Data handling and analysis convention ECG data (malaria)
V1.0

WorldWide Antimalarial Resistance Network (WWARN)

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Version History

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1. Scope

The purpose of this document is to present a clear and transparent methodology by which WWARN curates electrocardiographic (ECG) and other cardiac data from antimalarial efficacy and safety studies (including pharmacokinetic/pharmacodynamic studies) contributed to the WWARN repository.

2. Introduction

The cardiotoxicity of antimalarial medicines has received renewed interest in recent years. Quinoline antimalarials and structurally-related compounds have long been associated with cardiovascular adverse effects and are known to prolong the QT interval of the surface ECG. A prolonged corrected QT interval (QTc) is an indicator of increased risk of Torsade de Pointes (TdP), a polymorphic ventricular tachycardia which can degenerate in some cases into ventricular fibrillation and lead to sudden cardiac death. Because drug-induced TdP and other life-threatening ventricular tachyarrhythmias are very rare events, many individual patient data (IPD) from drug trials are required to study outlying participants, i.e. those who develop abnormal ECG intervals. This will help to identify risk factors, including drug administration, in those individual patients. Furthermore, as acute malaria illness is likely to have independent effects on the QT interval, the comparison of data from healthy volunteers and patients with malaria can contribute to further understanding the relationship between QT prolongation (and other cardiac adverse effects) and drug and disease effects.

WWARN has produced guidelines for investigational teams for the collection of standard 12-lead ECG data in antimalarial clinical trials, found in the WWARN Malaria Clinical Trials Toolkit. This is expected to contribute to capacity building for malaria clinical trials and to harmonize data collection methods which should enhance the ability to meta-analyse data from clinical trials. The presented methodology here aims to transform data obtained 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. Overall, this will be used to inform the cardiac risk assessment for antimalarial drugs.

3. Data curation

3.1 ECG recording procedure

There is considerable heterogeneity of QT interval recording procedures which affects the accuracy of the recording and resulting interval values. Therefore, information on the methodology (Table 1) is important when comparing studies.

ECG recording method (at study level): The clinical ECG database is typically derived from the collection of 12-lead surface ECGs, although other techniques might be used. These include 1- and 3-lead ECG recordings and sometimes Holter monitor recordings (i.e. continuous ECG recordings using 3 leads) but recordings using 1-3 leads are not acceptable for QT assessment. Management of data from Holter monitoring is not addressed in this document.

Equipment (at study level): The quality of the ECG data can depend on the use of modern equipment with the capacity for digital signal processing.

Calibration (at study level): The ECG is a plot of voltage on the vertical axis against time on the horizontal axis, recorded on special ECG graph paper that is divided into 1 mm^2 grid-like boxes. For paper ECGs only, paper speed and voltage therefore need to be calibrated to ensure accuracy of measurements. The ECG paper speed is 25 mm/sec in ordinary clinical situations but can be increased to 50 mm/sec to better define waveforms which enables more accurate measurement of ECG intervals. Similarly, the voltage is ordinarily set to 10 mm/mV but on occasion, particularly when the waveforms are small or very large, it is increased or reduced respectively.

Preparation of recording technique (at study level): The lead placement and patient position should be specified. Consistency of operator technique (e.g. skin preparation and lead placement) also influence ECG data quality.

Reading technique (at study level): Several methods for measuring ECG intervals have been used in clinical trials. The method chosen will depend on the level of precision appropriate for a given trial. At present, the gold standard for regulatory trials would usually involve the measurement by a few skilled blind readers (whether or not assisted by computer) who may operate from a centralised ECG laboratory (manual measurement and calculation). The level of agreement between the ECG readers should be determined. In more pragmatic trials, ECG reading by machine (automatic measurement and calculation) has a role in the rapid assessment of ECGs for safety, although should always be coupled with manually read intervals.

Lead choice for measurement (at study or patient level) and review procedure (at study level): While the most appropriate ECG lead(s) and methodology to measure the QT interval have not been established and a variety of methods exist (i.e. threshold, tangent, superimposed median beat, automated global median beat, longest QT method, and others), precordial leads and lead II are often used for the measurement. These details should be specified, and a consistent approach should be used for a given trial.

Table 1. Sample variables describing ECG methodology

Variable	WWARN map	Typical unit/options	Level[2]
Day of recording	obsdate	[DD/MM/YYYY]	Patient
Time of recording		[hh:mm:ss]	Patient
Reading flow		Single read, single over-read or double read	Study
Reading method	review method	Tangent method or median overlapped method	Study
Reading technique	ecgreadtype	Semi-automated, fully manual, manual with adjudication (manual over-read / computer-assisted) or combination of these. NB These options can be variable-specific rather than study-specific (e.g. heart rate [HR] might be derived from machine read while QT could be read manually) Some trials adopt the method of having every ECG read automatically, then a proportion checked manually, e.g. every 5th ECG. Not sure what category this would come under	Study
Reader		On site by non-cardiologist, on site by cardiologist, centralised laboratory, combination (on site and centralised)	Study
Type of recording		Paper and/or digital	Study
ECG device	ecgmachinespecification	Options are listed in Table 2 and 'other'. NB Studies may use a different device at different field sites	Study
Patient position	patient position	Lying, supine or non-resting, or not documented	Study
> 5 min		y/n, or not documented	Study
Lead choice	leadchoice	I, II, III, AVR, AVL, AVF, V1, V2, V3, V4, V5, V6 or overlapped median beat, or lead showing 'clearest' complexes[3]	Patient
Paper speed[1]	paperspeed	mm/sec	Study
Voltage		mm/mV	Study

[1] Only relevant if type of recording is paper
[2] Study level can be either Study or Patient but an override should be possible (i.e. if study level data is different for one patient)
[3] Sometimes reports do not specific which leads were clearest thus selected for measurement and sometimes several complexes at several leads were measured and median is taken, see Isbister GK, Page CB. Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice. Br J Clin Pharmacol. 2013;76(1):48-57.

Table 2. Commonly used ECG devices

Manufacturer	Model ECG
Mortara	ELI 150Rx
	ELI 250Rx
	ELI 150c
	ELI 250c
	ELI 230
	ELI 280
Cardionics	Cartouch
NihonKohden	ECG-1250K
Schiller	Cardiovit AT-10 Plus
	Cardiovit AT-102 Plus
	Cardiovit AT-2 Plus
	Cardiovit FT-1
	Cardiovit MS-2010
	Cardiovit MS-2015
GE Healthcare	MAC 800
	MAC 2000
	MAC 3500
	MAC 5500 HD

Curation remarks

If not otherwise specified, it should be assumed that study level data applies for all patients (e.g. paper speed/ voltage). If ECGs were recorded in different positions with corresponding time data, the data recorded in supine position should be mapped.

3.2 Normal sinus rhythm and normal intervals

A normal heart rhythm is called "normal sinus rhythm" with a heart rate between 50 and 100 beats per minute (in adults) and a normal impulse formation (P wave). Children have different normal. In the absence of any abnormalities, a completely normal rhythm will also have a normal PR interval (0.12-0.22 seconds), a normal QRS interval (0.05-0.12 seconds), a normal QT interval (0.15-0.50 seconds, more details see below). Also, all the waveforms must be of a normal shape with no ST changes or QT dispersion (the difference between the longest, QTmax, and the shortest, QTmin, QT intervals within a 12-lead ECG[1]).

Variables used to characterise the sinus rhythm are listed in Table 3. Any abnormality in these intervals indicates possible pathology. RR is important for QTc calculation but may be measured differently, for example immediately before the measured QT interval, as an average value or back calculated from HR.

[1] Sahu P, Lim PO, Rana BS, Struthers AD. QT dispersion in medicine: electrophysiological holy grail or fool's gold? QJM. 2000 Jul;93(7):425-31

Table 3. Variables describing normal intervals

Variable	WWARN map	Typical unit	Level
Heart rate (HR)	heartrate	bpm	Patient
RR interval (time between beats)	rrinterval	ms	Patient
PR interval	printerval	ms	Patient
QRS interval	qrsinterval	ms	Patient
QT interval	→ see below		
T wave height[1]		mm	Patient
ECG code(s) [‡]		list	Patient

[1] Amplitude in limb / precordial leads. NB T wave height is usually not reported (only described in statements)
[2] Controlled vocabulary in Appendix 1: Charte_Cardiabase.pdf

Curation remarks

Heart rate and RR interval are interchangeable. Ideally, heart rate and/or RR interval and the uncorrected QT interval are provided. In cases where only corrected QT intervals are provided, the QT interval can be back-calculated during the analysis stage if heart rate and/or RR interval and the correction method are known.

All information on any ECG abnormalities such as "bradycardia" (= slow heart rate, generally < 60 beats per minute, BPM, in adults), "tachycardia" (= fast hear rate, generally > 100BPM in adults), "dysrhythmia" (any rhythm abnormality), "sinus arrythmia" (= normal rhythm with heart rate variation >10 beats per minute, common in children, young adults and athletic individuals) and morphological changes (such as "ST elevation", ST depression, T wave inversion) should be captured. Morphological changes in the T-U complex are of particular interest in studies assessing cardiac safety of drugs. While the predictive value of changes in ECG morphology, such as the development of U waves (Figure 1), has not been established, information should be captured on changes in T and U wave morphologies. Typical findings could be "flat", "inverted" or "very tall" T wave, and "prominent" or "inverted" U wave. A list of the controlled vocabulary can be found in Appendix 1.

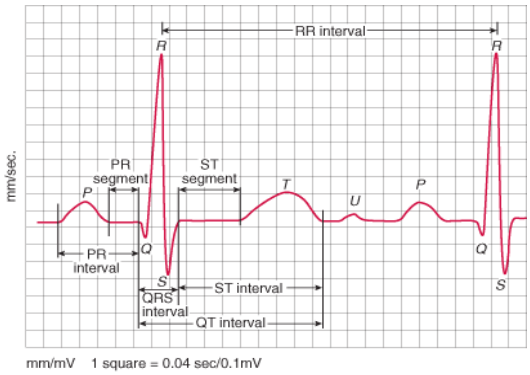

Figure 1. Waves of the ECG[2]

In children, normal heart rate ranges are much higher. Children aged 0-1 year have a normal range of 90-170 beats per minute, children 2-5 years 80-140 beats per minute, children 6-11 years up 60-130 beats per minute and children 12-17 up to 50-120 beats per minute.

[2] Taken from: https://lifeinthefastlane.com/wp-content/uploads/2011/01/waves-of-the-ecg.gif.

3.3 QT interval

The QT interval represents the duration of ventricular depolarisation and subsequent repolarisation and is measured from the beginning of the QRS complex to the end of the T wave. A delay in cardiac repolarisation creates an electrophysiological environment that favours the development of cardiac arrhythmias, most clearly TdP, but possibly other ventricular tachyarrhythmias as well. TdP can degenerate into ventricular fibrillation, leading to sudden death. While the degree of QT prolongation is recognised as an imperfect biomarker for proarrhythmic risk, in general there is a qualitative relationship between QT prolongation and the risk of TdP, especially for drugs that cause substantial prolongation of the QT interval. Therefore, the QT interval is an important variable to analyse when assessing drug-induced cardiotoxicity.

Because of its inverse relationship to heart rate, the measured QT interval is routinely corrected by means of various formulae to a less heart rate dependent value known as the QTc interval. It is not clear, however, whether arrhythmia development is more closely related to an increase in the absolute QT interval or QTc. Most drugs that have caused TdP clearly increase both the absolute QT and the QTc.

Various correction formulae have been suggested, of which Bazett's and Fridericia's corrections are the most widely used. Usual QT correction formulae tend to "overcorrect" (QTc appears longer) at fast heart rates and "undercorrect" (QTc appears shorter) at normal or slow heart rates. These factors should be taken into account when interpreting results from ECG safety studies conducted in malaria patients as acute malaria can cause fever, tachycardia and anorexia, all leading to activation of the sympathetic nervous system and shortening of the QT interval.
Because the best correction approach is a subject of controversy, uncorrected QT and RR interval data, heart rate data, as well as QT interval data corrected using Bazett's and Fridericia's corrections should ideally be captured for each study, in addition to QT interval data corrected using any other formulae. See Table 4 for a summary of variables describing the QT interval.

Table 4. Variables describing QT interval

Variable	WWARN map	Typical unit	Level
QT interval	qt	ms	Patient
QTcB interval	qtcb	ms	Patient
QTcF interval	qtcf	ms	Patient
QTc interval with other correction		ms	Patient
QT correction method		free text[1]	Study

[1] Fridericia, Bazett, other: formula

<u>Curation remarks</u>

If QT interval plus heart rate and/or RR interval are available QTcF, QTcB, and any other correction can be calculated during analysis. Similarly, if only corrected QT intervals are provided, the QT interval can be back-calculated if heart rate and/or RR interval and the correction method are known. But if available both, the QT and the QTc, should be mapped.

3.4 Mapping ECG traces

In some cases, actual ECG traces (paper copies or digital ECGs) might be shared with WWARN. These will be stored. Ideally, they are labelled with study ID, patient ID, date and time of recording (HH:MM:SS) so that they may be matched to the appropriate WWARN curated dataset IDs.

3.5 Multiple ECGs per time-point and ECGs recorded at screening

Often multiple ECG replicates are recorded (the number can vary but is generally 3 or more), 30– 120 seconds apart, to account for inherent variability; each recording lasting 10 seconds[3]. The mean value is then used for calculations, e.g. of the change in QT interval. Ideally, the individual values are mapped to maintain the information on the standard deviation. A normal ECG can be an inclusion criterion and so studies might report ECG data recorded hours or even days before the first dose of study drug is administered.

If only a mean or median value of a triplicate is available then this value will be mapped and retained in the repository; if all three values are available in addition to an aggregated value, the three values will be mapped and retained in the repository; if all three values are available but there is no aggregated value, they will be mapped and retained in the repository. If only aggregate data are available, it is mapped as such.

If the recording time of a triplicate falls within the same minute (and no seconds are provided), a dummy time (+1 second) will be added to ensure all three recordings are retained as each result needs a unique time for the repository.

In line with other variables, everything occurring prior to the first dose of study drug will be assigned negative relative times.

[3] Clinical Data Interchange Standards Consortium (CDISC) Therapeutic Area Data Standards User Guide for QT Studies. Version 1.0 (Provisional) 2014.