# Standard Operating Procedure for Electrocardiogram Reading

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# Standard Operating Procedure for Electrocardiogram Reading

## PURPOSE

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| A 12-lead electrocardiogram (ECG) is a non-invasive procedure that is used to ascertain information about the electrophysiology of the heart. Patients with certain cardiac conditions should not be included in the endTB trial (see exclusion criteria below). Also, medications used to treat multidrug-resistant tuberculosis can affect the repolarization of the heart, resulting in prolongation of the QT interval. The QT interval changes with heart rate. Thus, the QT interval must be corrected for the heart rate before comparisons can be made.  The purpose of this SOP is to ensure that all clinical staff understand how to assess for cardiac exclusion criteria; when to perform ECGs and how many should be performed; use the same procedures to measure the QT interval from the ECG and calculate the corrected QT interval using the Fridericia formula (QTcF); and record and report results. |

## SCOPE

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| --- |
| 1. Determine the schedule of ECGs (including determining the minimum number of ECGs to perform at a visit and the number of ECGs to be sent for central reading). 2. Perform an ECG on a study participant and record results. 3. For screening and baseline ECG, assess for ECG criteria for exclusion. 4. Measure QT interval manually and calculate corrected QT interval using the Fridericia formula (QTcF). 5. Record ECG results in the source documents and capture in case report form. 6. For visits that require an ECG for central reading, transmit the ECG to the vendor providing the service of central reads and storage. |

## RESPONSIBLE FUNCTIONS

|  |  |
| --- | --- |
| **Function** | **Activities** |
| **Study nurse, technician, or investigator** | * Determine the schedule of ECGs |
| **Study nurse, technician, investigator, or cardiologist** | * Perform ECG |
| **Study nurse, technician, investigator, or cardiologist** | * Assess ECG criteria for exclusion |
| **Investigator or cardiologist** | * Calculate QTcF |
| **Investigator or cardiologist** | * Record ECG results |
| **Study nurse, technician, CRA, or data entry staff** | * Transmit ECG for central read |

## DEFINITIONS and ABBREVIATIONS

**Electrocardiography** is the process of recording the electrical activity of the heart over a period of time using electrodes placed on the skin.

**ECG** Electrocardiograph (for the purpose of this SOP, ECG always indicates a 12-lead ECG).

**Electrodes** The electrodes detect the tiny electrical changes on the skin that arise from the heart muscle's electrophysiologic pattern of depolarizing during each heartbeat. The placement of the electrodes is described in Section 5, Figure 2 below. The names of the four limb leads are **RA** (right arm), **LA** (left arm), **RL** (right leg), **LL** (left leg) and the six precordial leads are called **V1, V2, V3, V4, V5, V6**.

**HR** Heart rate. Measured in beats per minute (bpm).

**LBBB** Left bundle branch block.

**Leads** The overall magnitude of the heart's electrical potential is measured from 12 different angles ("leads") and is recorded over a period of time (usually 10 seconds). Note in a 12-lead ECG only **10 electrodes** are placed on the patient's limbs and on the surface of the chest, but 12 different leads are recorded.

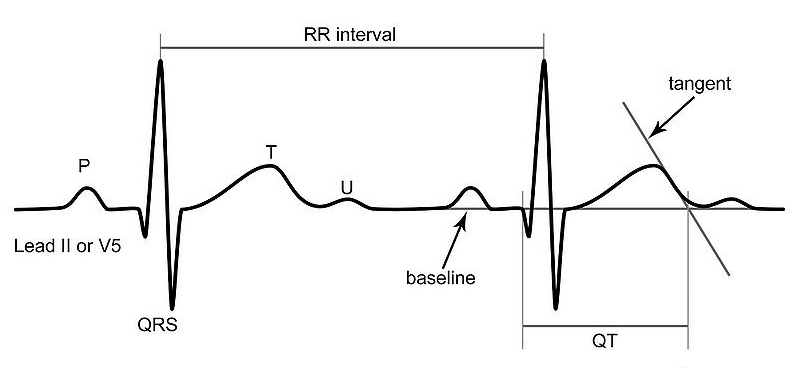
**RBBB** Right bundle branch block.

**STAT central reading.** Immediate ECG reading

**Waves, Complexes, and Intervals.** Figure 1 shows the important waves (P wave, T wave, U wave), complexes (QRS complex), and intervals (RR interval, QT interval). Key intervals are defined below.

* **QT interval (QT)** is the time from onset of the QRS complex to the end of the T wave. Measured in milliseconds (ms).
* **Corrected QT interval (QTcF**) uses the Fridericia formula to correct the QT interval for heart rate. Measured in milliseconds (ms).
* **RR interval (RR)** is the time from one point in the cardiac cycle to the same point on the next cardiac cycle. Measured in milliseconds (ms). The RR value in ms needs to be converted into seconds to permit calculation of the HR.

**Figure 1 – Key Waves, Complexes, and Intervals**



**Table 1 – Summary of timing and number of ECGs to perform on study participants, numbers of ECGs to send for central reading and data recording**

|  |  |  |  |
| --- | --- | --- | --- |
| **When to do an ECG and how many to perform** | **When to manually measure the QTcF** | **When to send ECGs for central reading** | **Data to record in the source documents**  **(then to capture in case report form)** |
| Screening (perform 3)  Baseline (perform 3)  Routine monitoring (perform 2)\*  Unscheduled visits (ECGs only done if clinically indicated) | On all ECGs performed | Screening (send 1 of the 3)  Baseline (send 1 of the 3)  Routine monitoring on select visits (send 1 of 2)\*  Unscheduled visits (ECGs only done if clinically indicated and sent for central read if a second opinion is needed) | Record for all ECGs performed:  - Participant ID, visit number, visit date, and ECG number  - HR  - QT (measured, see below)  - QTcF (calculated, see below)  - For ECGs with an abnormal result, record the severity grade  - Record the average QTcF if more than one ECG is performed |

\* See Table 2 below for the ECG schedule.

**Table 2 – Schedule of routine ECGs and ECGs to send for central reading**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Treatment** | | | | | | | | | | | | | | | | | | | | **Follow-Up** | | | | |
|  | Screening | Baseline | W 1 | W 2 | W 3 | W 4 | W 5 | W 6 | W 7 | W 8 | W 9 | W 10 | W 11 | W 12 | W 16 | W 20 | W 24 | W 28 | W 32 | W 36 | W 39 | W 43 | W 47 | W 53 | W 73 | W 104 |
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 27 | 31 |
| Routine ECG\* | X (3) | X (3) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) | X (2) |  |
| Central Reading\*\* | X (1) | X (1) | X (1) |  | X (1) |  | X (1) |  |  | X (1) |  |  |  |  | X (1) |  | X (1) |  | X (1) |  | X (1) |  |  |  | X (1) |  |

The number of routine ECGs to obtain or to send for central reading at each visit are in parentheses.

\* Routine ECGs are done at screening, baseline, at scheduled follow-up visits at Weeks 1 to 12, 16, 20, 24, 28, 32, 36, 39, 43, 47, 53, and 73 (23 monitoring visits).

\*\* ECGs are to be sent for central reading at screening, baseline, and on select routine monitoring visits at Weeks 1, 3, 5, 8, 16, 24, 32, 39, and 73 (12 monitoring visits).

## PROCEDURE

### Timing and number of ECGs across the study participation

1. All ECGs performed should be 12-lead ECGs done on the ECG machines provided by the endTB Clinical Trials. These “study ECG machines” have the ability to store a limited number of ECGs and transmit them electronically over an internet connection directly from the ECG machine for “central reading”. (When an approved study ECG machine is not available for whatever reason, an extra copy of the ECG should be printed out and instructions will be provided below on how to transmit them).
2. Routine ECGs are done at screening, baseline, at scheduled follow-up visits at Weeks 1 to 12, 16, 20, 24, 28, 32, 36, 39, 43, 47, 53, and 73 (see Table 2 above). Unscheduled ECGs may be done at any time during the study period during unscheduled visits if clinically indicated.
3. The minimum number ECGs being performed is based on the type of visit:
   * 1. At the screening and baseline visits, obtain three ECGs.
     2. At all other visits, including, scheduled follow-up (and unscheduled visits if an ECG is clinicaly indicated) obtain at least two ECGs.
4. The number of ECGs sent for a central reading during a visit is described below (how to transmit an ECG for a central reading is described in the section 5.5 of this SOP).
5. Not all ECGs performed are sent for a central reading.
6. For screening and baseline (for patients eligible following the screening visit) ECGs, send one of the three ECGs for central reading (which ECG to send of the three performed is described below).
7. For follow-up visit ECGs, send one of the two ECGs for central reading for routine visits for Weeks 1, 3, 5, 8, 16, 24, 32, 39, and 73 (which ECG to send of the two performed is described below).
8. For unscheduled visit ECGs, where an ECG was done for clinical reasons *or* for a follow-up visit ECGs where a central read is not required, the ECG can be sent for central reading to the vendor only if a reading is desired by the investigators or clinical staff (for example, in the case of wanting a second opinion on interpretation of an ECG that is not routinely sent for central reading).
9. Also note that any ECG can be sent for a STAT reading from the central reading vendor. When a STAT reading is requested the read will be done in less than 24 hours.

### How to perform an ECG on a study participant

The Investigator or delegated personnel should follow the procedures described below:

1. Connect the lead wires to the corresponding electrodes. Attach the limb lead wires first beginning with the right leg (See Figure 2).
2. Ensure that a 12-lead ECG is required by the study protocol and a specific machine is being utilized as stated in the protocol.
3. Wash hands and gather the following equipment and supplies:
   1. 12-lead ECG machine.
   2. ECG electrodes.
   3. Alcohol swabs.
   4. 2 x 2 gauze pads.
   5. Razor (optional, if hair removal is needed to ensure good electrode contact).
4. Introduce one’s self and verify the subject’s name and date of birth. Subject identifiers must match the clinical chart.
5. Ensure mobile phones, radios, electric fans and other electrical devices are turned off.
6. Ask the subject to remove clothing from the waist up, to take off any jewelry, and don a hospital gown that opens to the front. Leave the room while the subject changes into the gown. Ensure privacy by closing the curtain and/or the door.
7. Explain the ECG procedures and answer questions the subject may have regarding the ECG, as appropriate.
8. Ask the subject to lay flat on the exam table with legs uncrossed and arms to the side.
9. Ensure that the ECG is performed in a relaxed subject to avoid artifacts.
10. Wash hands and stand on the left side of the subject. Prepare the skin, where the electrodes will be placed, by rubbing the lower legs, lower forearms, and chest area with alcohol swabs. Dry the areas with gauze pads.
11. Apply the electrodes starting with the lower legs, lower forearms, and chest area. See Figure 1 below and the ERT Machine Quick Guide in the Appendix.
12. Turn on the machine and enter the subject’s name, date of birth, subject ID number, visit ID code, or other protocol specific information. Verify information against the patient chart.
13. Ask the subject to breathe normally, relax, and remain supine and motionless for 5 minutes.
14. Acquire the ECG reading.
15. Every effort should be made to obtain an ECG of good quality and free of artifact; repeat the ECG if artifacts are present until a satisfactory quality ECG is obtained.
16. When a satisfactory ECG is acquired, save (if able to save electronically), and print.
17. Print additional copies for the ECG tracing if any are needed.
18. Transmit a copy of the ECG for central reading if indicated (see Table 2 and Procedure Number 1 to determine if an ECG is needed to be sent centrally).
19. If more than one ECG is being performed, wait ~5-10 minutes between routine ECGs, and ~10 minutes if there is any clinical concern for prolonged QT interval.
20. Remove lead wires and electrodes from the subject. Adhesive swabs or a warm, moist washcloth may be used to remove adhesive gel from the skin.

**Figure 2 – Electrode Placement**

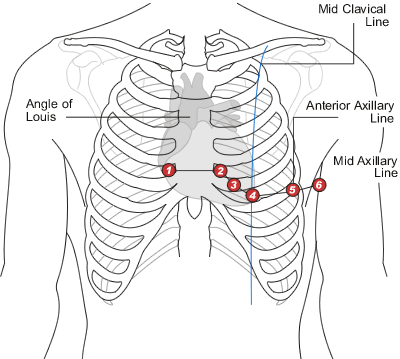
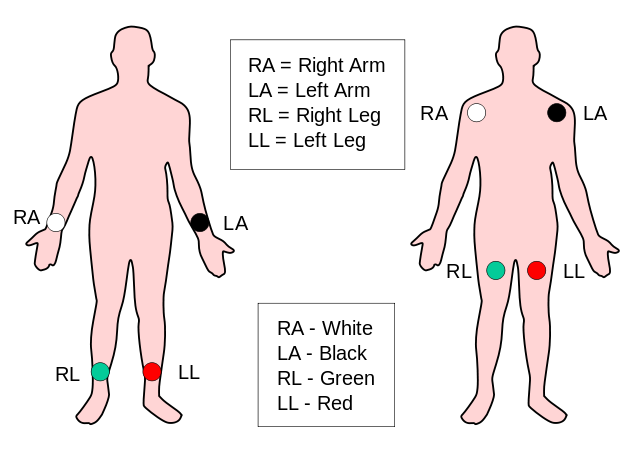
**Placement spots (limb leads)**

**(RA)** On the right arm, avoiding thick muscle

**(LA)** In the same location that RA was placed, but on the left arm

**(RL)** On the right leg, lateral calf muscle

**(LL)** In the same location that RL was placed, but on the left leg



**Placement spots (precordial leads)**

**(V1)** In the fourth intercostal space (between ribs 4 and 5) just to the right of the sternum (breastbone). Remember, the first rib you can palpate is the second rib.

**(V2)** In the fourth intercostal space (between ribs 4 and 5) just to the left of the sternum.

**(V3)** Between leads 2 and 4.

**(V4)** In the fifth intercostal space (between ribs 5 and 6) in the mid-clavicular line (the imaginary line that extends down the midpoint of the clavicle).

**(V5)** Horizontally even with V4, but in the anterior axillary line. (The anterior axillary line is the imaginary line that runs down from the point midway between the middle of the clavicle and the lateral end of the clavicle; the lateral end of the collarbone is the end closer to the arm.)

**(V6)** Horizontally even with V4 and V5 in the mid-axillary line. (The mid-axillary line is the imaginary line that extends down from the middle of the subject’s armpit.)

### For ECGs done at screening and baseline, assess for cardiac exclusion criteria (adapted to endTB protocol from version 3.3 and endTB-Q protocol from 2.2)

1. An arithmetic average of the two ECGs with highest QTcF intervals of greater than or equal to 450 ms. Screening ECGs may be repeated within the 14-day screening window in a patient whose initial screening QTcF interval was above this threshold.
2. Evidence of ventricular pre-excitation (e.g., Wolff Parkinson White syndrome);
3. Pre-excitation is caused by direct and slow activation of the ventricle through a bypass tract – not through the standard His-Purkinje conduction system. This direct activation occurs before the standard conduction and is called pre-excitation. Thus, the QRS is wider than usual and the PR interval is short. Pre-excitation can be intermittent.
4. Electrocardiographic evidence of either complete left bundle branch block or right bundle branch block OR incomplete left or right bundle branch block and QRS complex duration greater than or equal to 120 ms on at least one ECG, meeting the following criteria:
5. Left Bundle Branch Block (LBBB): QS (or rS) in lead V1, tall R in leads V6 and I;
6. Right Bundle Branch Block (RBBB): rSR’ in lead V1, deep S in V6 and leads I.
7. Evidence of second or third degree heart block;
8. 2nd degree heart block: each P wave is NOT followed by a QRS complex (only some P waves are followed by a QRS complex);
9. 3rd degree heart block: there is no consistent relationship between P waves and QRS complexes.
10. Bradycardia as defined by sinus rate less than 50 bpm;
11. Having a pacemaker implant;
12. Evidence of congestive heart failure;
13. Personal or family history of Long QT Syndrome;
14. Family history of sudden cardiac death with a doctor’s diagnosis of Long QT syndrome.
15. Personal history of arrhythmic cardiac disease, with the exception of sinus arrhythmia;
16. Obtained from patient’s clinical history.
17. Personal history of syncope (i.e. cardiac syncope not including syncope due to vasovagal or epileptic causes);
18. Obtained from patient’s clinical history. Cardiac syncope may or may not be preceded by palpitations. Sudden syncope without a prodrome is concerning for cardiac syncope.

### Manually determine the QTcF for each ECG performed.

1. For each ECG performed, the investigator, delegated personnel, or cardiologist should determine the QTcF and whether it is within normal limits (if abnormal, the event shoud be graded, see Table 3 below). As soon as the ECG is performed, confirm that there is a stable isoelectric baseline, that there is a low noise level, and that none of the limb or precordial leads were disconnected. If not, discard it and immediately repeat the ECG. Also, if there are frequent premature atrial contractions (PACs), premature ventricular contractions (PVCs), or sinus arrythmia, it may be necessary to repeat the ECG.
2. For Each ECG:
3. **Assess the rhythm**. If an abnormal rhythm (other than sinus tachycardia) is observed or suspected, have the ECG read by a cardiologist as soon as possible. If a cardiologist is not readily available on-site, consider sending the ECG for a STAT central reading if there are clinical concerns that a timely opinion on the interpretation of the ECG is needed).
4. **Determine the heart rate (HR)**. It is acceptable to take the HR determined by the ECG machine or to determine it by the formula HR = 60/(RR interval in seconds) (use calipers to measure the RR interval and calculate the HR). If the RR interval is measured manually, it should be measured in the same beat as the QT interval.
5. **Determine the QT and QTcF.** While the study-approved ECG machines do provide readouts of the QT interval and QTcF, it is preferred and required that all QT intervals and QTcF intervals are determined manually and then checked against the machine readouts.
6. To determine the QT interval it is preferred to use one of the limb leads that best shows the end of the T wave on a 12-lead ECG.
   * 1. Often, lead II may best show the end of the T wave.
     2. The clinician should use their best judgment to assess which lead best shows the end of the T wave. If the T wave is not clear in lead II, try leads V5 or V6.
7. The QT interval should be measured using calipers from the beginning of the QRS complex to the end of the T wave.
8. If the rhythm is irregular (e.g., atrial fibrillation), the QT interval should be averaged over 3 to 5 *representative* beats. The clinician should use their best judgment to assess which beats are *representative* of the patient’s HR. Calculate the QTcF for each beat, and then calculate the arithmetic average QTcF of the beats. If using a rhythm strip to measure QT on a complex, do not use the first beat/complex because the TP segment will generally be unclear.
9. Even if the rhythm is regular, averaging the QT interval over from more beats might give a more accurate estimation. This measurement is recommended in cases of prolonged QT interval or in case of large differences between the manually calculated QT and the machine calculated QT intervals.
10. U waves possibly corresponding to the late repolarization of cells in the mid myocardium should be included in the measurement only if they are large enough to seem to merge with the T wave (see Figure 1). Small U waves (< 1 mm) and those that are separate from the T wave should be excluded.
11. If the start of the Q wave or the end of the T wave fall in the middle of the horizontal boxes, estimate it to the nearest 1⁄4 of a horizontal box of the ECG machine printout.
12. For each ECG performed manually correct the QT interval for the heart rate to obtain the QTcF. For standardization, we will be using the Fridericia formula to correct for heart rate. The Fridericia formula performs better at lower and higher heart rates than other correction methods. QT correction according to the Fridericia formula can be performed in different ways, as below:
13. Using the QTcF nomogram in Appendix 1,\* select the use the uncorrected QT interval from the vertical axis and the patient’s heart rate from the horizontal axis. The QTcF corresponds to the cell at the intersection of the QT interval and heart rate. For example, for a heart rate of 90 bpm (corresponding to an RR interval of 0.667 seconds) and an uncorrected QT interval of 450 ms, the QTcF would be 515 ms; ***OR***
14. Using the Fridericia formula that is provided in the **QTcF Calculator Excel spreadsheet**, enter the QT (ms) and heart rate (beats per minute) and the spreadsheet will automatically calculate the QTcF. There are also highly detailed QTcF nomograms in other worksheets of the **QTcF Calculator Excel spreadsheet** for further clarity of how the QT interval changes with heart rate; ***OR***
15. Using other QTcF calculators (web-based or mobile applications), entering the QT (ms) and heart rate (beats per minute).

*\* Please note that QT correction using the QTcF nomogram (method i. above) is not as precise as using methods ii. or iii., which allow input of HR/RR and QT to single digits.*

1. Compare the manually calculated QTcF to the machine calculated QTcF readout. If there is a ≥ 20 ms difference between the machine readout and the manually produced result, then recheck the manually produced result. For differences of ≥ 20 ms that persist despite a recheck, have the ECG read by a cardiologist or consider sending the ECG for central reading (have it done as a STAT central reading if there are clinical concerns that a timely opinion on the interpretation of the ECG is needed).
   1. If the difference between the manually calculated QTcF and the machine calculated QTcF is < 20 ms, then record the manually calculated QTcF in the source documents and capture in the case report form.
   2. If the difference between the manually calculated QTcF and the machine calculated QTcF is ≥ 20 ms, then record the manually calculated QTcF in the source documents and capture in the case report form (and verify this result with either a cardiologist reading or a central reading).
2. For each ECG performed at a visit, repeat steps 4c-f to calculate the QTcF.
3. If two ECGs are performed, calculate the arithmetic average of the QTcF.
4. If more than two ECGs are performed, calculate the arithmetic mean of the highest 2 QTcF calculations (i.e., if 3 ECGs are perfomed, calculate the average of the QTcF of the highest 2 of the 3).
5. The arithmetic average of the QTcF carries more weight in clinical decisions; however, all ECGs performed should be recorded in the source documents and captured in the case report form.
6. If the follow-up or unscheduled mean QTc interval meets criteria for an adverse event (grading scale excerpted in Table 3 below; see ***SOP SP-018-CT Management of Specific Adverse Events*** for more details), then also record the grade in the source documents and capture in the case report form.

**Table 3 – Severity grading scale for QT prolongation**

| **Grade Severity\*** | **Grade 1 Mild** | **Grade 2 Moderate** | **Grade 3 Severe** | **Grade 4 Life-threatening** |
| --- | --- | --- | --- | --- |
| Definition | Average QTcF 450 – 480 ms | Average QTcF 481 – 500 ms | Average QTcF ≥ 501 ms without signs/symptoms of serious arrhythmia | Average QTcF ≥ 501 or > 60 ms change from baseline and one of the following: torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia |

1. Print copies of all ECGs performed and place them in the patient’s clinical chart.
2. If using non-study ECG machines, print an extra copy that can be used to scan or send by mail for central readings (details of how of transmission of ECGs done on non-study machines will be provided in a different communication).
3. Record the results in the source documents and capture in the case report form.

### Send the ECG readings via electronic transfer for central reading

1. The number of ECG readings sent for central reading is determined by visit purpose/week number:
2. For all patients that have a screening and baseline (for patients eligible following the screening visit) visits, one ECG is sent for a central reading.
3. At routine follow-up visits at Weeks 1, 3, 5, 8, 16, 24, 32, 39, and 73, a minimum of one ECG is sent for central reading.
4. At routine follow-up visits at Weeks 1, 3, 5, 8, 16, 24, 32, 39, and 73, a minimum of one ECG is sent for central reading.
5. More than the minimum number of ECGs for a visit can be sent for central readings if indicated.
6. For unscheduled visits that have an ECG for a clinical reason send any ECGs that have an abnormality on an ECG such as an arrhythmia, a QTcF greater than 480 ms, or a > 60 ms change from baseline, or some other cardiac concern. ECGs that are performed at an unscheduled visit that have no abnormalities do not need to be sent for central reads.
7. Consider sending more than the minimum ECGs if there is an abnormality on an ECG such as an arrhythmia, a QTcF greater than 480 ms, a > 60 ms change from baseline, or some other cardiac concern.
8. For visits where more than one ECG was performed, but only one is to be sent for central reading, choose the ECG that is of the highest quality. If all are of high quality, send the ECG with the longest QTcF.
9. A STAT reading from the central reading vendor can be requested on any ECG.
10. From standard, vendor-provided electrocardiographs, use a digital transfer method (details of how to electronically send an ECG from a vendor-provided machine will be specified in a different communication).
11. From local equipment or non-study ECG machines, print 2 copies of the original ECG. File one printed copy in the source documents of the patient (patient’s medical records). Give the other printed copy to the responsible study nurse. The study nurse should follow instructions from the contracted ECG core laboratory, ERT, on how to submit paper ECG traces for central reading.

## REFERENCES

* Al-Khatib SM, LaPointe NMA, Kramer JM, *et al.* What clinicians should know about the QT interval. *JAMA* 2015;**289**:2120–7. doi:10.1001/jama.289.16.2120

## SUPPORTING DOCUMENTS

* ERT ECG Machine Guide (endTB Site Study Document)

## APPENDIX

|  |  |
| --- | --- |
| **Number** | **Title** |
| A1 | SP-008-CT\_A1- QTcF nomogram |