Guidance on requirements for QTc measurement in ECG monitoring when introducing new drugs and shorter regimens for the treatment of Drug-resistant Tuberculosis
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<th>Acronyms</th>
<th>Definition</th>
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<tr>
<td>Bdq</td>
<td>Bedaquiline</td>
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<tr>
<td>bpm</td>
<td>beats per minute</td>
</tr>
<tr>
<td>Dlm</td>
<td>Delamanid</td>
</tr>
<tr>
<td>DR-TB</td>
<td>Drug-resistant TB</td>
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<td>ECG</td>
<td>Electrography</td>
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<tr>
<td>HR</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>ms</td>
<td>millisecond</td>
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<tr>
<td>QT</td>
<td>Uncorrected QT interval</td>
</tr>
<tr>
<td>QTc</td>
<td>Corrected QT</td>
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<tr>
<td>QTcB</td>
<td>Corrected QT interval by Bazett</td>
</tr>
<tr>
<td>QTcF</td>
<td>Corrected QT interval by Fredericia</td>
</tr>
<tr>
<td>QTcFrid</td>
<td>Corrected QT interval by Fredericia</td>
</tr>
<tr>
<td>s</td>
<td>seconds</td>
</tr>
<tr>
<td>STR</td>
<td>Shorter Treatment Regimen</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
Background

This document describes the steps necessary to measure the corrected QT (QTc) interval from electrocardiography (ECG) monitoring for patients being treated either with the shorter treatment regimen (STR) or the new drugs for drug-resistant TB treatment. In addition, guidance is provided in regard to the requirements that should be considered when procuring ECG machines for monitoring of patients. As long as automatic reporting of QTcF (as detailed in the document) is a feature of a machine, the choice of the actual machine to be procured is at countries’ discretion.
Basics of ECG

ECG is a non-invasive process of recording the electrical activity of the heart over a period of time using electrodes placed on the skin. These electrodes detect the tiny electrical changes arising from the heart’s muscles.

Each heartbeat follows the basic pattern of electrical activity across the heart, wherein the heart needs to recharge itself before the next heartbeat through a cycle of ventricular depolarization and repolarization. The figure below shows one electrophysiologic cycle or heartbeat which includes the PR interval (containing the P wave and PR segment), and the QT interval (containing the QRS complex, ST segment, and T wave).

**Figure 1. Diagram of one ECG period or one heartbeat**

![Diagram of one ECG period or one heartbeat](image)

**The QT interval**

**What is the QT interval?**
The QT interval (indicated in Figure 1) is that portion of the ECG that begins at the start of the QRS complex and ends at the end of the T wave. It expresses the time required for the ventricular myocardium to depolarize and re-polarize.

**Need to correct the QT interval**
The QT interval shortens at faster heart rates, and lengthens at slower heart rates. Since the QT interval is influenced by the heart rate, it needs to be corrected. A correction formula is required to come up with a corrected QT or QTc which estimates the QT interval at a heart rate of 60 beats per minute (bpm). This allows comparison of QT values over time at different heart rates.

**What is the importance of the QTc?**
The QTc, when prolonged means that the heart muscle takes longer than normal to recharge between beats. To have a prolonged QTc means one is at increased risk of arrhythmias, which when severe, can lead to syncope, cardiac arrest or sudden death. Prolonged QTc can be due to congenital defects, electrolyte imbalance, or medications, such as the new MDR-TB drugs, Bedaquiline (Bdq) and Delamanid (Dlm), as well as some repurposed drugs like Moxifloxacin and Clofazimine.
Methods to correct the QT interval
There are four formulae to correct the QT interval, namely Bazett, Fredericia (sometimes spelled Fridericia), Framingham and Hodges, of which Fredericia is the recommended one in the context of the introduction of new drugs and the shorter regimen. It is referred to as the QTcF or QTcFrid. The reason for the preference for Fredericia is that it was the formula applied to correct the QT interval of patients enrolled during the phase II studies of Bdq and Dlm.

The QTcF may be arrived at manually or generated automatically by the ECG machine. Challenge TB recommends automatic QTcF derivation. However, Challenge TB recognizes the reported errors of such automatically generated readings\(^1\), just as there are reported errors in manual reading\(^2\). Hence, until further evidence becomes available, Challenge TB recommends that automatic QTcF reports are supplemented by a manual reading.

ECG Machines

Which ECG machine is preferred?
Nowadays most ECG machines have an automatic QTcF reporting feature, Challenge TB recommends 12-lead ECG machines that have such a feature. However, care needs to be taken as some machines report QTc derived using the Bazett formula QTcB, which is not recommended. It is necessary for countries to make sure before procurement that QTcF is the one being generated. See below for a sample automatic printout of QTcF or QTcFrid from an ECG machine.

Figure 2. Sample printout showing QTcF (or QTcFrid)

What other features of ECG machines are desired?
Other features of ECG machines that are desired in the implementation of new drugs and the STR for DR-TB treatment include a built-in printer, battery operation option (with variations in capacity in terms of hours), portability, with handy dimensions, and light weight allowing machines to be easily brought to the field or from patient to patient in hospitals. Most machines also have memory storage which enables facilities to store ECG files into patient folders, and facilitates sending of files for referral to a specialist, if necessary. Machines also vary in cost. The Annex shows a table of sample 12-lead ECG models that may be considered for use in the Challenge TB project. As long as automatic reporting of QTcF is a machine feature, the choice of the actual machine to be procured is at the countries’ discretion. Note: Some of the models listed may not generate QTcF, therefore confirmation from the respective manufacturers is needed.

The corrected QT interval by Fredericia (QTcF)

What values are considered abnormal QTcF and what action is recommended?
The table below shows the normal and abnormal QTcF values among men, women (including adolescents and children). The WHO 2016 Guidelines consider a QTcF value of greater than 450 ms among males, or 470 ms among females, or an increase of 60 ms from baseline to be prolonged and

\(^1\) Postema PG and Wilde A: Current Cardiology Reviews 2014, 10, 287-294
requires that electrolyte testing and more frequent ECG monitoring be performed. A QTcF interval of more than 500 ms is considered dangerous and is reason to stop the use of Bdq and Dlm, and all other QT prolonging drugs in the regimen. Challenge TB recommends, in addition, that if feasible, preferably, all automatic readouts, are supplemented with manual QTcF calculation during the first few months of implementation. However, if this is not possible, only those with borderline QTcF readings must be supplemented with manual QTcF calculation. (See below for procedure). If there is good concordance between the manual and automatic QTcF measurements noted after some time, automatic readouts alone will suffice, with no need for manual validation.

Table of normal, borderline, prolonged, and dangerous QTcF values, among males and females.

<table>
<thead>
<tr>
<th>QTcF</th>
<th>Male</th>
<th>Female</th>
<th>Action needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;430 ms</td>
<td>&lt;450 ms</td>
<td>If feasible, supplement with manual reading*</td>
</tr>
<tr>
<td>Borderline</td>
<td>430-450 ms</td>
<td>450-470 ms</td>
<td>Supplement with manual reading*</td>
</tr>
<tr>
<td>Prolonged</td>
<td>&gt;450 ms</td>
<td>&gt;470 ms</td>
<td>Supplement with manual reading*</td>
</tr>
<tr>
<td></td>
<td>Increase of 60 ms from baseline</td>
<td></td>
<td>Do more frequent ECG monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Do electrolyte testing</td>
</tr>
<tr>
<td>Dangerous</td>
<td>500 ms</td>
<td></td>
<td>Discontinue Bdq, Dlm and all QT prolonging drugs</td>
</tr>
</tbody>
</table>

*See procedure for manual QTcF calculation below.

How is manual calculation of QTcF done?
The steps for manual QTcF calculation are as follows:
1. From the 12-lead ECG printout, choose Lead II, V5 or V6 as they usually best show the end of the T wave. But, staff should use their best judgment to assess which Lead best shows the end of the T wave.
2. Measure the QT interval from the beginning of the QRS complex to the end of the T wave. This is the uncorrected QT. Measure at least three successive beats, with the maximum interval taken, in case these three beats differ.

An example ECG tracing is provided below to illustrate the measurement of the QT interval, the RR interval and the Heart Rate (HR)*. Please refer to Figures 3, 5 and 6.

Figure 3. Sample ECG tracing showing QT intervals

[Image of ECG tracing]

*See procedure for manual QTcF calculation below.

http://www.mauvila.com/ECG/ecg_fundamentals.htm
The QT interval: the landmarks on Q and T are identified above.

a. In practice, make an imaginary line on Q and on T on one heartbeat on the selected lead
b. Count the number of small squares between Q and T: 8 small squares (in the example above)
c. Multiply the number of squares by the unit time per square (0.04 sec): 8 small squares x 0.04 sec = 0.32 seconds
d. Multiply the result by 1000: $QT = 320$ ms.

Note: In the example above, the ECG paper speed is 25 mm/sec. If the paper speed is 50 mm/sec the number of squares should be multiplied by 0.02.

There may be variations in the appearance of the QT interval. Sometimes, a large U wave >1mm (supposed to follow the T wave) is fused to the T wave and should be included in the QT measurement. Smaller u waves separate from the T wave should not be included. Sometimes, the T wave is notched. In this case, the maximum slope intercept method is used to define the end of the T wave, as shown below.

Figure 4. Defining the end of the T wave using the maximum slope intercept method

Left: The maximum slope intercept method defines the end of the T wave as the intercept between the isoelectric line with the tangent drawn through the maximum down slope of the T wave.

Right: When notched T waves are present, the QT interval is measured from the beginning of the QRS complex extending to the intersection point between the isoelectric line and the tangent drawn from the maximum down slope of the second notch, T2.

3. Some QTcF calculations need the RR interval while some need the heart rate (bpm)

3a. Measure the Heart Rate (HR): In Figure 5, the HR values in bpm for every 5 small squares are given. Starting on the square that coincides with the peak of the first R wave (R1) to the end of the 5th small square to the right, the HR is 300 bpm, then 150 bpm after the next 5 small squares, followed by 100 bpm, then 75 bpm, then 60 bpm every 5 small squares till the next R peak (R2) is reached.
The HR: the two landmarks on the two R waves are identified above.

a. Make two imaginary lines on two consecutive R waves.

b. Count the number of small squares between the two Rs and check the HR that coincides with the number (20 small squares coincide with 75 bpm). The HR is 75 bpm.

Or

3b. Measure the RR interval: the two Rs are identified in Figure 6.

The RR interval: the two landmarks on the 2 R waves are identified above.

1. Make two imaginary lines on two consecutive R waves.

2. Count the number of small squares between the two Rs: 20 small squares in the above example.

Multiply the number of small squares by the unit time per square (0.04): 20 small squares x 0.04 sec = 0.80 seconds. The RR interval is 0.80 sec.

Note: In the example above, the ECG paper speed is 25 mm/sec. If the paper speed is 50 mm/sec, the number of squares should be multiplied by 0.02.
4. Using the QTcF Nomogram below, locate the value of the QT interval obtained above (#2) on the first column of the Nomogram (indicated by the horizontal arrow) and the RR interval (#3B) on the second row of the Nomogram (indicated by the vertical arrow). Then find the value in the table that is common to both intervals (circled below). \( \text{QTcF} = 345 \text{ ms} \).

### QTcF Nomogram

<table>
<thead>
<tr>
<th>R-R Interval (sec)</th>
<th>Heart rate (beats per minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>45</td>
</tr>
<tr>
<td>310</td>
<td>50</td>
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<td>320</td>
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<td>500</td>
<td>145</td>
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<tr>
<td>510</td>
<td>150</td>
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</table>

### QTcF Interval (ms)

<table>
<thead>
<tr>
<th>Heart rate (beats per minute)</th>
<th>QTcF</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>45</td>
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<tr>
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<tr>
<td>150</td>
<td>150</td>
</tr>
</tbody>
</table>
Apply automatic calculators using applications on a smartphone OR visit a website on a computer. Samples are given below

4a. Download the app QxMD (Medical Calculator) from your smartphone.

Calculate (Medical Calculator) By
QxMD Medical Software

This needs the QT interval (#2 above) and the HR (#3A).

1. Open the QxMD application
2. Under Cardiology, go to ECG
   • ECG: Corrected QT
   • QT Correction?
     - Select Fredericia
     - Enter the manually counted QT interval (#2)
     - Enter the manually counted HR (#3A)
   • You will get the "Corrected QT Interval". This is the QTcF.

Or

4b. Go to the following website:


This needs the QT interval (#2) and the RR interval (#3B).

• Enter the manually counted QT interval (#2)
• Enter the RR interval (#3B)
• Click on “calculate”. Four QTc values will automatically appear using four different formulae.
• Choose QTcFredericia. This is the QTcF.

Note: Units should be in ms rather than sec.
4c. Go to the following website:

http://www.thecalculator.co/health/QTc-Calculator-385.html

This needs the QT interval (#2) and the HR (#3A).

- Enter the manually counted QT interval (#2)
- Enter the HR (#3A)
- Click on “calculate”. Four QTc values will automatically appear using four formulae
- Choose Fredericia. This is the QTcF.

Or

5. In the absence of smartphone applications and websites, use a calculator and the Fredericia formula. This needs the QT interval (#2) and the RR interval (#3b) obtained manually. An example is shown below.

\[ QTcF = \frac{QT}{3 \sqrt{RR}} \]

\[
QTcF = \frac{320 \text{ ms}}{3 \sqrt{0.80 \text{ sec}}} \\
= 344.71 \text{ ms (or 345ms)}
\]

Note that all four options using the QTcF Nomogram, the smartphone, computer and calculator arrived at a common QTcF value. Compare this with the automatic QTcF automatic output of the ECG machine. Note that if there is a difference of 30 ms between the manual reading and the generated output, a consultation with a cardiologist is needed for assessment.
Challenge TB recommendation for QTcF measurement

The QT interval must be corrected for the heart rate resulting in \(\text{QTc} \) which stands for corrected QT interval.

**The Fredericia formula is recommended in correcting the QT interval.**

- QTcF is the corrected QT when the Fredericia correction method is used.

**It is recommended to use ECG machines that automatically report the QTcF.**

However, due to reported errors of automatic reading, just as there are reported errors in manual reading, **supplemental manual verification** is recommended to all automatic readouts, if feasible; if this is not possible, supplemental manual reading may be limited to those with borderline (430-450 ms for males and 450-470 ms for females) and prolonged QTcF values (>450 ms for males; 470 ms for females).

- **Manual QTcF** is obtained by determining the uncorrected QT and RR intervals or HR on the ECG printout. These values can be used on the QTcF Nomogram, for calculations in **smartphone applications** or on **websites**
- Manual QTcF calculation may also be done on a **calculator** using the Fredericia formula.

\[
\text{QTcF} = \frac{QT}{3 \sqrt{RR}} 
\]

QTcF is the corrected QT interval using the Fredericia formula. QT in milliseconds (ms) and RR interval in seconds (s).

The above recommendation is in line with that of the WHO Companion Handbook for the Programmatic Management of Drug-resistant TB, 2016, except for the use of supplemental manual verification of the QTcF.
# ANNEX - Potential 12-lead ECG machines for use in the Challenge TB project

<table>
<thead>
<tr>
<th>Model and Price</th>
<th>Technical Specifications</th>
<th>Power</th>
<th>Remarks</th>
<th>Link</th>
</tr>
</thead>
</table>
| Welch Allyn Schiller AT-2 Pulse ECG EKG | MEASUREMENTS: - QTC can be determined  
MEMORY & COMPUTER SPECS: - Can connect to computer and external monitor - Bidirectional communication with SEMA data management system by Shiller  
SIZE & WEIGHT: - Not specified  
OTHER FEATURES: - Full keyboard with direct function keys - Comes with ECG measurement software - 8.5” x 11” print outs | Rechargeable battery—last 1 hour when fully charged | Advertised as easy to use and ideal for hospitals and clinics - Already being used in the field | http://www.schiller.ch/us/us/product/cardiovit-t-102-plus |
| Nihon Kohden Cardiofax5 $1985 | MEASUREMENTS: - ECG test takes 5secs - QTC can be determined - Sampling rate of 500 per sec  
MEMORY & COMPUTER SPECS: - Transfer data to computer via SD memory card  
SIZE & WEIGHT: - 210x69x280mm - 2kg  
OTHER FEATURES: - 12 lead - Built in printer | | | www.cardiologyshop.com/nikocawslin.html |
| GE MAC800 $2376 | MEASUREMENTS: - QTC can be determined  
MEMORY & COMPUTER SPECS: - Memory storage for 300 ECG readings  
SIZE & WEIGHT: - 3 kg - 7 inch TFT screen  
OTHER FEATURES: - Easy to use keypad - Built-in printer | Li-ion battery, 2 hours to charge; 4 hrs of use | Used in Vietnam (STREAM) | https://www.moormedical.com/index.cfm?MAC-800-Resting-ECG-System/&PG=CTL&CS-HOM&FN=ProductDeta il&PID=17210&spx=1 |
| BENEHART R-12 $1390 | MEASUREMENTS: - QTC can be determined  
MEMORY & COMPUTER SPECS: - Automated diagnosis - Can retrieve previous ECG reports  
SIZE & WEIGHT: | Li-ion battery last 3.5 hrs | Used in Ukraine | http://www.mindray.com/en/product/BeneHeart_R12.html |
| Cardioline US AR600adv | MEASUREMENTS: | - Measures QTc  
- Storage of up to 20 full ECG exams  
- PC archive option  
SIZE & WEIGHT:  
- 250 x 60 x 185 mm (length x height x depth)  
OTHER FEATURES:  
- Full print preview (requires less paper)  
- 12 lead  | - Dual power supply  
- Rechargeable internal batteries (1.5 hrs; 10 hrs to charge) or power source | http://www.cardiolines.com/Product/ar600adv-ECG-Machine.html |
| Cardiocare 2000 | MEASUREMENTS: | - Measures QTc, Heart rate, PR, QRS, PRT  
MEMORY & COMPUTER SPECS:  
- Connects to computer  
SIZE & WEIGHT:  
- 296 x 92.5 x 305.5mm  
- 2.98kg  
OTHER FEATURES:  
- 12 channels  
- Built-in printer  | - Uses batteries or can plug in  