

Collection of ECG data in antimalarial clinical trials v1.2

Guidance document

WorldWide Antimalarial Resistance Network (WWARN)



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1. Purpose/scope

While a protocol should describe which ECG data are to be collected and when for a particular clinical trial, it is important that sites understand the rationale and best practice for collecting such data to ensure robust and relevant trial results. This document provides guidance for a general process for collecting the standard 12-lead clinical trial ECG data, to support any trial-specific instructions. It does not include ambulatory (e.g. Holter) ECGs. The document, which is not prescriptive, may be adapted by sites as required.

2. Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
CRF	Case Record Forms
ECG	Electrocardiograph/electrocardiogram
GCP	Good Clinical Practice
ISF	Investigator Site File
PI	Principal Investigator
PK	Pharmacokinetic
PR	Interval from the beginning of the P wave to the start of the QRS complex
QTc	Corrected QT interval measure (e.g. QTcB, QTcF – see below)
RR	Interval between R wave and next R wave
SOP	Standard Operating Procedure

3. Definitions

Cardiac arrhythmia: An abnormal heart rhythm due to problems with the heart's electrical conduction. The heart may beat irregularly, too fast (tachycardia) or too slow (bradycardia), and while these abnormalities may or may not be experienced as symptoms, at their most severe they may be fatal.

Electrocardiogram (ECG): A graph (called a trace) recorded on paper and/or electronically that represents the heart's electrical activity by magnifying its small electrical impulses. Deviations from what is considered a normal ECG may or may not be clinically relevant. Electrodes are attached externally to the patient which allow the electrical activity of leads (imaginary line between two ECG electrodes) to be measured. A standard 12-lead ECG (3 limb leads, 3 augmented limb leads and 6 precordial leads) only requires 10 electrodes as some leads share electrodes. Other leads may be used for more specialised purposes. *See later figure for electrode placement.*

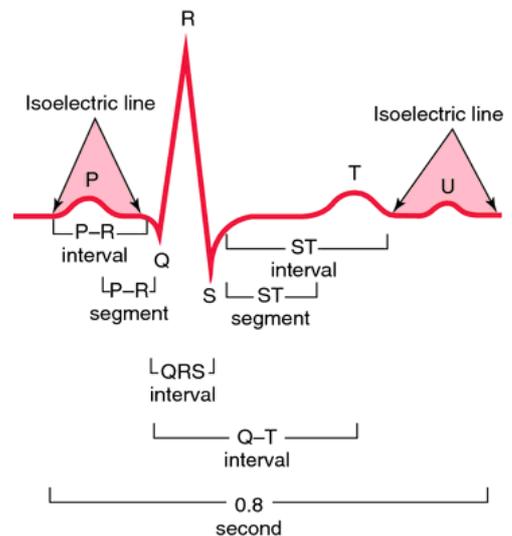


Figure 1. Electrocardiogram.

Essential Documents: Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.¹

Investigator Site File (ISF): Files of Essential Documents held by the Investigator. NB on occasion sites may also hold the Sponsor's Essential Documents, where the Principal Investigator (PI) assumes a Sponsor-investigator role.

PK (pharmacokinetics): The study of a drug's absorption, distribution, metabolism, and excretion in the body.

QT interval: One of several intervals measured in an ECG (see **Error! Reference source not found.**). The time between the start of the Q wave and end of the T wave in the heart's electrical cycle, measured in seconds or milliseconds. The QT interval is determined by specific leads of an ECG machine and may be an unreliable or unconfirmed measure. Therefore, what an ECG machine reports can vary from what a cardiologist will determine by assessing the same trace.

QT prolongation: A congenital or acquired lengthening of the QT interval, leading to an increased risk of ventricular tachyarrhythmia (including torsades de pointes, a potentially fatal abnormal heart rhythm). QT interval in healthy subject depends on age, gender and mainly heart rate. Hence the prolongation of QT interval above 500msec is to be considered as abnormal. All other recommendations regarding acceptable ranges of repolarisation duration are based on QTc (see below). NB QT prolongation is one of many possible deviations from a normal cardiac function, therefore other measurements are important components reported as part of an ECG trace.

QTc: As the QT interval is dependent on the heart rate it is corrected (the 'c') to increase the possibility of detecting patients at increased risk of arrhythmia. There are a number of different methods, including Bazett's (QTcB) and Fridericia's (QTcF) formulas. Both Fredericia and Bazett corrected QT intervals should be calculated to assess which correction best removes the rate dependence of the adjusted QT interval.

4. Associated forms

None

5. Procedure

5.1 Background and rationale for collecting ECG data in antimalarial clinical trials

Cardiac safety of antimalarials to date

Quinolines (e.g. quinine) and related compounds have clinically significant cardiovascular effects. Drugs in this class can exacerbate malaria-associated orthostatic hypotension; and several have been shown to delay ventricular depolarization slightly (Class 1c effect). This results in widening of the QRS complex; but only quinidine and halofantrine have clinically significant effects on ventricular repolarization (Class 3 effect). Both drugs cause potentially dangerous QTc prolongation, and halofantrine has been associated with sudden death. The parenteral quinoline formulations (chloroquine, quinine, and quinidine) are predictably hypotensive when injected rapidly, and cardiovascular collapse can occur with self-poisoning.² Other antimalarials such as piperazine usually prolong the QTc interval at therapeutic doses (mainly after the last dose of treatment) but without symptoms or evidence of cardiovascular toxicity in treatment trials.^{2,3} A systematic review in 2018 concluded that dihydroartemisinin-piperazine was associated with a low risk of sudden unexplained death but that this was not higher than the baseline rate of sudden cardiac death.⁴ In addition, artesunate may cause transient non-clinically significant ECG abnormalities and artesunate-amodiaquine and mefloquine have been associated with arrhythmias and/or bradycardias. The latter are therefore contraindicated (not recommended) for patients with a history of QT prolongation or other cardiac risk factors, and in patients that are taking other drugs with similar effects or that may increase antimalarial levels.²

It is important to note that malaria itself may also adversely affect the QT interval. There are consistent differences in cardiovascular state between acute illness in malaria and recovery that prolong the QT interval and have been misinterpreted as resulting from antimalarial cardiotoxicity.^{2,3}

Monitoring participants for cardiac safety

The extent of monitoring for adverse events (AEs) to detect cardiac adverse drug reactions (ADRs) in clinical trials will depend on the phase of trial or specific safety concerns about a given antimalarial drug. In general, once a drug not intended to treat arrhythmias has been assessed in laboratory or animal studies as suitable for introduction into human clinical trials, ECG changes (such as QT prolongation) are important to quantify in early phase trials. Continued evaluation of changes may also be important in later phase trials, even after licensing, if there are gaps in knowledge about a drug's potential cardiac effects or if available data suggest cause for concern. Sometimes ECGs will be the prime focus of a trial, such as in so-called thorough QT/QTc studies (TQT). According to the FDA, all new drugs with systemic bioavailability (irrespective of preclinical profile) should have a thorough QTc/QT trial performed.⁵ In clinical trials, a prolongation of QTc > 500 ms during therapy has been a threshold of particular concern.⁵

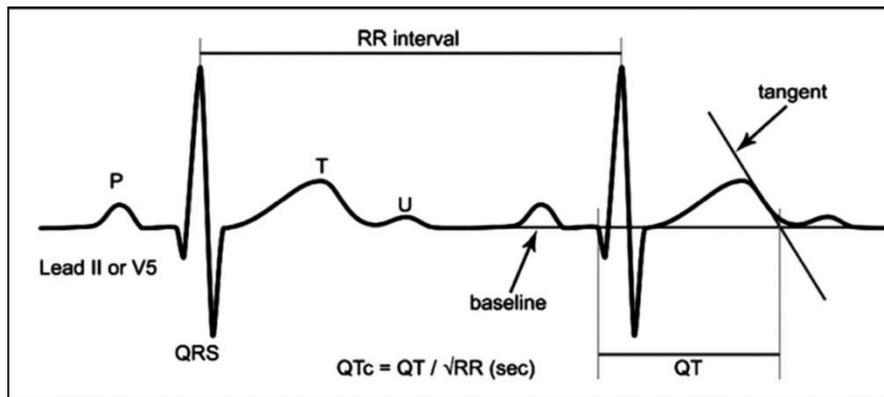


Figure 2: ECG interval measurements

The PR, QRS, QT, RR, HR, QTcB, QTcF intervals should be measured to identify any threshold of concern. The ECG reading methods and thresholds of concern should be pre-specified in the protocol and both Fredericia (QTcF) and Bazett (QTcB) corrected QT intervals calculated to assess which correction best removes the rate dependence of the adjusted QT interval.

General points about trial-design

ECGs are scheduled to achieve the trial's endpoints and should consider several factors:

- Matching what is known or anticipated about the pharmacokinetics (PK) of the drug, including the expected time of maximum drug concentration (C_{max}). Baseline ECGs are used as a reference to provide a pre-drug comparison. Scheduling further follow-up ECGs, after Day 7, may allow for interpretation of the data once initial malaria symptoms that may influence cardiac function have resolved (e.g. fever) and once drug concentrations are minimal.
- Sources of variability in ECG measurements such as QT intervals include gender, age, heart rate, position, autonomic tone, meals, menstrual cycle, time of day, illness, and technical issues. Given this considerable variability, ECGs should be conducted at rest and may need to be conducted in triplicate (typically 1 minute apart) to obtain average measures.
- All other procedures at the same time-point (e.g. blood draws, blood pressure measurements) should be scheduled after the ECG.

Risk of ventricular arrhythmia is increased by other factors such as heart disease (e.g. myocardial ischaemia, heart failure, atrial fibrillation), bradycardia (slow heart rate) or sinoatrial blocks, some diseases (e.g. hypothyroidism, hypoxia) and electrolyte imbalances (e.g. potassium, magnesium, calcium) as well as with Congenital Long QT syndrome. Numerous medicines have been associated with ECG changes; a list of medicines and clinical factors associated with prolonged QTc intervals and/or torsades de Pointes is available at www.crediblemeds.org. Therefore, aside from demographics (including gender, age, race), relevant data about a participant's medical history, concomitant medicines and laboratory assessments are important to also collect and consider when assessing ECG results.

Enquiring about other concurrent symptoms (e.g. fainting/syncope, palpitations, convulsions/seizures, and pounding/pain in the chest area) all also help in determining a diagnosis and relationship of the event to the trial drug of abnormal ECG results observed. For ECG abnormalities such as QT prolongation, correlation with **dose and concentration** of the trial drug in the blood at the time of an AE will be informative. **Concomitant medications** should be considered as contributory, alone or through a potential interaction with the trial drug, and the trial drug's concentrations may also be influenced by interactions or with food

(usually fat). **Food consumption** data are therefore also important considerations, as are the vital signs, laboratory assessments (e.g. blood potassium, magnesium and calcium), which may be influenced by underlying dehydration) other cardiac assessments (e.g. echocardiogram), and genotyping for cardiac ion channel mutations.

5.2 Planning for collecting ECGs in clinical trials

Staffing

The team should be staffed with suitably qualified and trained personnel who know the protocol, how to use the machines being used (including any specific labelling requirements), and how to upload data to a central database if necessary. Qualifications and training are documented in up to date CVs or training records as usual, ultimately stored in the Investigator Site File (ISF).

Trials that involve intensive ECG data collection will require more staff than usual, and there may be trial-specific requirements for how quickly ECGs are interpreted and reported, and by whom (e.g. a cardiologist, if one is not already part of the team). Time points, such as dosing, that rely on a clinician or cardiologist's assessment of ECGs require careful planning so that the required staff is present in the trial facility in good time. It is critical that all required staff (including night staff) understand the need to conduct ECGs at a strictly specific time point when necessary.

Equipment and consumables

The type and brand of ECG machine will depend on the accuracy and precision of results required. It may be that trial sites use their own machines or those supplied by a sponsor but it is important that the same brand (and the same method, i.e. digital versus paper) is used throughout a trial and for each participant, for consistency and homogeneity, and that machines are regularly serviced. The number of machines will depend on availability and budget but must suit the trial schedule. For example, if ECGs for multiple participants are scheduled close together, particularly if assessments overlap, sufficient ECG machines should be provided. There should be at least one back-up machine available in case of malfunction, and a copy of each machine's performance data should be stored in the ISF.

Digital ECGs are the standard in that they are less expensive to handle and manually analyse and better for accurate analysis and for long-term data storage, as ECG paper is usually thermal and therefore the quality of the trace decreases over time. ECG electrodes (and thermal paper, if used), should be supplied in sufficient quantities and stored according to the manufacturer's instructions, usually in the original packaging and away from heat and light. It is important to monitor stocks and expiry dates continually (bags of electrodes should be labelled with the date they are opened as they have a limited lifespan once opened), especially if supplies have come from overseas, to ensure the facility does not run out at a critical time point. There should also be sufficient quantities of alcohol wipes, gauze swabs, potentially razors for shaving chest hair if needed, and all the required source documents (e.g. medical notes templates).

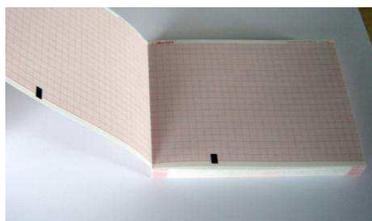


Figure 3: Thermal paper



Figure 4: Electrode

5.3 During a trial

Preparation for ECGs

Staff should be familiar with the planned ECG time points in advance so that they can check equipment and consumables in good time. At the start of a visit or time point, each ECG machine should be checked as working, and it may be necessary to synchronise the ECG's internal clock with the trial facility clock if assessments are done in strict relation to dosing and other assessments.

Before each time point, the machine is programmed with required demographic data to allow identification during analysis, for instance the trial name or number, participant number, visit, date and time, date of birth and gender.

Standard ECG (to be adapted per protocol as necessary)

A typical ECG is 10 seconds simultaneously recorded on 12 leads (if possible 25 mm/s 10mm/mV) with an A4 print out (or digital recording) and all leads displayed in a single page. There are many ECG formats, two preferred being 6x2 and 4x3. Regardless of format, it should include a "rhythm lead" with all individual cardiac beats, typically lead II, to allow rhythm statements. The tracing should clearly show the lead ID, calibration pulse, recording speed and grid.

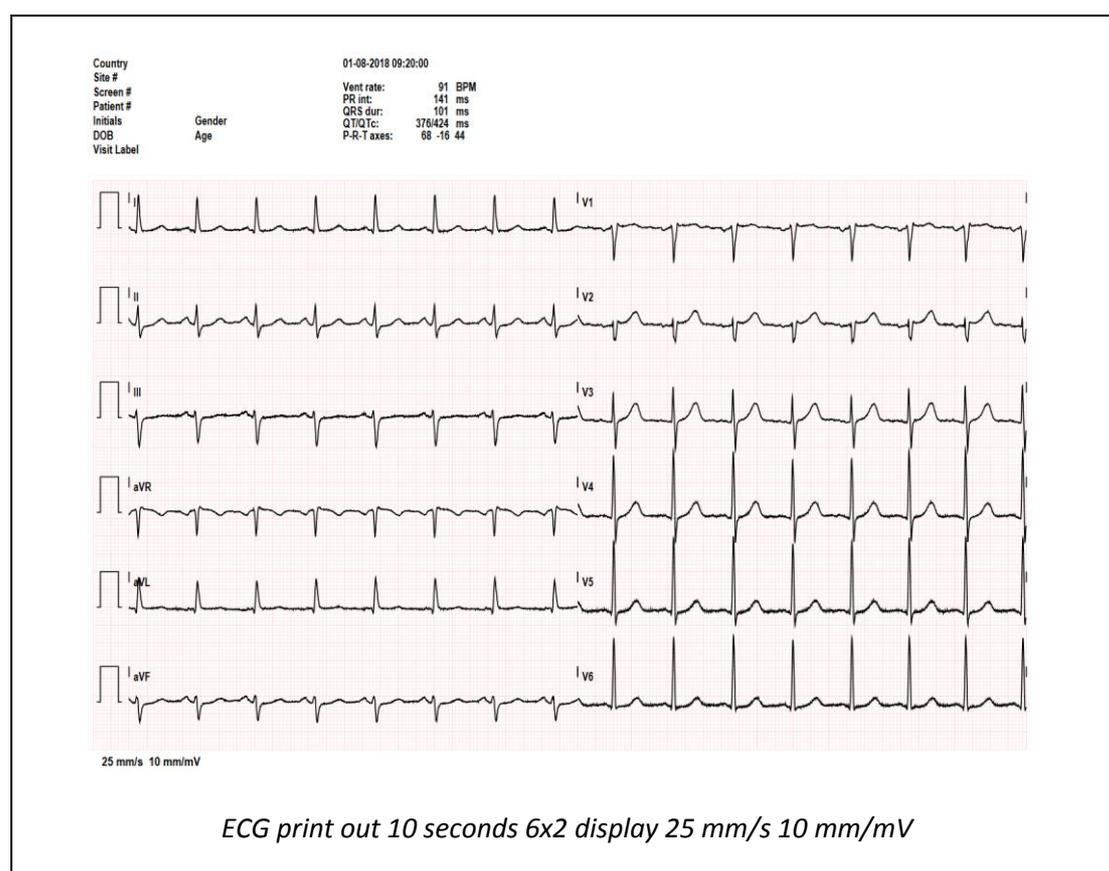


Figure 5: typical ECG tracing

Staff members should introduce themselves to the participant, ensure privacy, explain briefly what will happen (e.g. that the procedure is external only) and check the participant's ID is consistent with the research documentation. Unless otherwise specified, the participant should rest in a relaxed supine position with legs uncrossed for at least 5 minutes before the ECG and be asked to breathe normally throughout. The staff member should clean their hands according to standard practice, prepare the participant's skin (Figure 6) and place electrodes (Figure 7) starting with the lower legs, lower forearms and chest. Leads are then attached to the corresponding electrodes. Do not talk to, or touch the participant before/during the recording, after electrodes have been placed. Keep ambient noise to a minimum and avoid contact with anything metallic. To avoid artefacts (false readings), remove the ECG machine from AC power when recording.

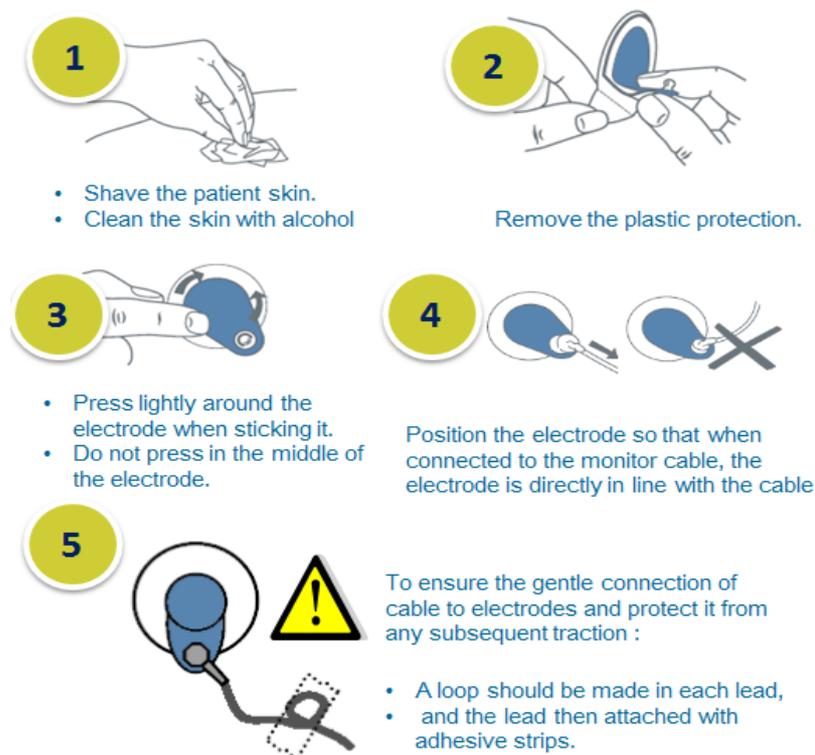


Figure 6. Skin and electrode preparation.

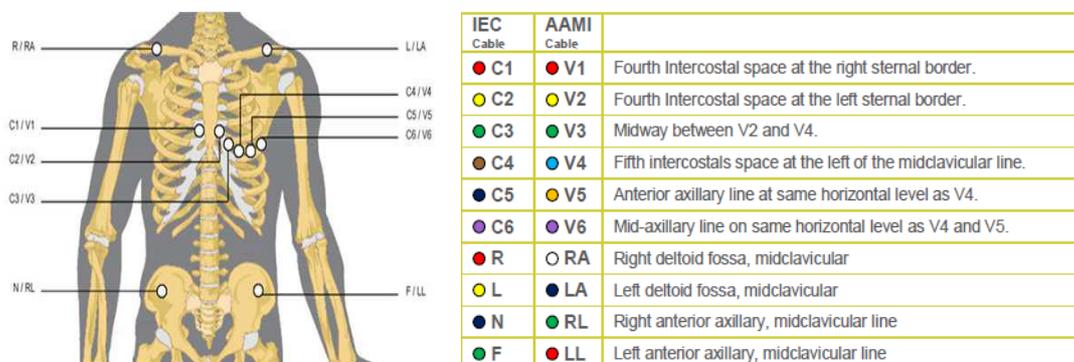


Figure 7. Electrode positioning (Mason Likar placement).

Immediately after each ECG the quality of the trace should be reviewed as to whether there were missing leads, lead inversion, a flat trace, major noise or mandatory demographic information missing. If necessary the ECG will be repeated, labelled appropriately, with a note of the reason for any protocol noncompliance, in which case the issue should be reported up the team for decisions about further action. The lead wires and electrodes are then removed using a warm wet cloth or alcohol wipes unless otherwise indicated.

Interpretation/assessment of ECG at the site

Investigators interpret ECG traces in terms of whether findings are considered normal or abnormal, and, if the latter, whether clinically significant (or relevant). These are assessed for each participant and often across participants, together with other emerging data on cardiac and non-cardiac AEs. There should be clear planning before the trial as to when and how these reviews are done, including how ECG traces are transferred to and collected from, for instance, a cardiologist outside the facility. While automated reports may be used as an initial indication of the cardiac function, the manual reading (by a clinician or cardiologist) may result in different final data; the analysis plan should specify which data are included in the analysis dataset. There should be a clear mechanism for feedback of clinical interpretations and recommendations for specific actions (e.g. a need for a repeat ECG, dose adjustment/suspension or trial withdrawal).

Each trial will have pre-determined thresholds for concern, which may or may not be pre-programmed into the ECG machines. When alerts, whichever way they are generated, are identified, the ECG may need to be repeated, and appropriate care for the patient arranged as per trial- or facility-specific requirements. Any AEs or serious AEs will then be documented and reported according to trial-specific or routine facility requirements, and in consideration of applicable guidelines or laws. Detailed narratives are required for all serious cardiac events, including for torsades de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope and seizures. Similarly, any events that led to withdrawal of the participant from the trial or dose reductions require thorough review with the wider trial team.

Centralised readings

To achieve specific endpoints, the Sponsor may require ECGs be sent to a central specialist centre for standardized interpretation, usually blinded to trial arm, time etc. The central reader may then perform an ad-hoc analysis in compliance with regulatory requirements. The standard format for ECG files is XML which can be accepted broadly by all readers and, depending on the objective of the study, the analysis may be categorical, of central tendency, PK/PD modelling or any other relevant analyses. Any queries raised by the central team should be resolved promptly so that they do not delay the analysis.

5.4 Data management and analysis

Data management and analysis are trial-specific. However, trial teams should consult CDISC data standards for cardiovascular, QT and uncomplicated malaria studies where relevant, to ensure outputs are suitable for FDA submission and/or future pooled analyses.^{6, 7, 8} As both can provide relevant information on clinical risk assessment, QT/QTc interval data are usually reported as analyses of central tendency (e.g., means, medians) as well as categorically (e.g. number and % of participants with increases in QTc intervals > 30 and > 60 msec or with QTc intervals greater than 500msec).⁵

5.5 End of trial activities

As mentioned, original thermal paper ECGs have a limited lifespan (typically of around 5 years). If there is a digital database (central reading) there is usually no need to keep local scans. However, ECGs will not be stored indefinitely on the machine, and may be over-written after a certain number. Otherwise, sites may scan paper ECGs and keep an electronic record. All Essential Documents for the conduct of a clinical trial should then be archived (whether paper or electronic) as per the site and sponsor requirements and in accordance with relevant guidelines and laws.

6. References

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