

Collection of ECG data in Covid-19 clinical trials

What?

- What is the purpose and scope of this toolkit?
- Learn the rationale for collecting ECG data in Covid-19 clinical trials and trial design considerations

[Background and rationale for collecting ECG data in Covid-19 clinical trials](#)

[General points about trial-design + Planning for collecting ECGs in clinical trials](#)

How?

- Learn how to plan for collecting ECGs in clinical trials
- Guidance on ECG conduct, documentation, interpretation and assessment of ECGs at sites including data management, analysis and end of trial activities

[End of trial activities](#)

[Data management and analysis](#)

Toolkit

[ECG conduct + Documentation, interpretation and assessment of ECGs at sites](#)

About

About this toolkit - Definitions and notes



BACKGROUND

This toolkit is not prescriptive and may be adapted for use by anyone according to need. We would appreciate feedback on any errors or suggestions as to how it may be improved.

Suggested citation: IDDO Guidance document. Collection of ECG data in Covid-19 clinical trials v1.1

This toolkit was adapted from an IDDO document (version 1.1 7th July 2020) adapted from one originally developed by the WorldWide Antimalarial Resistance Network (<https://www.wwarn.org/>) in collaboration with Cardiabase by Banook group (<http://www.banookgroup.com/>) and the Liverpool School of Tropical Medicine, with funding from the European & Developing Countries Clinical Trials Partnership (EDCTP).

ADR Adverse Drug Reaction
AE Adverse Event
CRF Case Record Forms
ECG Electrocardiograph/
electrocardiogram

GCP Good Clinical Practice
HR Heart rate
ISF Investigator Site File
PK Pharmacokinetic

ABBREVIATIONS



*Normal and abnormal ECG findings

A normal adult heart rhythm has a heart rate (HR) of between 60 and 100 beats per minute (bpm) and a normal impulse formation (P wave). Children's normal HR ranges are higher.[2] A normal adult sinus rhythm will also have a normal PR interval (0.12-0.22 seconds), QRS interval (0.05-0.12 seconds), and QT interval (see below). All waveforms will be 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)[3]. While deviations from what is considered a normal ECG may or may not be clinically relevant, abnormalities may include bradycardia, (generally <60 bpm in adults), tachycardia (generally > 100 bpm in adults), dysrhythmia (any rhythm abnormality), sinus arrhythmia (normal rhythm with HR variation >10 bpm), and morphological changes such as ST elevation or ST depression. Morphological changes in the T-U complex are of particular interest in studies assessing the cardiac safety of drugs. Information should therefore be captured on changes in T and U wave morphologies. Typical findings could be flat, inverted or very tall T waves, and prominent or inverted U waves.

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

QT interval: The duration of ventricular depolarisation and subsequent repolarisation, measured from the beginning of the QRS complex to the end of the T wave. The QT interval is determined by specific leads of an ECG machine and ECG machine reports 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. The QT interval in a healthy subject depends on age, gender and HR.



DEFINITIONS

DEFINITIONS & NOTES

Cardiac arrhythmia: An abnormal heart rhythm due to problems with the heart's electrical conduction. The heart may beat irregularly, to 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 plot of voltage against time, representing the heart's electrical activity by magnifying its small electrical impulses, recorded on ECG graph paper and/or electronically (see schematic of an ECG trace in Figure 1). Electrodes are attached externally to the patient which allow the electrical activity of leads (imaginary lines 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.

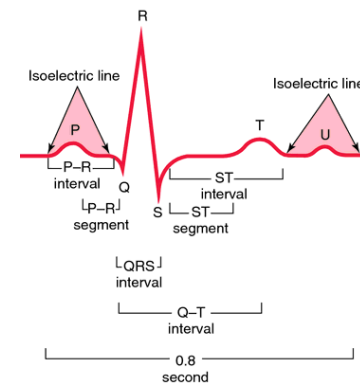


Figure 1: ECG trace schematic

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 according to Good Clinical Practice (GCP) held by the Investigator.

***Continues at Normal and abnormal findings**

QT prolongation: A congenital or acquired lengthening of the QT interval, leading to an increased risk of ventricular tachyarrhythmia (including Torsades de Pointes, TdP, a potentially fatal abnormal heart rhythm). 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.

QTc: As there is an inverse relationship between HR (the RR interval between beats) and the QT interval, it is corrected (the 'c') to increase the possibility of detecting patients at increased risk of arrhythmia.[4] There are a number of different methods, including Bazett's (QTcB) and Fridericia's (QTcF) formulas. In general, QTcB is known to over-adjust QT when HR is high. Though the former is no longer routinely warranted for reporting by the FDA, there is evidence it best corrects for HR in a very young paediatric population.3, [3, 5] There may be other sub-populations or diseases where QTcB may also be appropriate. RR is important for the QTc calculation and may be measured immediately before the measured QT interval, as an average value, or back calculated from HR (RR=60/HR). Because the best correction approach is a subject of controversy, uncorrected QT and RR interval data, HR data, as well as QTc should ideally be captured for each study. See page 1. for details on values considered important in clinical trials.

1. What?

Background and rationale for collecting ECG data in Covid-19 clinical trials



BACKGROUND

PURPOSE/SCOPE

While a clinical trial protocol will describe which ECG data are to be collected and when, it is important that relevant site staff understand the rationale and best practice for the practical collection of such data to ensure robust and relevant results.

This toolkit provides comprehensive generic guidance for standard 12-lead clinical trial ECG data, to support trial-specific instructions. It does not cover ambulatory (e.g. Holter) ECGs.

Covid-19 is a novel SARS-CoV-2 viral infection with no drugs currently registered for its prevention or treatment. However, various “re-purposed” drugs marketed for different conditions are under evaluation or being used off-label. There are also investigational products and vaccine candidates under clinical development.

The extent of monitoring for adverse events (AEs) to detect potential cardiac adverse drug reactions (ADRs) in Covid-19 trials will depend on its phase and/or specific safety concerns about a given 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. According to the FDA, all new drugs with systemic bioavailability (irrespective of preclinical profile) should have a thorough QTc/QT (TQT) trial performed where ECGs will be the prime focus.[6]

ECG monitoring may also be important in later phase trials, and even after licensing, if there are gaps in knowledge about a drug’s potential cardiac effects or if available data suggest cause for concern. Where a drug is re-purposed from its original licensed indication, as is the case for Covid-19, it is important to study its effect in the new population, particularly as different doses or regimens may be necessary and patients may have different morbidities. The threshold for QTc prolongation in trials to determine enrolment or withdrawal due to an AE will depend on what is known about the drug, the trial design and population, including risk-tolerance. Increases in QT/QTc to >500 ms or of >60 ms over a baseline value are often used as a threshold, though lower (and gender-specific values, e.g. >450 ms males and >460 ms females) may also be appropriate depending on the trial context.[6]

RATIONALE



2. What?

Background and rationale for collecting ECG data in Covid-19 clinical trials



BACKGROUND

RE-PURPOSING

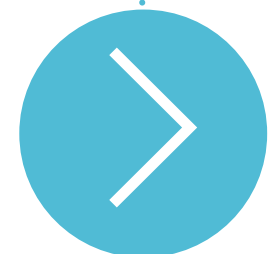
While the situation is continually changing, some drugs are being investigated for re-purposing for Covid-19 prevention or treatment that have a known potential for adverse cardiac effects. This has included the aminoquinolines chloroquine and hydroxychloroquine that are marketed for the treatment of Plasmodium vivax or ovale malaria and certain rheumatological conditions. Although generally safe and well tolerated at recommended doses, they may be potentially fatal in overdose. In malaria trials, chloroquine was found to delay ventricular depolarization slightly through a Class 1c effect, causing slight widening of the QRS complex and prolongation of QT intervals, but has not been associated with conduction disturbances or arrhythmias.[7] Moreover, a recent review of the arrhythmogenic cardiotoxicity of the quinolines in malaria did not reveal harm associated with chloroquine, although variable definitions, procedures and analytical methods precluded a systematic analysis of the QT interval. Parenteral chloroquine formulations are, however, predictably hypotensive when injected rapidly.[8] Hydroxychloroquine use in rheumatology has been associated with conduction disturbances and cardiomyopathy, though data are somewhat limited.[9, 10] A recent study using VigiBase® found reports of potentially lethal acute cardiac proarrhythmic effects leading to ventricular arrhythmias described mainly with azithromycin but also with hydroxychloroquine, and a stronger signal when used in combination. Hydroxychloroquine was also associated with potentially lethal heart failure when exposure was prolonged over several months.[11]

Chloroquine and hydroxychloroquine (with or without azithromycin that also prolongs the QT interval) are being investigated in Covid-19 treatment trials at doses higher than for licensed indications, although data are still emerging and have been affected by controversy about the quality of publications.[12] For interpretation of results it is important to understand where doses are by mg of base or salt. While doses will likely be lower in prevention trials, a consideration is the different risk of harm versus benefit profiles when a drug is used in a 'healthy' population. Other drugs under investigation for prevention, treatment or support of Covid-19, may also have the potential for QT prolongation or other cardiac safety concerns. For example, remdesivir, favipiravir, lopinavir/ritonavir and macrolides.[13]

CARDIAC EFFECTS OF COVID-19

Aside from possible adverse drug effects, it is important to note that Covid-19 itself can cause cardiac injury. While the situation is not yet clear due to the limited studies with varying methodologies, and differences in populations (including many with underlying cardiovascular pathologies predisposing them to severe Covid-19 disease), there is evidence of Covid-19-associated myocarditis, arrhythmias, heart failure and myocardial dysfunction.[14] This further complicates interpretation of trial cardiac data, including QT interval changes, and AE causality assessments.

COVID-19



3. How?

General points about trial-design



TRIAL DESIGN

GENERAL

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 a drug's concentrations may also be influenced by interactions with food, such as fat. Food consumption data are therefore also important considerations, as are the vital signs, symptoms (e.g. diarrhoea), 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.

SCHEDULING ECGS

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 study drug, including the expected time of maximum drug concentration (T_{max}). Baseline ECGs are used as a reference to provide a pre-drug comparison. Scheduling further follow-up ECGs may assist in the interpretation of the data, particularly once initial Covid-19 symptoms that may influence cardiac function have resolved and once study drug concentrations are minimal.
- Sources of variability in ECG measurements such as QT intervals, include gender, age, HR, 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 multiple times to obtain average measures (e.g. in triplicate typically 1 minute apart for thorough ECG studies, but the necessity of triplication should be assessed for COVID-19 studies because of the potentially increased risk of infection due to the prolonged time of being proximity of the patients).
- All other procedures at the same time-point (e.g. blood draws, blood pressure measurements) should be scheduled after the ECG so as not to interfere with measurement. As it is not possible to perform multiple assessments at the exact same time, measurement of key data will take priority at the scheduled time. E.g. for trials where PK measurement is the primary endpoint, PK blood sampling would happen at the exact protocol-scheduled time with the co-scheduled ECGs done in the minutes leading up to that time point.

OTHER IMPORTANT DATA FIELDS

As indicated above, aside from demographics (including gender, age, race), relevant data about a participant's medical history (including time of menstrual cycle), concomitant medicines (including contraception modality) and laboratory assessments are also important to collect and consider when assessing ECG results.[15, 16],

Risk of ventricular arrhythmia is increased by other factors such as heart disease (e.g. myocardial ischaemia, heart failure, atrial fibrillation), bradycardia or sino-atrial blocks, some diseases (e.g. hypothyroidism, hypogonadism), hypoxia and electrolyte imbalances (e.g. potassium, magnesium, calcium) as well as with Congenital Long QT syndrome.[17]

Numerous other medicines have been associated with ECG changes and a list of such medicines and clinical factors associated with prolonged QTc intervals and/or TdP is available at www.crediblemeds.org, together with a clinical decision-support tool for safe prescribing (<https://medsafetyscan.org/>). Information on potential drug interactions may be found at https://www.drugs.com/drug_interactions.html.

Enquiring about other concurrent symptoms (e.g. fainting/syncope, palpitations, convulsions/seizures, and pounding/pain in the chest area) when abnormal ECG results are observed help in determining a diagnosis and relationship of the AE to the trial drug.

4. How?

Planning for collecting ECGs in clinical trials



PLANNING

STAFFING

As Covid-19 is a highly infectious disease, there should be proper planning to prevent cross-infection between patients and staff.

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

Trials that involve intensive ECG data collection, particularly when participants are enrolled in groups such as in early phase and healthy volunteer trials, 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 just prior to dose require particularly careful planning so that the required staff is present in the trial facility in good time and a system is in place to review data as they emerge. It is also important that all required staff (including night staff) understand the need to conduct ECGs at a strictly specific protocol time point when necessary.

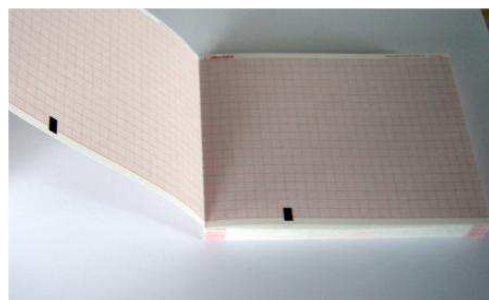


Figure 2: Thermal paper



Figure 3: Electrode

EQUIPMENT & CONSUMABLES

The type and brand of ECG machine will depend on the accuracy and precision of results required. Trial sites use their own machines or those supplied by a sponsor but it is important for consistency and homogeneity that the same brand (and the same method, i.e. digital versus paper) is used throughout a trial and for each participant, and that machines are regularly serviced. The number of ECG machines required will depend on availability and budget, but must suit the trial schedule. For example, as for staff, 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 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 (Figure 2) and therefore the quality of the trace decreases over time. ECG electrodes (Figure 3) 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. 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).

5. How?

ECG conduct



ECG CONDUCT

PREPARATION

Staff should be familiar with the ECG time points in advance so 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 its internal clock with the trial facility clock if assessments are done in strict relation to dosing and other assessments. If so, it is recommended this step be included in a clinic/visit set-up checklist.

Before each time point, the machine is programmed with the 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.

SCHEDULING ECGS

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 ones 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 4).

Country	01-08-2018 09:20:00
Site #	
Screen #	Vent rate: 91 BPM
Patient #	PR int: 141 ms
Initials	QRS dur: 101 ms
DOB	QT/QTc: 376/424 ms
Visit Label	P-R-T axes: 68 -16 44

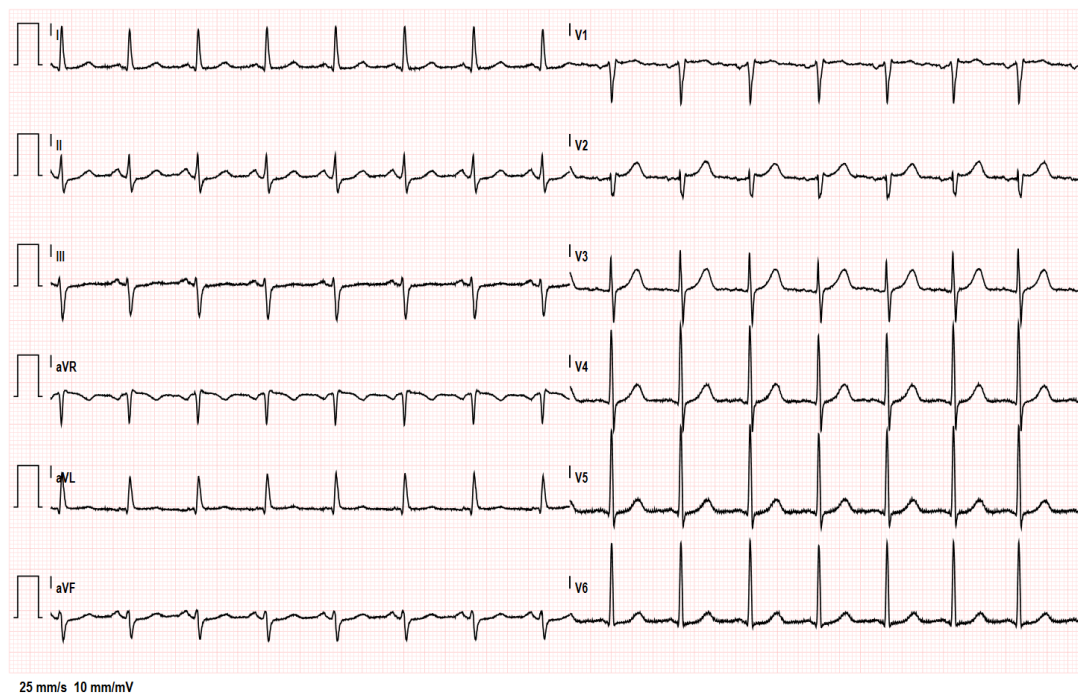


Figure 4: typical ECG tracing - ECG print out 10 seconds 6x2 display 25 mm/s 10 mm/mV

6. How?

ECG conduct



ECG CONDUCT

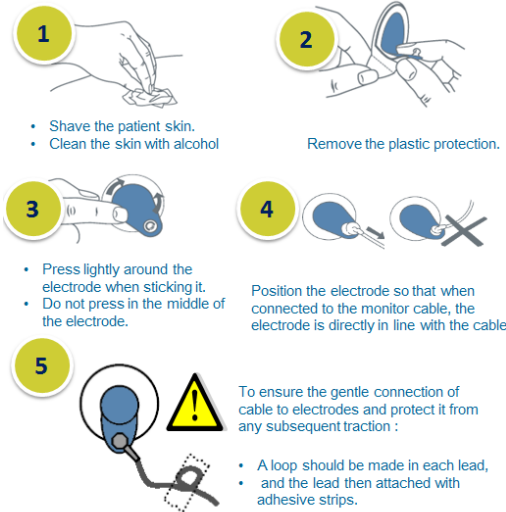


Figure 5. Skin and electrode preparation.

Immediately after each ECG the quality of the trace should be reviewed, to assess 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 highlighted for decisions about further action. The lead wires and electrodes are then removed using a warm wet cloth or alcohol wipes unless otherwise indicated.

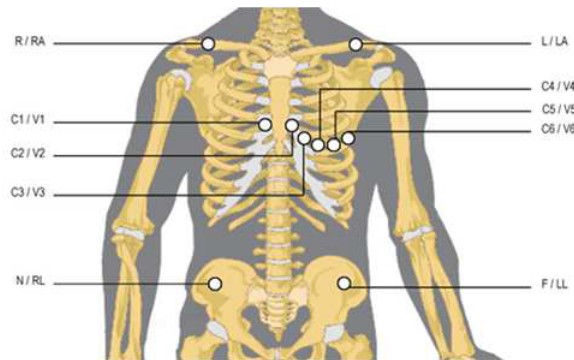


Figure 6. Electrode positioning (Mason Likar placement).

IEC Cable	AAMI Cable	
● C1	● V1	Fourth Intercostal space at the right sternal border.
● C2	● V2	Fourth Intercostal space at the left sternal border.
● C3	● V3	Midway between V2 and V4.
● C4	● V4	Fifth intercostals space at the left of the midclavicular line.
● C5	● V5	Anterior axillary line at same horizontal level as V4.
● C6	● V6	Mid-axillary line on same horizontal level as V4 and V5.
● R	○ RA	Right deltoid fossa, midclavicular
● L	● LA	Left deltoid fossa, midclavicular
● N	● RL	Right anterior axillary, midclavicular line
● F	● LL	Left anterior axillary, midclavicular line

Staff members should introduce themselves to the participant (if conscious) and 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 5) and place electrodes (Figure 6) starting with the lower legs, lower forearms and then 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.

7. How?

Documentation, interpretation and assessment of ECGs at the site



HOW

DOCUMENTATION, INTERPRETATION & ASSESSMENT

A manual record of the ECG conduct is maintained in the source with notes of any problems during the procedure to explain deviations from protocol time if relevant ([Appendix 1](#)). Investigators and/or cardiologists then review and interpret ECG traces (and may in fact re-calculate intervals) in good time in terms of whether findings are considered normal or abnormal, and, if the latter, whether or not these abnormalities are clinically significant (or relevant), according to standard practice or protocol-specific guidelines ([Appendix 2](#)). The final data may then be entered into the case record form (CRF, [Appendix 3](#)).

There should be clear planning before the trial as to when and how clinician reviews are done, including whether assessors should be blinded to the allocation of intervention if any, or how ECG traces are transferred to and collected from, for instance, a cardiologist outside the facility. There should also 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. It may also be pertinent to prompt staff through the source or separate document in the clinic for events that signal immediate clinical attention. E.g. through the following text with trial-specific values for x:

INFORM DOCTOR IMMEDIATELY IF:

- Heart rate $<x$ or $>x$ beats per min
- PR interval $>x$ msec
- QRS $>x$ msec
- QTcF $>x$ msec
- Shortened QTcF $<x$ msec

When any alerts 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 and regulations.

Detailed narratives should be developed for all serious cardiac events, including for sudden death, TdP, 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.

8. How?

Centralised readings



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.

DATA MANAGEMENT & ANALYSIS

While automated ECG readings may be used as an initial indication of cardiac function, as mentioned above, manual calculations by a clinician or cardiologist may be done and this will often result in different data. Therefore the analysis plan should specify which data are included in the analysis dataset. These findings are then assessed for each participant and often across participants, together with other emerging data on cardiac and non-cardiac AEs according to the interim or final analysis plan. Data management and analysis are trial-specific. However, teams should consult CDISC data standards for cardiovascular, QT and Covid-19 studies where relevant, to ensure outputs are suitable for regulatory submission (if required) and/or facilitate future systematic review and meta-analyses.^[18, 19, 20] 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).⁶

While some data points are participant-specific, other methodological variables are trial-specific meta-data which are important to record to understand the data fully and to facilitate subsequent reviews and meta-analyses:

Variable	Typical unit/options
Reading flow	Single read, single over-read or double read
Reading method	Tangent method or median overlapped method
Reading technique	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 might be derived from machine read while QT could be read manually) Some trials have every ECG read automatically, then a proportion checked manually, e.g. every 5th ECG
Reader	On site by non-cardiologist, on site by cardiologist, centralised laboratory, combination (on site and centralised)
Type of recording	Paper and/or digital
ECG device	NB Although not ideal, studies may use a different device at different sites, and this should then be specified for each site
Patient position	Lying, supine or non-resting, or not documented
Paper speed (if relevant)	mm/sec (could be patient/record-specific)
Voltage	mm/mV (could be patient/record-specific)

Table 1: Sample trial-level variables (meta-data) describing ECG methodology

END OF TRIAL ACTIVITIES

If there is a digital database (central reading) there may be 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 have been conducted (machine-specific). As mentioned, original thermal paper ECGs have a limited lifespan (typically of around 5 years) so sites may scan paper ECGs and keep an electronic record. All Essential Documents for the conduct of a clinical trial should then be archived as per site and sponsor requirements and in accordance with relevant GCP guidelines and regulations.

9. How?

References and appendices list



APPENDICES

EXAMPLES

Examples only for illustrative purpose and adaptation for each trial:

Appendix 1: Example source document

Appendix 2: Example review and interpretation of ECG

Appendix 3: Example case record form

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