Guidance on requirements for QTc measurement in ECG monitoring when introducing new drugs and shorter regimens for the treatment of Drug-resistant Tuberculosis

USAID FROM THE AMERICAN PEOPLE
KNCV TUBERCULOSIS FOUNDATION
CHALLENGE TB

Contents

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Acronyms

Bdq	Bedaquiline
bpm	beats per minute
Dlm	Delamanid
DR-TB	Drug-resistant TB
ECG	Electrography
HR	Heart Rate
ms	millisecond
QT	Uncorrected QT interval
QTc	Corrected QT
QTcB	Corrected QT interval by Bazett
QTcF	Corrected QT interval by Fredericia
QTcFrid	Corrected QT interval by Fredericia
s	seconds
STR	Shorter Treatment Regimen
USAID	United States Agency for International Development
WHO	World Health Organization

Background

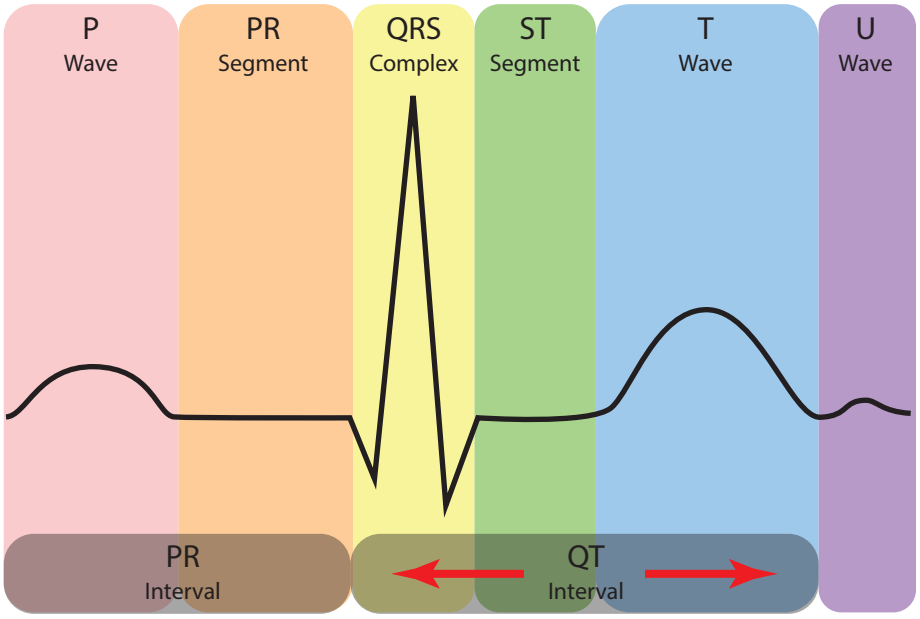
This document describes the steps necessary to measure the corrected QT (QTc) interval from electrocardiography (ECG) monitoring for patients being treated either with the shorter treatment regimen (STR) or the new drugs for drug-resistant TB treatment. In addition, guidance is provided in regard to 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



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.

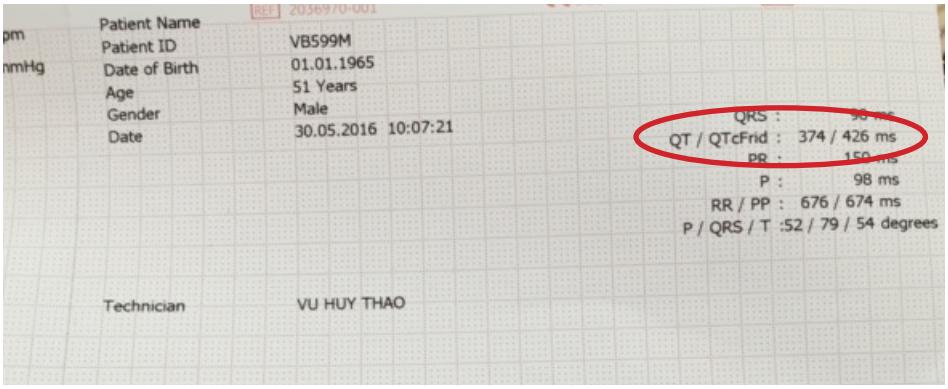
The QTcF may be arrived at manually or generated automatically by the ECG machine. Challenge TB recommends automatic QTcF derivation. However, Challenge TB recognizes the reported errors of such automatically generated readings[1], just as there are reported errors in manual reading[2]. Hence, until 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
2 Wiskin S,Uri R, Sands A, et. al. Heart Rhythm 2005; 2:569-574

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.

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

**See procedure for manual QTcF calculation below.*

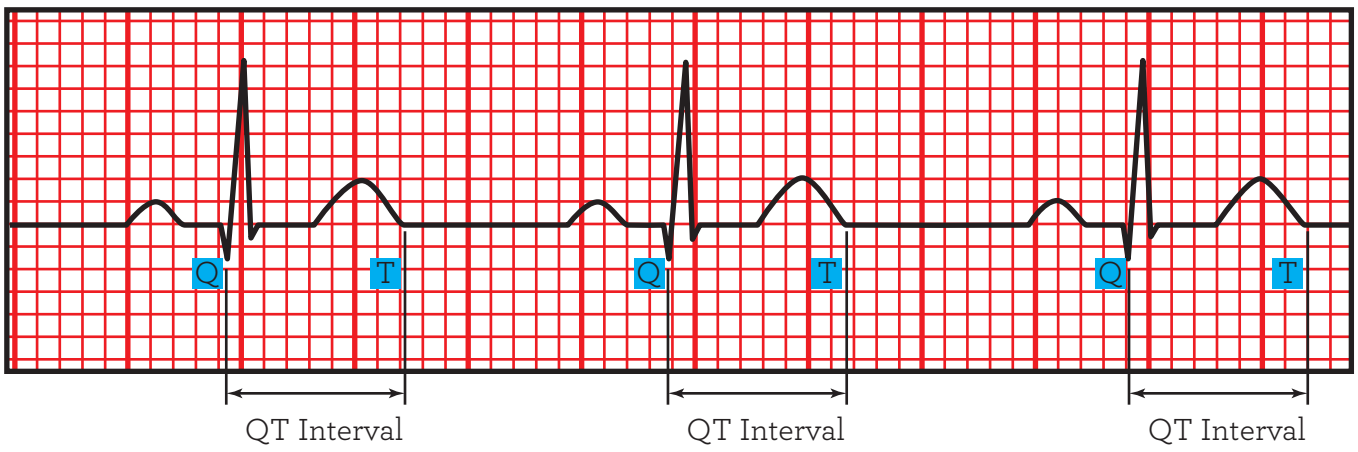
How is manual calculation of QTcF done?

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)[3]. Please refer to Figures 3, 5 and 6.

Figure 3. Sample ECG tracing showing QT intervals



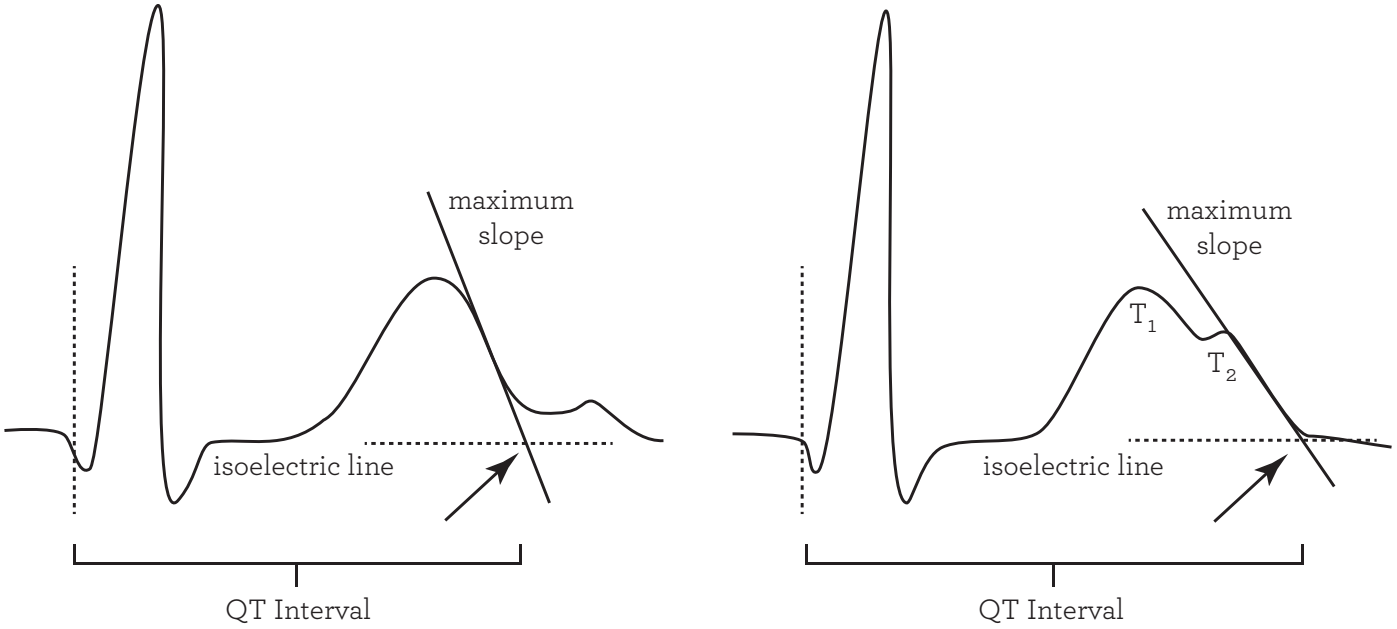
3 http://www.mauvila.com/ECG/ecg_fundamentals.htm

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



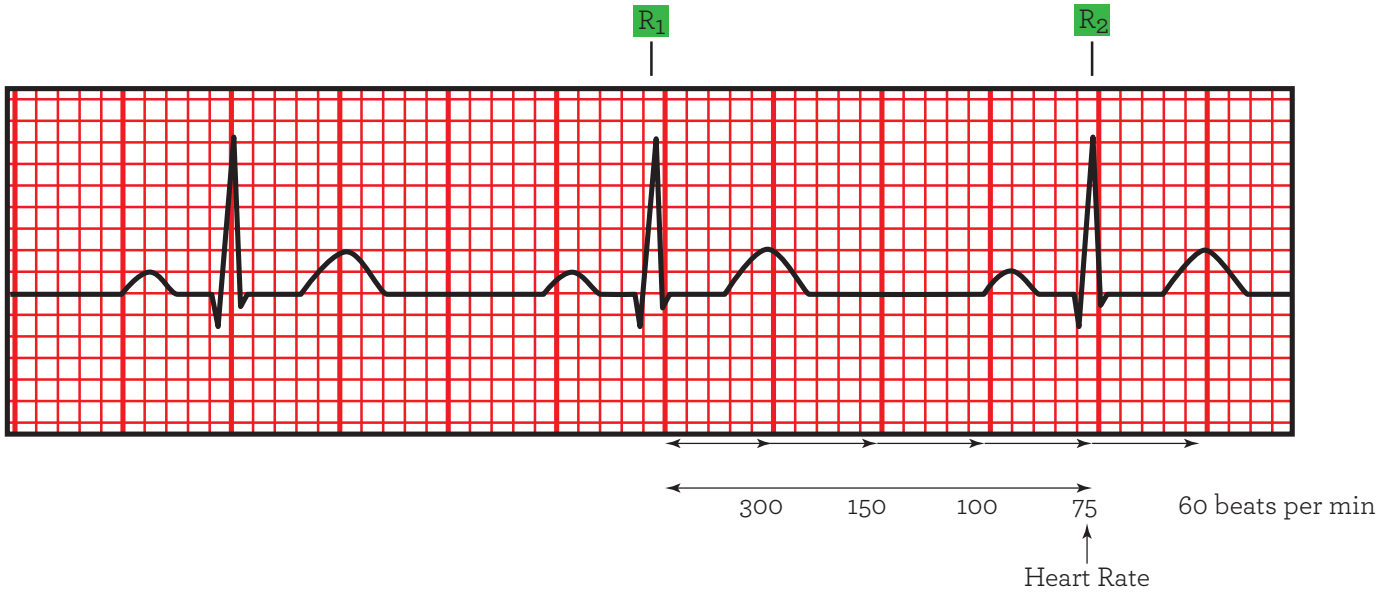
Left: *The maximum slope intercept method defines the end of the T wave as the intercept between the isoelectric line with the tangent drawn through the maximum down slope of the T wave.*

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.

Figure 5. Sample ECG tracing showing the heart rate

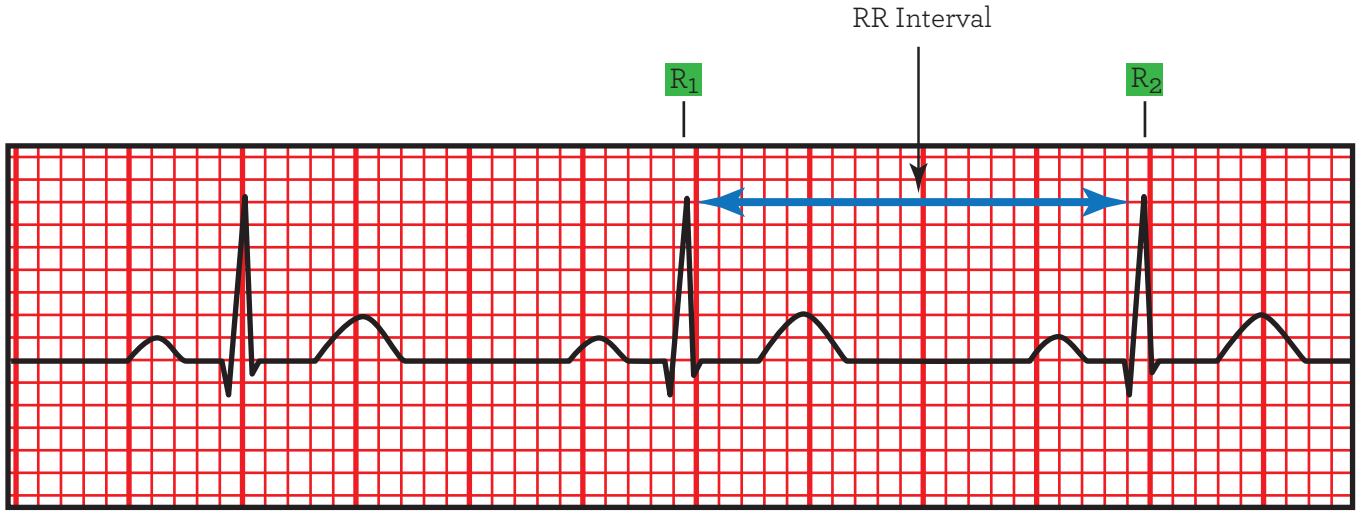


The HR: the two landmarks on the two R waves are identified above.
a. Make two imaginary lines on two consecutive R waves.
b. Count the number of small squares between the two Rs and check the HR that coincides with the number (20 small squares coincide with 75 bpm). The HR is 75 bpm.

Or

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

Figure 6. Sample ECG tracing showing the RR interval



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). **QTcF = 345 ms**.

QTcF Nomogram

Heart rate (beats per minute)	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130	135	140	145	150
R-R Interval (sec)	1.33	1.20	1.09	1.00	0.92	0.86	0.80	0.75	0.71	0.67	0.63	0.60	0.57	0.55	0.52	0.50	0.48	0.46	0.44	0.43	0.41	0.40
QT Interval (msec)																						
300	273	282	291	300	308	316	323	330	337	343	350	356	362	367	373	378	383	388	393	398	403	407
310	282	292	301	310	318	326	334	341	348	355	361	368	374	379	385	391	396	401	406	411	416	421
320	291	301	311	320	329	337	345	352	359	366	373	379	386	392	397	403	409	414	419	424	429	434
330	300	311	321	330	339	347	355	363	371	378	385	391	398	404	410	416	421	427	432	438	443	448
340	309	320	330	340	349	358	366	374	382	389	396	403	410	416	422	428	434	440	446	451	456	461
350	318	329	340	350	359	368	377	385	393	401	408	415	422	428	435	441	447	453	459	464	470	475
360	327	339	350	360	370	379	388	396	404	412	420	427	434	441	447	454	460	466	472	477	483	489
370	336	348	359	370	380	390	399	407	416	424	431	439	446	453	460	466	473	479	485	491	497	502
380	345	358	369	380	390	400	409	418	427	435	443	451	458	465	472	479	485	492	498	504	510	516
390	354	367	379	390	401	411	420	429	438	446	455	462	470	477	484	491	498	505	511	517	523	529
400	363	376	389	400	411	421	431	440	449	458	466	474	482	490	497	504	511	518	524	531	537	543
410	373	386	398	410	421	432	442	451	460	469	478	486	494	502	509	517	524	531	537	544	550	556
420	382	395	408	420	431	442	452	462	472	481	490	498	506	514	522	529	536	543	550	557	564	570
430	391	405	418	430	442	453	463	473	483	492	501	510	518	526	534	542	549	556	563	570	577	584
440	400	414	427	440	452	463	474	484	494	504	513	522	530	539	547	554	562	569	577	584	590	597
450	409	423	437	450	462	474	485	495	505	515	524	534	542	551	559	567	575	582	590	597	604	611
460	418	433	447	460	472	484	496	506	517	527	536	545	554	563	571	580	588	595	603	610	617	624
470	427	442	457	470	483	495	506	517	528	538	548	557	566	575	584	592	600	608	616	623	631	638
480	436	452	466	480	493	505	517	528	539	549	559	569	578	587	596	605	613	621	629	637	644	651
490	445	461	476	490	503	516	528	539	550	561	571	581	590	600	609	617	626	634	642	650	658	665
500	454	471	486	500	514	526	539	550	562	572	583	593	603	612	621	630	639	647	655	663	671	679
510	463	480	495	510	524	537	549	561	573	584	594	605	615	624	634	643	651	660	668	676	684	692
520	472	489	505	520	534	547	560	572	584	595	606	617	623	636	646	655	664	673	681	690	698	706
530	482	499	515	530	544	558	571	583	595	607	618	628	639	649	658	668	677	686	694	703	711	719
540	491	508	525	540	555	568	582	594	606	618	629	640	651	661	671	680	690	699	708	716	725	733
550	500	518	534	550	565	579	592	605	618	630	641	652	663	673	683	693	702	712	721	729	738	746
560	509	527	544	560	575	590	603	616	629	641	653	664	675	685	696	706	715	725	734	743	751	760
570	518	536	554	570	585	600	614	627	640	652	664	676	687	698	708	718	728	738	747	756	765	774
580	527	546	563	580	596	611	625	638	651	664	676	688	699	710	720	731	741	751	760	769	778	787
590	536	555	573	590	606	621	636	649	663	675	688	700	711	722	733	743	754	763	773	783	792	801
600	545	565	583	600	616	632	646	660	674	687	699	711	723	734	745	756	766	776	786	796	805	814

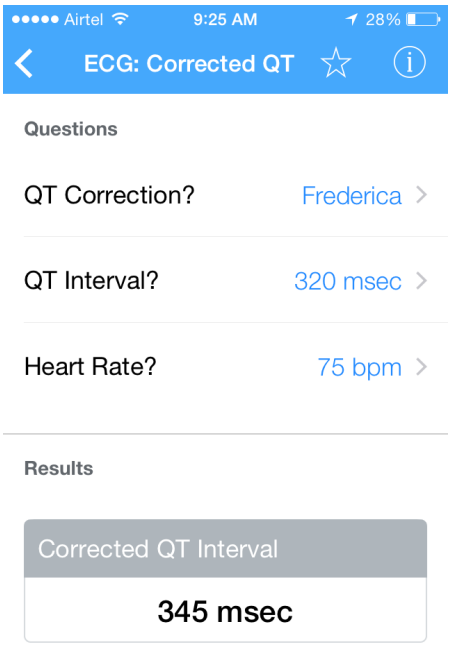
Or

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).



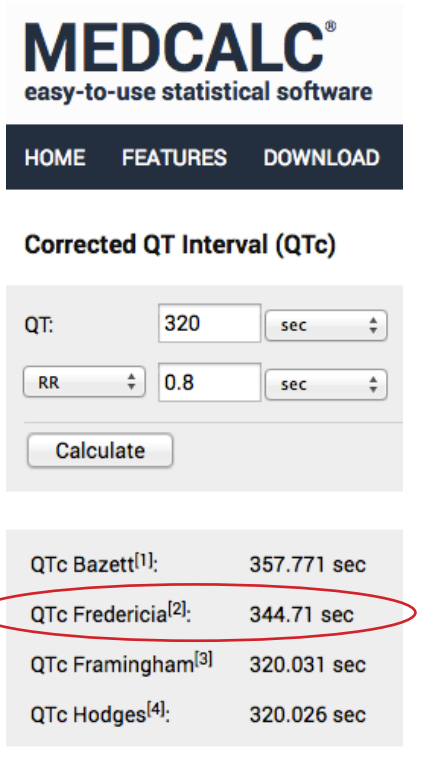
1. Open the QxMD application
2. Under Cardiology, go to ECG
   - ECG: Corrected QT
   - QT Correction?
     - Select Fredericia
     - Enter the manually counted QT interval (#2)
     - Enter the manually counted HR (#3A)
   - You will get the **"Corrected QT Interval". This is the QTcF.**

Or

4b. Go to the following website:

https://www.medcalc.org/clinicalc/corrected-qt-interval-qtc.php

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.**

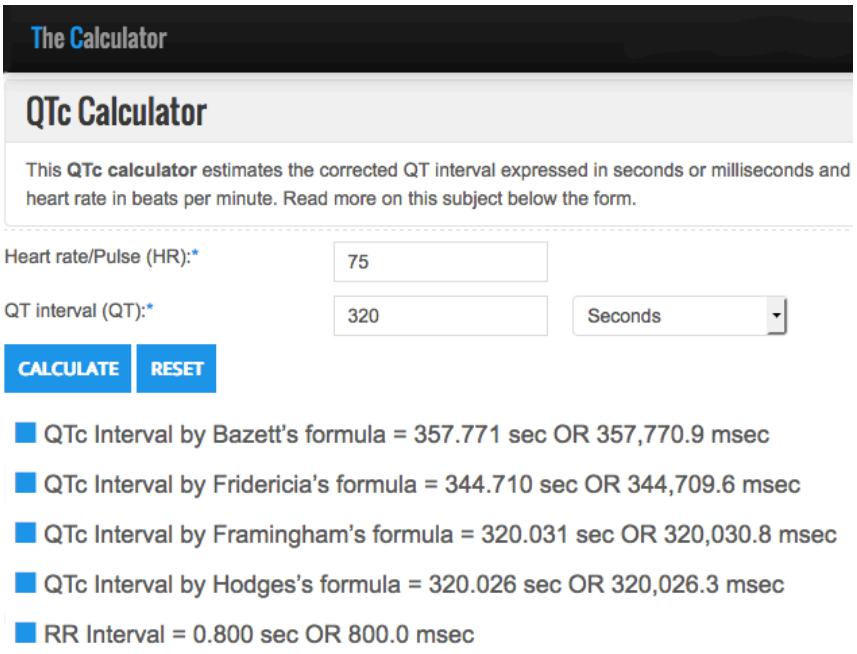
Note: Units should be in ms rather than sec.

Or

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.

$$QT_{cF} = \frac{QT}{\sqrt[3]{RR}}$$

$$\textbf{QTcF} = \frac{QT}{\sqrt[3]{RR}} = \frac{320\ ms}{\sqrt[3]{.80\ sec}}$$

= 344.71 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 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**.**

$$QT_{cF} = \frac{QT}{\sqrt[3]{RR}}$$

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

LARGER PORTABLE MODELS WITH BUILT-IN PRINTERS				
Model and Price	Technical Specifications	Power	Remarks	Link
Welch Allyn Schiller AT-2 Pluse ECG EKG **Price:Contact Company** 	**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		-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-102-plus
Nihon Kohden CardiofaxS **$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	Rechargeable battery—last 1 hour when fully charged	Used in Vietnam (BDQ/STR regimen)	www.cardiologyshop.com/nikocawsiin.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.mooremedical.com/index.cfm?/MAC-800-Resting-ECG-System/&PG=CTL&CS=HOM&FN=ProductDetail&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

	-8 inch high resolution color display -128x365x305(HxWxD) -4.9 kg **OTHER FEATURES**: -Full print preview (requires less paper) -12 lead			
Cardioline US AR600adv **$1695** 	**MEASUREMENTS**: -Measures QTc **MEMORY & COMPUTER SPECS**: -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**: -Record either automatic, manual or pre-programmed -Built-in printer	-Dual power supply Rechargeable internal batteries (1.5 hrs; 10 hrs to charge) or power source		http://www.cardiolineus.com/Product/ar600adv-ECG-Machine.html
Cardiocare 2000 **List Price: $2,595** 	**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	Used for endTB project in Kazakstan	http://ordamed.kz/production/med/funkcionalnaya_diagnostika/electrocard_bionet/433-elektrokardiograf-cardiocare-2000-bionet-co-ltd-yuzhnaya-koreya-rk-mt-5004292-14092007-g.html

http://www.challengetb.org