ml
Primaquine	PQ	ng/ml
Proguanil	PG	ng/ml
Pyrimethamine	PYR	ng/ml
Pyronaridine	PYN	ng/ml
Quinine	QN	ng/ml
Sulfadoxine	SUL	µg/ml

Table 3: Standard units of measurement for antimalarial drugs

Mmol/L.min = mmol*molecular weight/L.min

Drug/metabolite	Molecular weight
Artemether	298.4
Amodiaquine	355.9
Artemisinin	282.3
Artesunate	384.4
Atovaquone	366.8
Clindamycin	425.0
Chloroquine	319.9
Dihydroartemisinin	284.4
Doxycycline	444.4
Lumefantrine	528.9
Mefloquine	378.3

Proguanil	253.7
Primaquine	259.4
Piperaquine	535.5
Sulfadoxine	310.3
Quinine	324.4
Pyrimethamine	248.7

Table 4: Molecular weights used to standardize measurement of antimalarial drug/metabolite concentrations

<http://chem.sis.nlm.nih.gov/chemidplus/ProxyServlet?objectHandle=Search&actionHandle=clear&nextPage=chemidheavy.jsp>

7.4 Calculating normalised dose

To distinguish true differences in pharmacokinetic parameters from differences in administered dose, the following method will be used to calculate normalised dose:

Recommended dose (mg/kg)/actual dose (mg/kg)*concentration

Drug/metabolite	Recommended total dose (range) mg/kg
Artemether	10.2 (8.4-24) mg/kg
Amodiaquine	30 (22.5-45) mg/kg
Artesunate IV (per dose)	2.4 mg/kg
Artesunate oral	12 (6-30) mg/kg
Atovaquone	45 mg/kg
Clindamycin	140 mg/kg
Chloroquine	75 mg/kg
Dihydroartemisinin	12 (6-300) mg/kg
Doxycycline	24.5 mg/kg
Lumefantrine	72 (60-90) mg/kg
Mefloquine	35 mg/kg
Proguanil	18 mg/kg
Primaquine	0.25 mg/kg
Piperaquine	54 (48-78) mg/kg
Sulfadoxine	25 (25-70) mg/kg
Quinine	10 mg/kg
Pyrimethamine	1.25 (1.25-3.5) mg/kg

http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf

8. Summary Statistics

Once a dataset has been transformed to the WWARN standardised format, the data table is imported into STATA and a standard do-file run which will produce the following tables and graphs for visualization on explorer and for inclusion in the study report:

1. **A summary of the study** including the total number of participants, day 7 drug/metabolite concentration, by treatment outcome and treatment allocation.
2. **Information on drug/metabolite concentrations** including number of samples, sample matrix and units of measurement
3. **Assay methods**
4. **Any biologically implausible concentrations** excluded from the final analysis
5. **Data description, graphs and tables** presenting day 7 drug/metabolite concentration:
 - 5.1. by treatment outcome;
 - 5.2. by treatment allocation;
 - 5.3. by treatment outcome and treatment allocation;
 - 5.4. by age category;
 - 5.5. normalised to recommended dose by age category;
 - 5.6. by treatment outcome and age category;
 - 5.7. by treatment allocation and age category; and
 - 5.8. By site.
6. **Scatter plots** of all observed concentrations over time by treatment outcome.

The WWARN Data Manager will communicate any problems encountered during curation – for example, merging files (e.g. PK samples with different unique pids to the clinical data), biologically implausible results, coded/abbreviated variables not explained in a data dictionary/SSQ - with the data submitter to resolve queries or obtain missing data.

The summary data will be compared to any data reported in publications or manuscripts. Any discrepancies will be communicated to the data submitter.

9. Study Report

A study report is produced from the MS Access database and sent to the data contributor for validation of results.

The report will include all graphs and tables visible on explorer and a list of individual patient treatment outcomes.

10. WWARN Explorer

The [WWARN Explorer](#) is an online, open-access tool which allows users to perform custom queries and visualise the results using dynamic interactive maps.

10.1 WWARN Explorer outputs

WWARN Explorer displays the following outputs per study:

- I. Basic study information: study title, study site, country, year, number of samples, sample matrix, day 7 drug and/or metabolite concentration by treatment outcome and (treatment allocation)
- II. Patient disposition: Number of patients, day 7 concentrations, lost to follow-up, re-infections, ACPR and recrudescence.
- III. Box graphs and tables of day 7 drug/metabolite concentration by treatment outcome, treatment allocation, age category and site.
- IV. Scatter plots of all observed drug and/or metabolite concentrations over time, by treatment outcome
- V. Further details include:
 - Treatment regimen
 - Sampling scheme
 - Target dose
 - Assay method
 - Patient demographics
 - Dependant on data submitted, additional analyses may include box plots and tables showing day 7 concentration by age category, normalised concentration by age category, concentration by treatment outcome and age (see 8.5)
 - Acknowledgements
 - Links to publications

10.2 Approval of results

Data submitters are able to review results obtained from the WWARN Pharmacology DMSAP in a comprehensive Study Report. The submitter's approval is required for study outputs to become available on WWARN Explorer. Data submitters may request screenshots of their data, as they will appear on WWARN Explorer, before approval.

11. DMSAP versioning

The Pharmacology DMSAP has five main elements:

11.1 A set of variables (the Pharmacology Dictionary)

The variables imported from the data submitters - the pharmacology dictionary - define the types of analysis that will be possible with the dataset. Version 1.0 of the Pharmacology DMSAP focuses on the essential variables necessary to explore the association of drug concentrations with treatment outcome. Additional variables may be included in future versions of the pharmacology dictionary and DMSAP.

11.2 Management of missing values

Missing values are omitted from the analyses by version 1.0 of the Pharmacology DMSAP. In future versions, multiple imputations or other strategies may be applied to minimise data loss.

11.3 Outputs

The outputs from version 1.0 are described in the Study Report (Section 9) and the WWARN Explorer (Section 10). New outputs under consideration for future versions include:

- Non compartmental analysis (NCA)
- Including moving averages in the scatter plots
- Allowing multi-study visualisations, allowing data from one study to be plotted against other studies in the WWARN data repository.

11.4 Integration of cross modular integration into a common platform

In addition to clinical and pharmacology data, some studies have *in vitro* and/or molecular data recorded on individual patients presenting the possibility for cross-modular analyses. Work is ongoing so that future versions can report cross modular

analysis, allowing the association of drug concentrations with treatment outcome, adjusted by molecular or *in vitro* level of resistance, to be explored.

11.5 Pooled analysis of individual patient data

Pooling individual datasets from several clinical trials conducted in different locations and at different times should facilitate defining thresholds for the pharmacokinetic parameters that are associated with therapeutic response, and determining patient factors that influence drug concentrations. Informing optimal dosing in key target populations could contribute to delaying antimalarial resistance. The first pooled pharmacokinetic analysis is takes place in 2011; the methods will be presented in a separate Statistical Analysis Plan.

12. Conclusion

This data management and statistical analytical plan is an evolving document that aims to be in line with current Pharmacology practice. In situations where there is no clear guidance, WWARN has used an approach based on advice from a broad group of experts. WWARN encourages feedback on the DMSAP methodology and will endeavour to incorporate suggestions into future versions or bring major issues into a wider forum for open discussion. Comments and suggestions should be directed to pharmacology@wwarn.org.

13. References

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2679050/?tool=pubmed>

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

<http://www.sapmaker.com/>

<http://www.medicinemigo.com/medical-research/clinical-trials/Statistical-Analysis-Plan-For-Clinical-Trials.html>

14. Annexes

14.1 Annex A: Pharmacology dictionary

Baseline patient data:

- Unique patient identifier
- Site
- Date of inclusion
- Patient age or date of birth
- Weight
- Age
- Gender
- Treatment/group allocation

Treatment:

- Generic name treatment received
- Dose (in mg) of each dose administered
- Day, date and time of each dose administered
- Route of administration
- Treatment regimen

Concentration data:

- Name drug/metabolite measured taken
- Sample matrix
- Units of measure
- Day, date, time, protocol time samples were taken
- Concentration result
- Upper(ULOQ) and Lower Limits of Quantification (LLOQ)

Outcome:

- WWARN generated day of measurement
- WWARN generated treatment outcome (PCR adjusted and unadjusted)
(<http://www.wwarn.org/research/clinical/methodology>)
- Study day of treatment outcome
- Study treatment outcome
- Study PCR if available