Guide for QTc monitoring and management of drug-resistant TB patients with QT-prolonging agents

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CHALLENGE TB

Contents

Acknowledgements

This guidance is an updated version of the 2017 document prepared by Mamel Quelapio and Maria Idrissova, with the contributions of Gunta Dravniece, Celeste Edwards, Agnes Gebhard, Inge Koppelaar, Marcela Tommasi, and Fraser Wares (KNCV Tuberculosis Foundation).

KNCV acknowledges the inputs provided by colleagues from the World Health Organization (WHO) - Geneva (Ernesto Jaramillo, Oyere Onuma), The Union (Alberto Piubello, Valerie Schwoebel), PATH (Olga Pavlova) and the United States Agency for International Development (USAID) (Alex Golubkov, Anh Innes, YaDiul Mukadi, and Edmund Rutta) in the development of this guidance.

Design/Layout - Tristan Bayly.

This document was developed by Challenge TB through the technical support of KNCV Tuberculosis Foundation, and uses elements from the WHO *Companion Handbook for the Programmatic Management of DR-TB*, 2014 and the endTB *Clinical and Programmatic Guide for Patient Management with New TB Drugs*, version 4.0, January 2018.

Version: 0.5
Date: 5 December 2018
Funding: USAID/CTB
Technical Support: KNCV Tuberculosis Foundation

The Global Health Bureau, Office of Health, Infectious Disease and Nutrition (HIDN), United States Agency for International Development, financially supports this guide through Challenge TB under the terms of Agreement No. AID-OAA-A-14-00029. This guidance document is made possible by the generous support of the American people through the United States Agency for International Development (USAID). The contents are the responsibility of Challenge TB and do not necessarily reflect the views of USAID or the United States Government.

Acronyms

Bdq	Bedaquiline
bpm	beats per minute
BMI	Body mass index
Cfz	Clofazimine
CR	Conditional risk
CTB	Challenge TB
Dlm	Delamanid
DR-TB	Drug-resistant TB
ECG	Electrocardiography
Eto	Ethionamide
F	Female
FQ	Fluroquinolones
Hgb	Hemoglobin
HR	Heart rate
IV	Intravenous
KR	Known risk
Lfx	Levofloxacin
M	Male
Mfx	Moxifloxacin
ms or msec	millisecond
PR	Probable risk
Pto	Prothionamide
QT	Uncorrected QT interval
QTc	Corrected QT interval
QTcF	Corrected QT interval by Fredericia or Fridericia
QTcFr	Corrected QT interval by Framingham
RR-TB	Rifampicin-resistant TB
s or sec	second
STR	Shorter DR-TB treatment regimen
TdP	Torsades de pointes
TSH	Thyroid stimulating hormone

Background

The advent of new and repurposed medicines for drug-resistant TB (DR-TB) has opened positive alternatives for patients not responding well or not tolerating conventional anti-TB agents. However, repurposed agents for DR-TB like Moxifloxacin (Mfx), and to a lesser extent, Levofloxacin (Lfx), Clofazimine (Cfz), and new DR-TB drugs such as Bedaquiline (Bdq) and Delamanid (Dlm), may prolong the QT interval in the electrocardiogram (ECG), which, if not addressed in time, may lead to life-threatening arrhythmias, such as torsades de pointes (TdP).

Purpose of the document

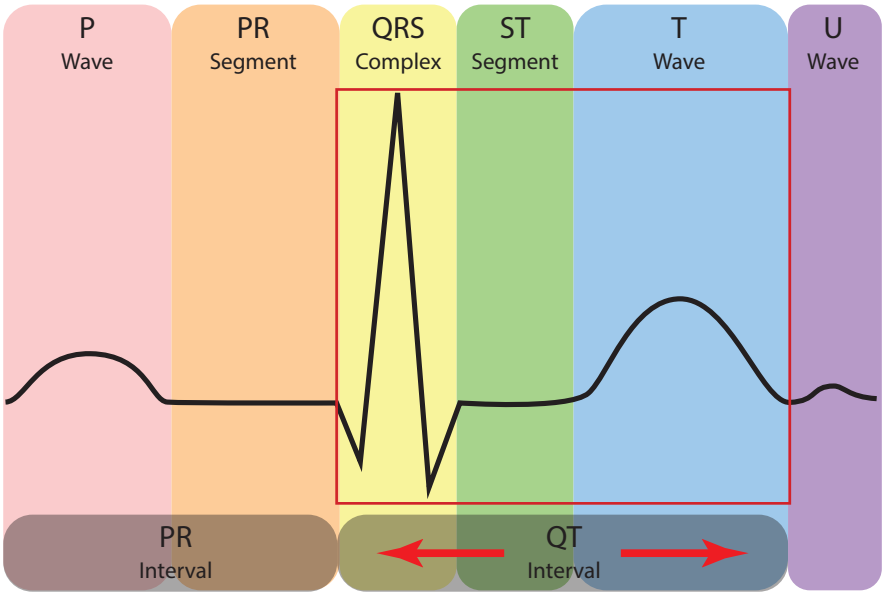
This document describes the steps necessary to determine the corrected QT (QTc) interval in ECG monitoring of patients receiving QT-prolonging medicines for the treatment of DR-TB. It also provides guidance in the management of QTc prolongation.

Basics of ECG

The ECG is a non-invasive process of recording the electrical activity of the heart over a period of time. The ECG detects tiny electrical changes arising from the heart's muscles.

Each heartbeat (**Figure 1**) 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 (heartbeat) which includes the PR interval (containing the *P wave* and PR segment), and the **QT interval** highlighted in a box containing the QRS complex, ST segment, and *T wave*.

Figure 1: Diagram of one electrophysiologic cycle of the heart period or one heartbeat



The QT interval

What is the QT interval?

The QT interval is that portion of the ECG that begins at the start of the QRS complex and ends at the termination of the *T wave* (**Figure 1**). The QT interval is important because it expresses the time required for the ventricular myocardium to depolarize and re-polarize, or the time it takes for the heart muscle to recharge between beats. It is measured in seconds (s) or milliseconds (ms).

Why does the QT interval need to be corrected?

The QT interval is influenced by the heart rate (HR). It shortens at faster HRs, and lengthens at slower HRs; hence, the QT interval 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 HR of 60 beats per minute (bpm). This allows comparison of QT values on ECGs taken at different times.

What is the normal QTc value?

The QTc is considered normal at <450 ms in males (M), and <470 ms in females (F). It can vary by up to 75 ms in the same individual at different times during the same day. Because of this, it is recommended that the ECG for QTc monitoring be done at approximately the same time of the day. The QTc interval has a circadian profile with diurnal variability exhibiting a significant QTc increase in the morning hours (when the QTc is usually measured) and a consecutive decline to baseline levels.

The 2017 version of this guide considered an increase of 60 ms from the baseline QTc as prolonged. However, given the nature of the QTc interval, the increase of 60 ms from baseline may not be a reliable basis for QTc prolongation. However, an increase of 60 ms may flag the need for closer follow-up especially when the ECGs were done at approximately the same time of the day on different days.

What is the importance of the QTc?
When the QTc is prolonged, it 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.

What are the causes of QTc prolongation?
While some anti-TB drugs are associated with QTc prolongation, it is not always drug-induced. There is suggestive evidence that at least one risk factor was present before drug-induced QTc prolongation occurred in patients, and in 70% of cases, two risk factors were present. Hence, it is very important to thoroughly assess DR-TB patients before attributing QTc prolongation solely to anti-TB drugs.

Table 1 shows unmodifiable and potentially modifiable risk factors for drug-induced QT prolongation and TdP. Examples of unmodifiable risk factors include the female gender (present in 70% of cases), increasing age (linearly increased risk after 60 years), genetic predisposition, previous drug-induced QTc prolongation, structural heart disease/left ventricular dysfunction, and impaired elimination of medicines due to renal or hepatic disease. Potentially modifiable risk factors include electrolyte imbalance (hypokalemia, hypomagnesemia, hypocalcemia), hypothyroidism, structural and functional heart problems, drug interactions, low body mass index (BMI), drug overdose, or rapid IV administration. There are also conditions common among DR-TB patients that increase the risk for QTc prolongation. These include HIV infection due to the potential additive clinical risk factors especially in advanced disease and multiple medications, malnutrition, starvation, severe vomiting, and diarrhea which can lead to hypokalemia.

Table 1: Risk factors for drug-induced QTc prolongation

Unmodifiable risk-factors	Potentially modifiable risk-factors (acquired risk-factors)

• Female gender
• Increasing age
• Genetic predisposition
  – Congenital long QT syndrome
  – Family history of sudden death
• History of previous drug-induced QTc prolongation
• Structural heart disease/left ventricular dysfunction
• Impaired elimination due to renal or hepatic disease
	• Electrolyte imbalance
	  - Hypokalemia
	  - Severe hypomagnesemia
	  - Hypocalcemia
	• Hypothyroidism
	• Structural and functional heart problems
	  – Recent conversion from atrial fibrillation (absolute or relative bradycardia
	  – Ischemic and congestive heart disease
	  – Ischemic cardiomyopathy
	  – Dilated or hypertrophic congestive heart disease
	  – Congestive heart failure
	• Drug interactions
	  – >1 QT-prolonging medicines
	  – Medicines that inhibit the metabolism of another QT-prolonging medicine
	  – Medicines that cause electrolyte abnormalities or renal or hepatic dysfunction
	• Low BMI: starvation, wasting syndrome or obesity
	• High drug concentrations due to overdose or rapid IV administration

Annex 1 lists the medications with known risk (KR), possible risk (PR), and conditional risk (CR) for TdP. In this list, the fluoroquinolones (FQ) fall under medications with KR, while Cfz and the new drugs, Bdq and Dlm fall under PR. Non-TB drugs with KR that may be administered for adverse events or comorbidities among DR-TB patients include antiemetics (ondansetron and domperidone), antipsychotics (haloperidol, chlorpromazine), antibiotics (erythromycin and clarithromycin), antifungal (fluconazole), methadone, etc. https://www.crediblemeds.org/healthcare-providers/
It is therefore important to review the list of medications patients are taking during DR-TB treatment.

What are the ways to determine the corrected QT interval (QTc)?

When performing ECG on a patient:

- Ensure that the patient is in a relaxed state to avoid artifacts or ECG 'noise'. Clean the patient's skin, if necessary, to ensure good contact with the electrode. **Annex 2** describes and illustrates the types of significant ECG noise which may cause problems in data processing and analysis, in which case, the ECG should be repeated.
- Ensure that the ECG machine is calibrated, with a paper speed set at 25 mm/s which is the standard speed. The ECG waves are recorded on special graph paper that is divided into 1 mm^2 grid-like squares. Each 1 mm (small) square corresponds to 0.04 s (40 ms), with heavier lines forming larger squares that include five small squares, and hence, represent 0.20 s (200 ms) intervals. **Annex 3** provides more details about ECG calibration.

Determining the QTc value

The QTc value can be automatically generated by the ECG machine or obtained by measurements made manually on the ECG tracing. Whether automatically or manually calculated, the QTc is arrived at using any of four formulae, among which the Fredericia (QTcF) formula (sometimes spelled Fridericia) and the Framingham (QTcFr) formula are considered to provide optimal correction. However, Frdericia is preferred when measuring the QTc of patients on QT-prolonging anti-TB medicines especially the new DR-TB drugs, as this was the formula applied during the phase II studies of Bdq and Dlm, and during the STREAM trial.

A. Automatic generation of the QTc

Most ECG machines nowadays automatically generate the QT and the QTc values using a correction formula. Machines generating the QTcF (QTc by the Fredericia formula) are advised. However, while automatic QTc generation saves staff time and effort, automatically generated QTc values have possible errors because of the inconsistency between ECG manufacturers in the algorithm used for calculation. Moreover, there is a mechanical difficulty to identify the *T* and *U waves* when they are superimposed on each other. *U waves* are usually seen in hypokalemia which is frequent in DR-TB patients, therefore it is crucial to manually recognize these waves and to know when they must be counted as part of the QT interval.

For the above reasons, it is recommended to supplement automatic QTc generation with manual reading. If it is not feasible to do a manual reading in all cases, it should at least be done on those with QTcF readings that are borderline and above (>450 ms for M and >470 ms for F), and in those where the *T* and *U waves* are superimposed or connected.

If there is a discrepancy of 30 ms between the automatically generated QTcF and the manual reading obtained, it is advisable to consult a cardiologist for further assessment.

B. Manual determination of the QTc

To manually determine the QTc, a) measure the uncorrected QT interval (QT), and b) measure the RR interval (or the HR, in case of some applications).

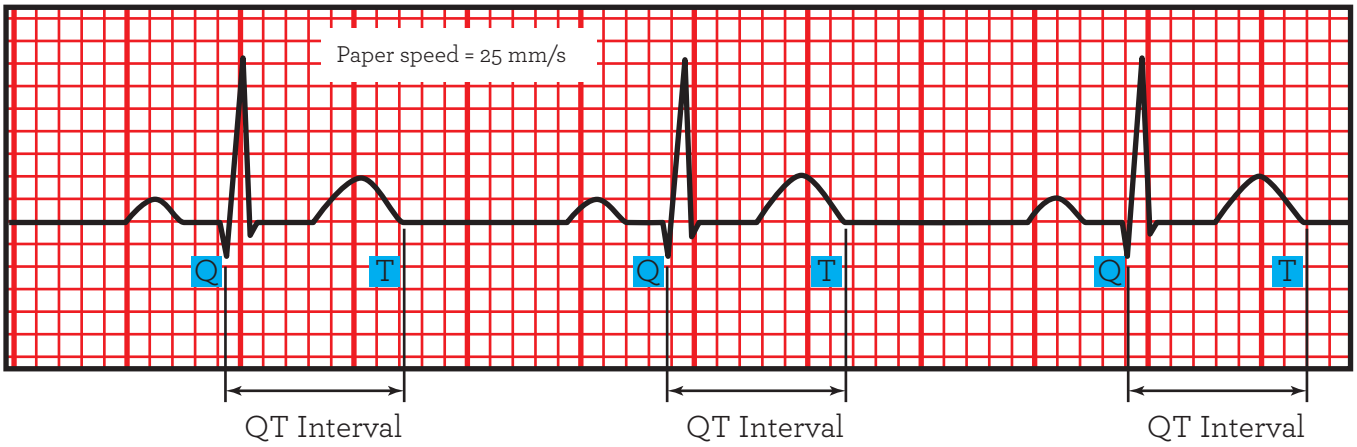
Steps in manual QTc determination:

1. Measure the uncorrected QT interval (QT)

From the ECG rhythm strip, choose either lead II, V5 or V6, where the end of the *T wave* is usually clear. However, if the end of the *T wave* is not clearly seen, best judgment should be made to assess which lead best shows the end of the *T wave*.

Measure the QT interval of at least three successive beats, and take the beat with the maximum interval. If the rhythm is irregular, average the QT interval of 3-5 beats.

Figure 2: The QT interval



The QT interval: the landmarks on Q and T are identified in the above figure.

- In practice, make an imaginary vertical line on Q and on T on one heartbeat on the selected lead.
- Count the number of small squares between Q and T. If the start of the *Q wave* or the end of the *T wave* falls in the middle of a small square, estimate it to the nearest ¼ of the square. The QT interval in **Figure 2** spans 8 small squares.
- Multiply the number of small squares by the unit time per square (0.04 s). (With a paper speed of 25 mm/s, a small square of 1mm is equal to 0.04 s).
- Using **Figure 2** as an example:

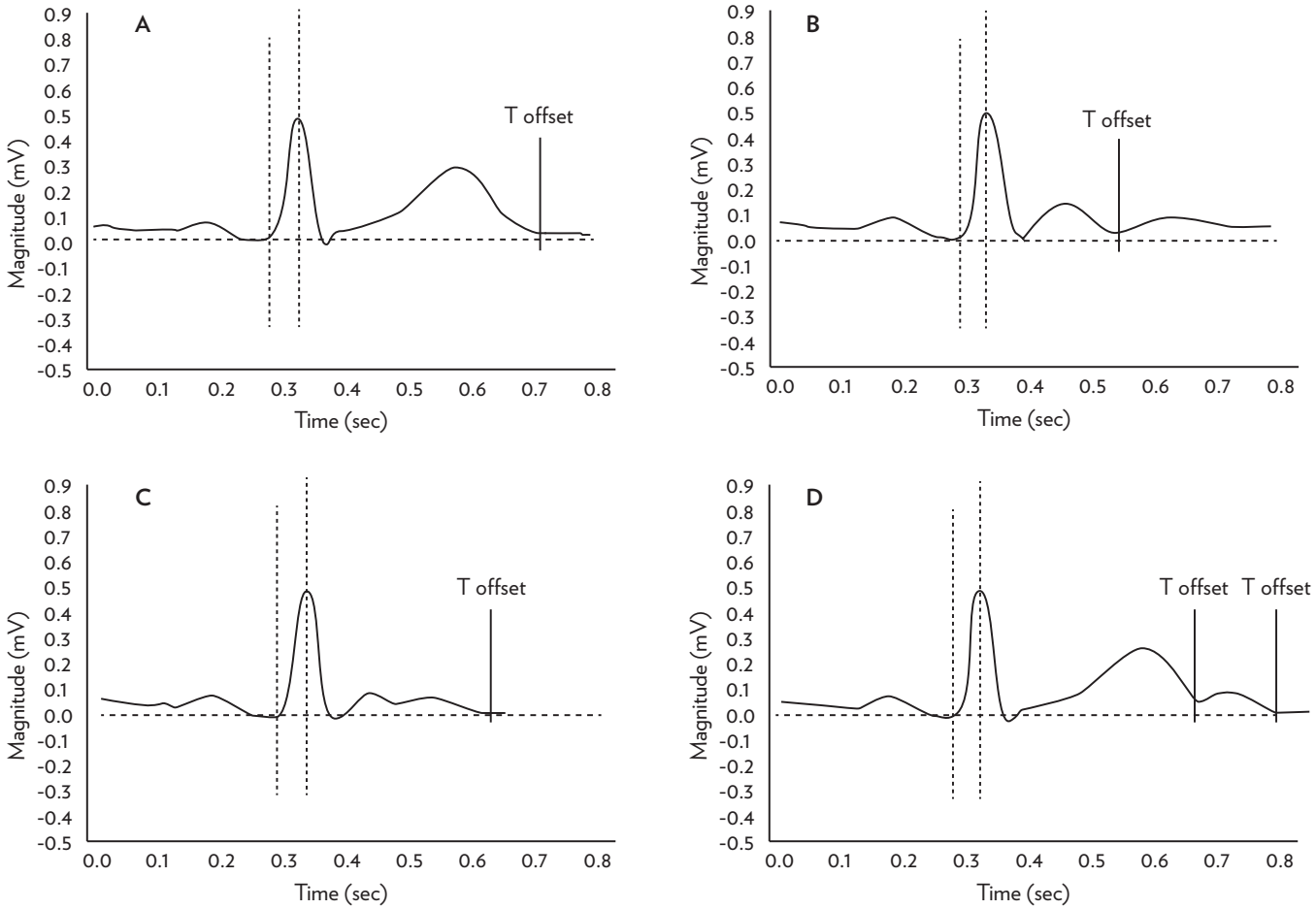
  QT= 8 small squares X 0.04 s = 0.32 s (**320 ms**)

  Note: in case the speed is 50 mm/s, 1 mm will be 0.02 s or 20 ms, where QT = 0.16 s (160 ms)

Sometime, the main difficulty lies in correctly identifying the point where the descending limb of the *T wave* intersects with the isoelectric line, particularly when the *T and U waves* are close together. Examples are shown in **Figure 3**.

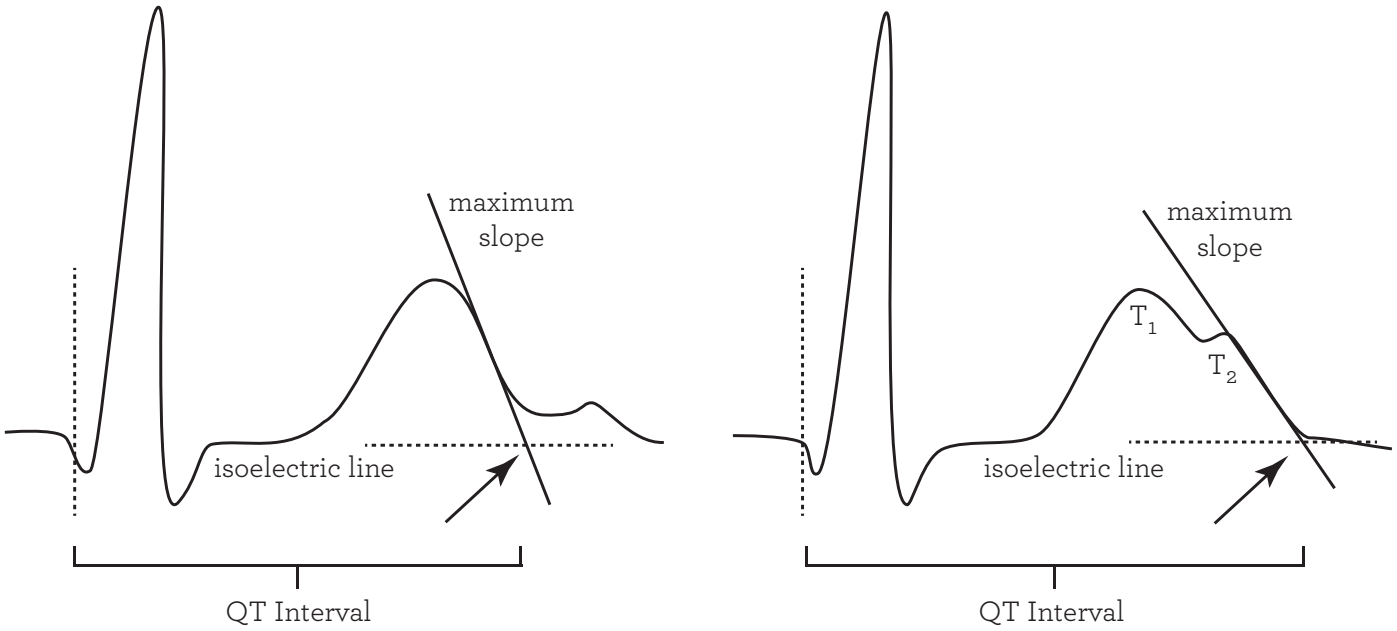
- Large *U waves* (> 1 mm) that are fused to the *T wave* are to be included in the QT measurement, while smaller *U waves* and those that are separate from the *T wave* are to be excluded.

Figure 3: Illustrations of *T wave* morphology and *U waves*



A. Normal *T wave* morphology: the end of the *T wave* is the point when the descending limb returns to baseline
B. *T wave* is followed by a distinct *U wave*: the end of the *T wave* is the point when the descending limb of the *T wave* returns to baseline before the onset of the *U wave*
C. *T wave* is biphasic with *T1* and *T2 waves* of similar amplitude: end of *T wave* is the point when T2 returns to baseline.
D. When a second low-amplitude repolarization wave interrupts the terminal portion of the larger *T wave* (*T2* or *U wave*): the end of the *T wave* is measured both at the nadir of the two waves (1) and the final return to baseline (2). The maximum slope intercept method may be used to define the end of the *T wave* (**Figure 4**)

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



Left QT interval: 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*.

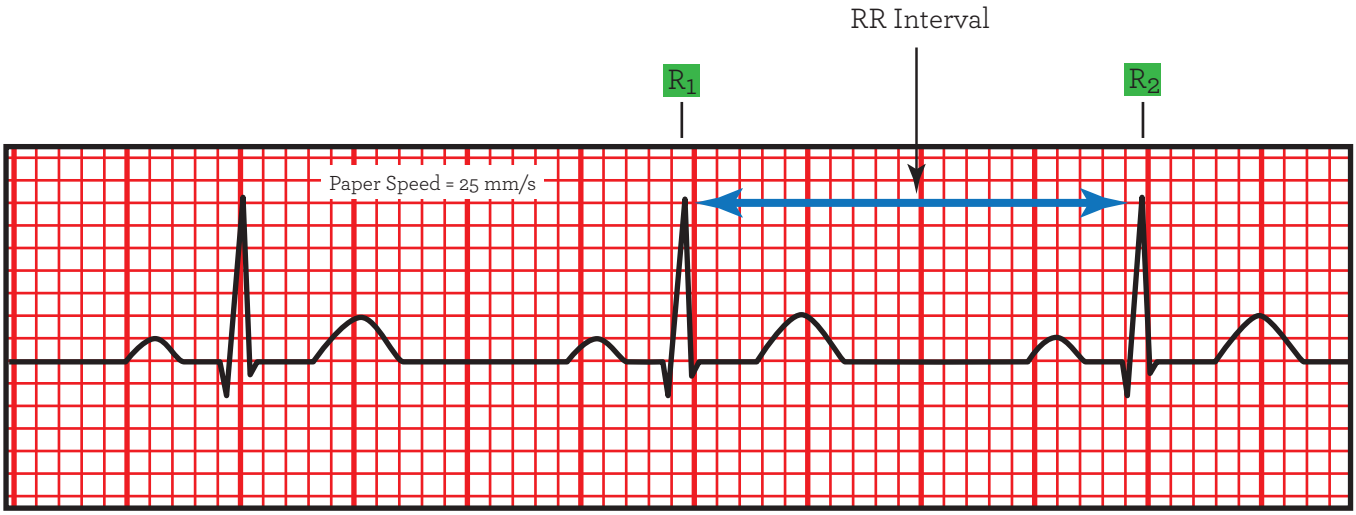
Right QT interval: When notched *T waves* are present, the QT interval is measured from the beginning of the QRS complex extending to the intersection point between the isoelectric line and the tangent drawn from the maximum down slope of the second notch, T2. When in doubt, the longer QT interval measurement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

2. Measure the RR interval or the HR

2a. Measure the RR interval

- The RR interval is the area between two consecutive Rs of the QRS complex in the ECG rhythm strip, as shown in **Figure 5**. The two landmarks on the 2 *R waves* are identified.

Figure 5: The RR interval



- Using the heartbeat where the QT interval was determined in the earlier step, make two imaginary lines on two consecutive *R waves*. Measure the RR interval of this beat.
- Count the number of small squares between the two *R waves*. The RR interval in **Figure 5** spans 20 small squares.
- Multiply the number of small squares by the unit time per square (0.04 s). As above, assuming the paper speed is 25 mm/s, every small square = 0.04 s
- Using **Figure 5** as an example:

  RR= 20 small squares X 0.04 s = 0.80 s (**800 ms**)

2b. Measure the HR

There are applications that ask for the HR instead of the RR interval in order to calculate the QTc.

- To measure the HR in beats per minute (bpm), use the formula:

HR = 60/RR

- Thus, using **Figure 5** as an example:

  HR = 60/0.80 s
  HR = 75 bpm

3. Determine the QTc (corrected QT)

The manual method of QTc determination can be done with any of the following methods that apply the Fredericia QT correction formula a) using a manual calculator, or b) using an application downloaded from a smartphone called QxMD, or c) using the QTcF nomogram, or d) using an electronic calculator downloaded from the website:
https://www.medcalc.org/clinicalc/corrected-qt-interval-qtc.php

a) Using a manual calculator:
The Fredericia formula is as follows:

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

Where:
QTcF = the corrected QT interval using the Fredericia formula
QT = the time between the start of the QRS complex and the end of the *T wave*
RR = the time between the start of one QRS complex and the start of the next QRS complex.

Applying the Fredericia formula in the above example where the calculated QT interval was 320 ms (**Figure 2**), and the RR interval was 0.80 s (**Figure 5**), the *QTcF* value would be 345 ms. Mind the units (s or ms) used in the calculation.

$$QT_{cF} = \frac{320}{\sqrt[3]{0.80}}$$

$$= 344.71 \text{ ms (or 345 ms)}$$

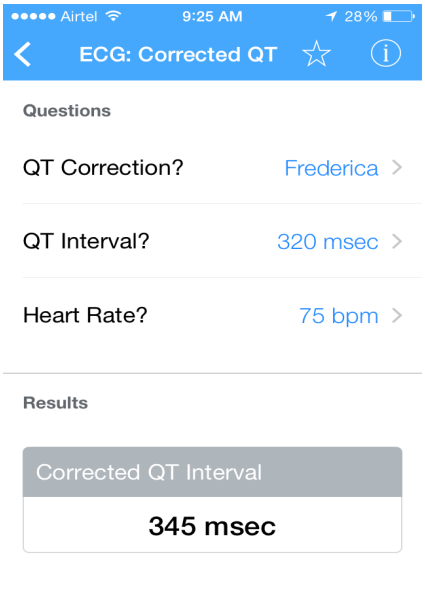
*(See **Annex 6** for an exercise to calculate the QTcF from a real patient's ECG rhythm strip)*

OR

b) Applying the smartphone application QxMD (Figure 6)

Figure 6: QTcF determination using the smartphone application QxMD (Medical Calculator)

Calculate (Medical Calculator) By
QxMD Medical Software



This method needs the QT interval and the HR.

1. Open the downloaded QxMD application
2. Under Cardiology, go to ECG
   - ECG: Corrected QT
   - QT Correction?
     - Select Fredericia
     - Enter the manually counted QT interval (320 ms in **Figure 2**)
     - Enter the HR (75 bpm 2b)
     - Click calculate
   - You will get the **'Corrected QT Interval'**, this is the QTcF.

OR

c) Using the QTcF Nomogram (Figure 7)

The leftmost column in the QTcF Nomogram shows the uncorrected QT interval; the first row is the HR, and the second row is the RR interval. Using the QT interval previously obtained, 320 ms (**Figure 2**), and the RR interval of 0.80 s (**Figure 5**) or the HR of 75 bpm, an intercept can be obtained in the QTcF nomogram which is the QTcF value. In this case, it is 345 ms.

*(See **Annex 6** for an Exercise on calculating the QTcF from the ECG rhythm strip of a real patient)*

Figure 7: QTcF determination using the QTcF Nomogram

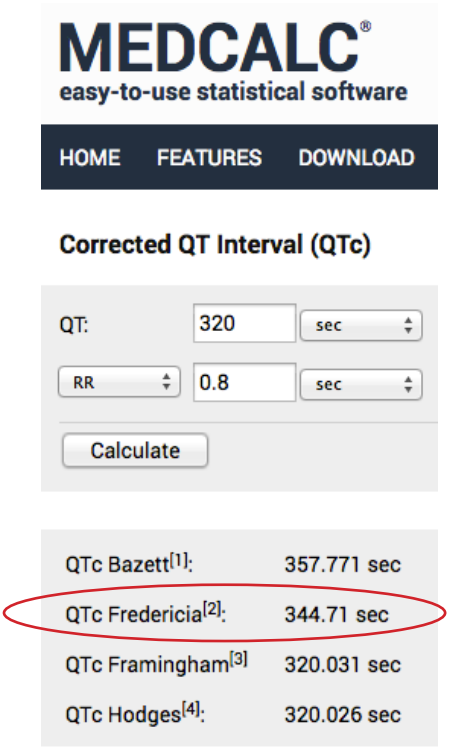
Heart rate (beats per minute)		45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130	135	140	145	150
RR Interval (sec)		1.33	1.20	1.09	1.00	0.92	0.86	0.80	0.75	0.71	0.67	0.63	0.60	0.57	0.55	0.52	0.50	0.48	0.46	0.44	0.43	0.41	0.40
QT Interval (msec)	300	273	282	291	300	308	316	323	330	337	343	350	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

d) Using an electronic calculator downloaded from the website (Figure 8)

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

Figure 8: QTcF determination using an electronic calculator from the website



- Enter the manually counted QT interval (320 ms in **Figure 2**)
- Enter the RR interval (0.8 s in **Figure 5**)
- Click on "calculate". *Four QTc values will automatically appear using four different formulae.*
- **Choose QTcFredericia. This is the QTcF.**

Note: All the QTc results using the manual calculator, the smartphone application (QxMD), the Fredericia nomogram, and the electronic calculator arrived at a common QTcF value. Compare this with the automatically generated QTcF from the ECG machine. As previously mentioned, if there is a **difference of 30 ms** between the automatically generated value vs. the manual reading, it is advised to consult a cardiologist.

When is QTcF prolonged and what action is recommended?
The QTcF is considered *prolonged* when it is ≥450 ms among males and ≥470 ms among females. It is considered *dangerous* when it is >500 ms for both males and females. The recommended actions for these abnormal QTcF values are shown in the algorithms below, and in a table with a severity grading scale and the corresponding management.

For QTcF > 500 ms (**Figure 9a**), QT-prolonging anti-TB drugs need to be discontinued altogether if signs and symptoms (palpitations, tachycardia. lightheadedness, fainting, syncope, chest pain, loss of consciousness) are observed. Hospitalization is advised preferably in a facility that can manage TdP. Other concomitant conditions are managed, and ECG needs to be monitored. In asymptomatic patients with QTcF >500 ms, QT-prolonging medicines are to be stopped sequentially starting with ancillary drugs and anti-TB drugs that have the shortest half-life (FQs), followed by Cfz, Dlm, and then Bdq. These medicines have the following half-life: Mfx: 15-16 hours; Lfx: 6-8 hours; Cfz: 25 days; Dlm: 38 hours; Bdq: 5.5 months. Consider hospitalization, manage other conditions and monitor the ECG.

For QTcF <500 ms but >450 ms (M) and >470 ms (F) (**Figure 9b**), consider discontinuing first the QT-prolonging ancillary agents while managing other concomitant conditions and monitoring the ECG.

Figure 9a: Algorithm for monitoring and managing QTcF prolongation (QTcF >500 ms) among DR-TB patients

QTcF >500 ms confirmed by repeat ECG done ≥30 min apart
Note: Calculate QTcF manually following the recommended procedure.

Asymptomatic

- ✓ Consider hospitalization.
- ✓ Check electrolytes (K, Mg, and Ca) and manage accordingly (**Annex 4**).
- ✓ Stop QT-prolonging drugs **sequentially** starting with ancillary drugs* and DR-TB drugs with the shortest half-life Mfx/Lfx, followed by Cfz, Dlm, then Bdq.**
- ✓ **Repeat ECG after ≥24 hours but < 48 hours.**

Signs/Symptoms present: e.g., palpitations, tachycardia, light-headedness, fainting, syncope, chest pain, loss of consciousness

- ✓ Hospitalize.
- ✓ Check electrolytes (K, Mg and Ca) and manage accordingly (**Annex 4**).
- ✓ Stop **ALL** QT-prolonging drugs.
- ✓ **Repeat ECG after ≥24 hours but < 48 hours.**

QTcF still >500 ms and still asymptomatic

- ✓ Check TSH and manage accordingly (**Annex 5**).
- ✓ Check Hgb and consider blood transfusion, as necessary.
- ✓ Refer to the Case management committee, if needed.
- ✓ **Do at least weekly ECG until normal.**

QTcF still >500 ms and signs/symptoms still present

- ✓ Check TSH and manage accordingly (**Annex 5**).
- ✓ Check Hgb and consider blood transfusion, as necessary.
- ✓ Refer to the Case Management Committee, if needed.
- ✓ **Do at least weekly ECG until normal.**

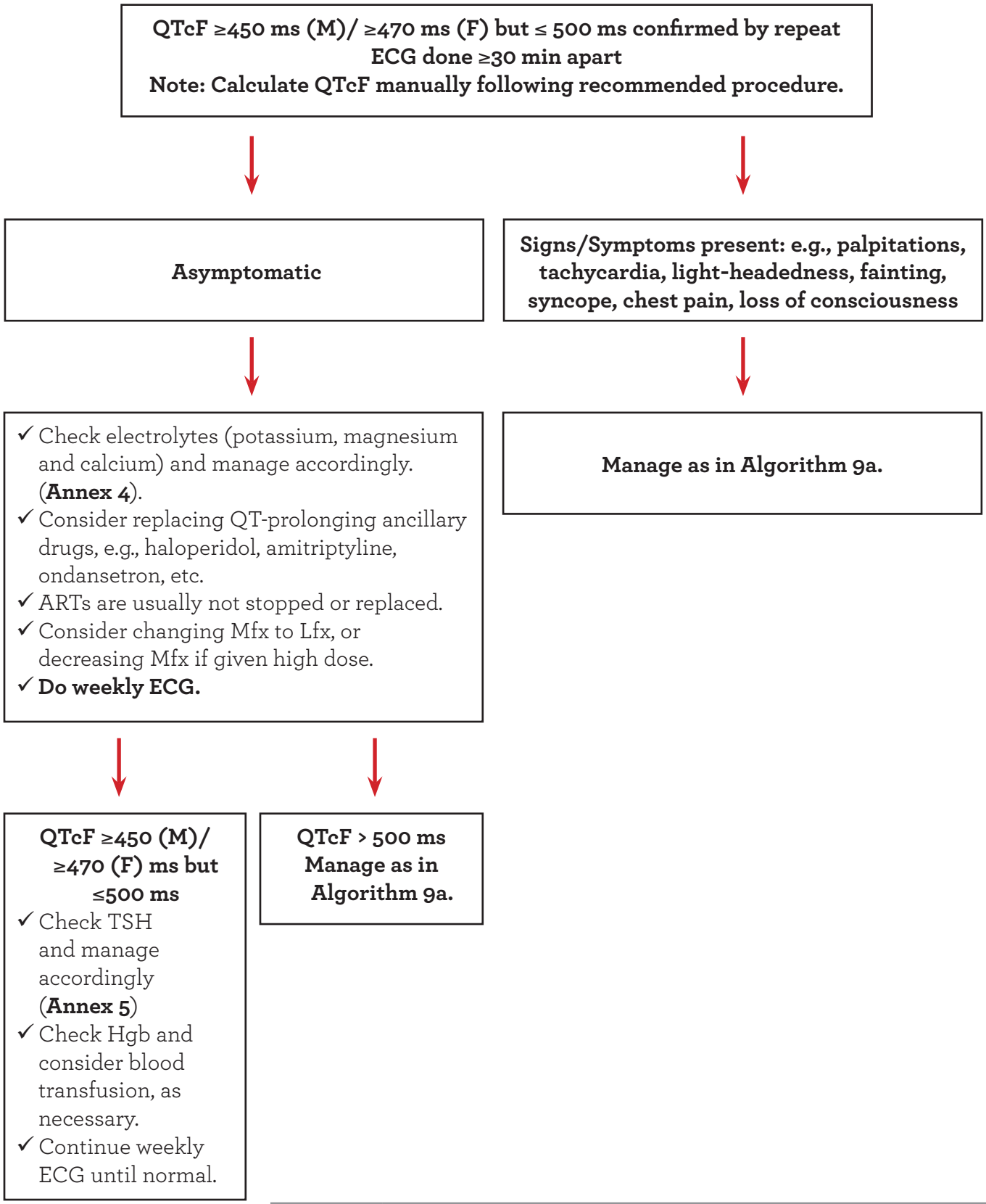
QTcF <450 ms (M)/<470 ms (F); patient stable

- ✓ **Critical QT-prolonging drugs can be added back.**
- ✓ Consider the following adjustments, in consultation with the case management committee:
  - Use Lfx if previously on Mfx, and DST shows susceptibility.
  - Restart Bdq/Dlm, if previously on Bdq/Dlm (while suspending all other QT-prolonging drugs).
  - Suspend Cfz permanently, if not critical.
- ✓ **Do weekly ECG and on an ad hoc basis until stable.**

*List of QT-prolonging drugs: https://crediblemeds.org/new-drug-list/ (**Annex 1**)
** Half-life of medicines: Mfx: 15-16 hrs; Lfx: 6-8 hrs; Cfz: 25 days; Dlm: 38 hrs; Bdq: 5.5 months

Note: Because of the long half-life of Bdq, if the QTcF is prolonged even if the drug is no longer being given, continue ECG monitoring until the QTcF normalizes.

Figure 9b: Algorithm for monitoring and managing QTcF prolongation (QTcF ≥450 ms (M)/≥470 ms (F) but ≤ 500 ms) among DR-TB patients



Annex	Guide
Annex 4a	Potassium replacement therapy
Annex 4b	Magnesium replacement therapy
Annex 4c	Calcium replacement therapy
Annex 5	Severity grading and clinical management of hypothyroidism

Acknowledgment: Jennifer Furin, Alberto Piubello

Table 2. Severity grading scale of QT prolongation and management

Prolonged QT interval **Possible anti-TB drug causes: Mfx, Cfz. Bdq, Dlm,** **Other causes:** Hypokalemia, hypothyroidism, other drugs (e.g., clarithromycin, quinidine, fluconazole, antipsychotics: haloperidol, chlorpromazine, anti-emetics: ondansetron and domperidone, etc.) Refer to https://www.crediblemeds.org/healthcare-providers/				
Normal Value	**Grade 1** **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Potentially Life-Threatening**
Male (M): <450 **Female (F): <470**	M: QTcF 450 – 480 ms F: QTcF 470 – 480 ms	QTcF 481 – 500 ms	> 500 ms on at least two separated ECGs (>30 min apart) without signs and symptoms of arrhythmia	> 500 ms and life-threatening consequences (Tdp or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)
Action	• Check electrolytes and replete as necessary. • Check TSH and Hgb and manage accordingly. • Monitor ECG more closely; at least weekly until QTcF has returned to < Grade 1.	• Check electrolytes and replete as necessary. • Check TSH and Hgb and manage accordingly. • Monitor ECG more closely; at least weekly until QTcF has returned to grade 1 or less.	• Consider hospitalization and replete electrolytes as necessary. • Stop the QT-prolonging agents sequentially starting with ancillary drugs, DR-TB drugs with the shortest half-life: Mfx/Lfx, then Cfz, Dlm, then Bdq. • Check TSH and Hgb and manage accordingly. • Repeat ECG after 24 hours but <48 hours.	• Hospitalize and replete electrolytes as necessary. • Stop all suspected causative drugs. • Check TSH and Hgb and manage accordingly. • Repeat ECG after 24 hours but <48 hours.

Modified from the endTB Clinical and Programmatic Guide for patient management with new TB drugs, version 4.0, January 2018

Annexes

Annex 1 – List of QT-prolonging agents

Generic Name	Brand Name
Abarelix (PR)	Plenaxis
Aclarubicin (KR)	Aclacin and others
Alfuzosin (PR)	Uroxatral
Amantadine (CR)	Symmetrel and others
Amiodarone (KR)	Cordarone and others
Amisulpride (CR)	Solian and others
Amitriptyline (CR)	Elavil (Discontinued 6/13) and others
Amphotericin B (CR)	Fungilin and others
Amsacrine (acridinyl anisidide) (CR)	Amsidine
Anagrelide (KR)	Agrylin and others
Apalutamide (PR)	Erleada
Apomorphine (PR)	Apokyn and others
Aripiprazole (PR)	Abilify and others
Arsenic trioxide (KR)	Trisenox
Artemether + Lumefantrine (PR)	Coartem
Artenimol+piperaquine (PR)	Eurartesim
Asenapine (PR)	Saphris and others
Astemizole (KR)	Hismanal
Atazanavir (CR)	Reyataz and others
Atomoxetine (PR)	Strattera
Azithromycin (KR)	Zithromax and others
Bedaquiline (PR)	Sirturo
Bendamustine (PR)	Treanda and others
Bendroflumethiazide or bendrofluazide (CR)	Aprinox and others
Benperidol (PR)	Anquil and others
Bepridil (KR)	Vascor
Betrixaban (PR)	Bevyxxa
Bortezomib (PR)	Velcade and others
Bosutinib (PR)	Bosulif
Buprenorphine (PR)	Butrans and others
Cabozantinib (PR)	Cometriq
Capecitabine (PR)	Xeloda
Ceritinib (PR)	Zykadia

Generic Name	Brand Name
Chloral hydrate (CR)	Aquachloral and others
Chloroquine (KR)	Aralen
Chlorpromazine (KR)	Thorazine and others
Cilostazol (KR)	Pletal
Cimetidine (CR)	Tagamet and others
Ciprofloxacin (KR)	Cipro and others
Cisapride (KR)	Propulsid
Citalopram (KR)	Celexa and others
Clarithromycin (KR)	Biaxin and others
Clofazimine (PR)	Lamprene
Clomipramine (PR)	Anafranil
Clotiapine (PR)	Entumine
Clozapine (PR)	Clozaril and others
Cocaine (KR)	Cocaine
Crizotinib (PR)	Xalkori
Cyamemazine (cyamepromazine) (PR)	Tercian
Dabrafenib (PR)	Tafinlar
Dasatinib (PR)	Sprycel
Degarelix (PR)	Firmagon and others
Delamanid (PR)	Deltyba
Desipramine (PR)	Pertofrane and others
Deutetrabenazine (PR)	Austedo
Dexmedetomidine (PR)	Precedex and others
Dextromethorphan/ Quinidine (PR)	Nuedexta
Diphenhydramine (CR)	Benadryl and others
Disopyramide (KR)	Norpace
Dofetilide (KR)	Tikosyn
Dolasetron (PR)	Anzemet
Domperidone (KR)	Motilium and others

Legend	
Code	Risk for TdP
KR	Known risk
PR	Possible risk
CR	Conditional risk

Generic Name	Brand Name
Donepezil (KR)	Aricept
Doxepin (CR)	Sinequan and others
Dronedarone (KR)	Multaq
Droperidol (KR)	Inapsine and others
Efavirenz (PR)	Sustiva and others
Eliglustat (PR)	Cerdelga
Encorafenib (PR)	Braftovi
Eperisone (CR)	Myonal and others
Eribulin mesylate (PR)	Halaven
Erythromycin (KR)	E.E.S. and others
Escitalopram (KR)	Cipralex and others
Esomeprazole (CR)	Nexium and others
Ezogabine (Retigabine) (PR)	Potiga and others
Famotidine (CR)	Pepcid and others
Felbamate (PR)	Felbatol
Fingolimod (PR)	Gilenya
Flecainide (KR)	Tambocor and others
Fluconazole (KR)	Diflucan and others
Fluorouracil (5-FU) (PR)	Adrucil and others
Fluoxetine (CR)	Prozac and others
Flupentixol (PR)	Depixol and others
Fluvoxamine (CR)	Faverin and others
Furosemide (frusemide) (CR)	Lasix and others
Galantamine (CR)	Reminyl and others
Garenoxacin (CR)	Geninax
Gatifloxacin (KR)	Tequin
Gemifloxacin (PR)	Factive
Granisetron (PR)	Kytril and others
Grepafloxacin (KR)	Raxar
Halofantrine (KR)	Halfan
Haloperidol (KR)	Haldol (US & UK) and others
Hydrochlorothiazide (CR)	Apo-Hydro and others
Hydrocodone - ER (PR)	Hysingla ER and others
Hydroxychloroquine (CR)	Plaquenil and others
Hydroxyzine (CR)	Atarax and others
Ibogaine (KR)	None

Generic Name	Brand Name
Ibutilide (KR)	Corvert
Iloperidone (PR)	Fanapt and others
Imipramine (melipramine) (PR)	Tofranil
Indapamide (CR)	Lozol and others
Inotuzumab ozogamicin (PR)	Besponsa
Isradipine (PR)	Dynacirc
Itraconazole (CR)	Sporanox and others
Ivabradine (CR)	Procoralan and others
Ketanserin (PR)	Sufrexal
Ketoconazole (CR)	Nizoral and others
Lacidipine (PR)	Lacipil and others
Lansoprazole (CR)	Prevacid
Lapatinib (PR)	Tykerb and others
Lenvatinib (PR)	Lenvima
Leuprolide (PR)	Lupron and others
Levofloxacin (KR)	Levaquin and others
Levomepromazine (methotrimeprazine) (KR)	Nosinan and others
Levomethadyl acetate (KR)	Orlaam
Levosulpiride (KR)	Lesuride and others
Lithium (PR)	Eskalith and others
Loperamide (CR)	Imodium and many other OTC and Rx brands
Lopinavir and ritonavir (PR)	Kaletra and others
Maprotiline (PR)	Ludiomil and others
Melperone (PR)	Bunil and others
Memantine (PR)	Namenda XR and many others
Mesoridazine (KR)	Serentil
Methadone (KR)	Dolophine and others

Legend	
Code	Risk for TdP
KR	Known risk
PR	Possible risk
CR	Conditional risk

Generic Name	Brand Name
Metoclopramide (CR)	Reglan and others
Metolazone (CR)	Zytanix and others
Metronidazole (CR)	Flagyl and many others
Midostaurin (PR)	Rydapt
Mifepristone (PR)	Korlym and others
Mirabegron (PR)	Myrbetriq
Mirtazapine (PR)	Remeron
Moexipril/HCTZ (PR)	Uniretic and others
Moxifloxacin (KR)	Avelox and others
Necitumumab (PR)	Portrazza
Nelfinavir (CR)	Viracept
Nicardipine (PR)	Cardene
Nilotinib (PR)	Tasigna
Norfloxacin (PR)	Noroxin and others
Nortriptyline (PR)	Pamelor and others
Nusinersen (PR)	Spinraza
Ofloxacin (PR)	Floxin
Olanzapine (CR)	Zyprexa and others
Omeprazole (CR)	Losec and others
Ondansetron (KR)	Zofran and others
Osimertinib (PR)	Tagrisso
Oxaliplatin (KR)	Eloxatin
Oxytocin (PR)	Pitocin and others
Paliperidone (PR)	Invega and others
Palonosetron (PR)	Aloxi
Panobinostat (PR)	Farydak
Pantoprazole (CR)	Protonix and others
Papaverine HCl (Intra-coronary) (KR)	None
Paroxetine (CR)	Paxil and others
Pasireotide (PR)	Signifor
Pazopanib (PR)	Votrient
Pentamidine (KR)	Pentam
Perflutren lipid microspheres (PR)	Definity and others
Perphenazine (PR)	Trilafon and others
Pilsicainide (PR)	Sunrythm
Pimavanserin (PR)	Nuplazid
Pimozide (KR)	Orap
Pipamperone (PR)	Dipiperon (E.U) and others

Generic Name	Brand Name
Piperacillin/ Tazobactam (CR)	Tazosyn and Zosyn
Posaconazole (CR)	Noxafil and others
Primaquine phosphate (PR)	
Probucol (KR)	Lorelco
Procainamide (KR)	Pronestyl and others
Promethazine (PR)	Phenergan
Propafenone (CR)	Rythmol SR and others
Propofol (KR)	Diprivan and others
Prothipendyl (PR)	Dominal and others
Quetiapine (CR)	Seroquel
Quinidine (KR)	Quinaglute and others
Quinine sulfate (CR)	Qualaquin
Ranolazine (CR)	Ranexa and others
Ribociclib (PR)	Kisqali
Rilpivirine (PR)	Edurant and others
Risperidone (PR)	Risperdal
Romidepsin (PR)	Istodax
Roxithromycin (KR)	Rulide and others
Saquinavir (PR)	Invirase(combo)
Sertindole (PR)	Serdolect and others
Sertraline (CR)	Zoloft and others
Sevoflurane (KR)	Ultane and others
Solifenacin (CR)	Vesicare
Sorafenib (PR)	Nexavar
Sotalol (KR)	Betapace and others
Sparfloxacin (KR)	Zagam
Sulpiride (KR)	Dogmatil and others
Sultopride (KR)	Barnetil and others
Sunitinib (PR)	Sutent
Tacrolimus (PR)	Prograf and others
Tamoxifen (PR)	Nolvadex (discontinued 6/13) and others

Legend	
Code	Risk for TdP
KR	Known risk
PR	Possible risk
CR	Conditional risk

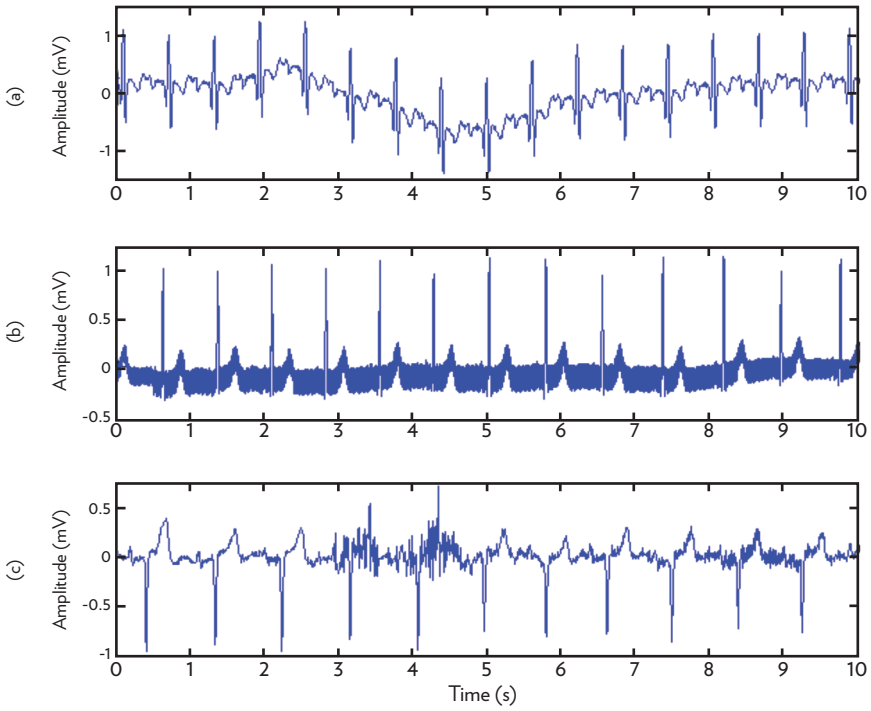
Generic Name	Brand Name
Telaprevir (CR)	Incivo and others
Telavancin (PR)	Vibativ
Telithromycin (PR)	Ketek
Terfenadine (KR)	Seldane
Terlipressin (KR)	Teripress and others
Terodiline (KR)	Micturin and others
Tetrabenazine (PR)	Nitoman and others
Thioridazine (KR)	Mellaril and others
Tiapride (PR)	Tiapridal and others
Tipiracil and Trifluridine (PR)	Lonsurf
Tizanidine (PR)	Zanaflex and others
Tolterodine (PR)	Detrol and others
Toremifene (PR)	Fareston
Torsemide (torasemide) (CR)	Demadex and others
Tramadol (PR)	Crispin and others
Trazodone (CR)	Desyrel (discontinued 6/13) and others
Trimipramine (PR)	Surmontil and others
Tropisetron (PR)	Navoban and others
Valbenazine (PR)	Ingrezza
Vandetanib (KR)	Caprelsa
Vardenafil (PR)	Levitra
Vemurafenib (PR)	Zelboraf
Venlafaxine (PR)	Effexor and others
Voriconazole (CR)	VFend
Vorinostat (PR)	Zolinza
Ziprasidone (CR)	Geodon and others
Zotepine (PR)	Losizopilon and others
Zuclopenthixol, Zuclopentixol (PR)	Cisordinol and others

Legend	
Code	Risk for TdP
KR	Known risk
PR	Possible risk
CR	Conditional risk

Source: https://www.crediblemeds.org/healthcare-providers/
(accessed on November 11 2018) Please visit the website for a more up-to-date list.

Annex 2 – ECG noise: common types

Before one proceeds to determine the QTc value, the noise level of the ECG should be evaluated and kept to a minimum, if not totally avoided. Noise is manifested as artifacts that may be caused by a) baseline wander (patient's respiration and body movement), b) powerline interference (electromagnetic field of nearby machines, the effect of loops in the cable, improper grounding of the patient or the ECG machine); c) electromyographic noise (electrical activity of the muscle), d) electrode-contact noise (loss of contact between the electrode and the skin) impedance, e) poor channel conditions, and f) motion artifacts. Some types are illustrated below.



a) Baseline wander

b) Powerline interference

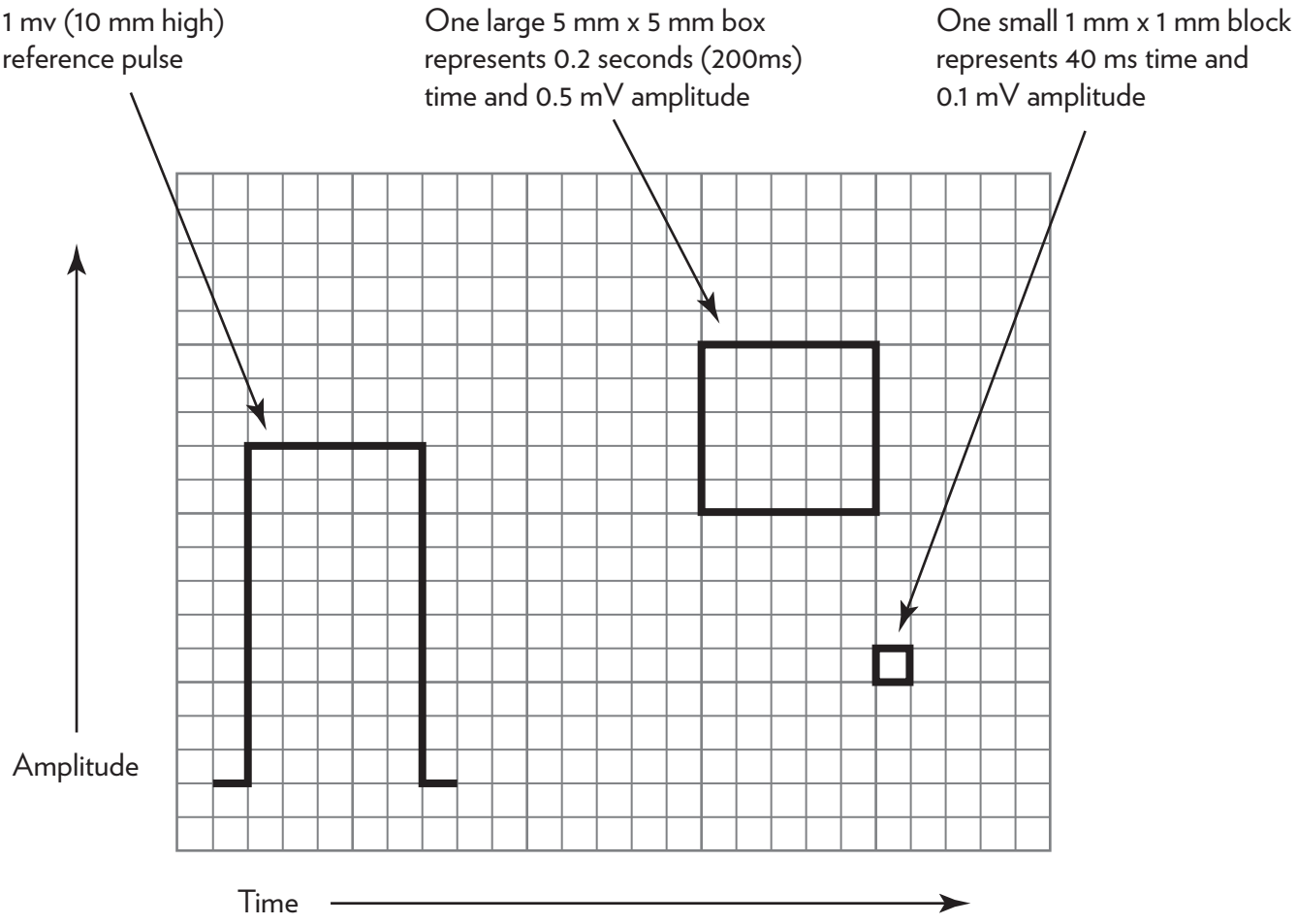
c) Electromyographic noise

Annex 3 – Calibration of the ECG machine

The standard calibration of the ECG is 10 mm/milliVolt (mV) and a paper recording speed of 25 mm/s, wherein 1 mV calibration signal is expected to produce a rectangle of 10 mm height and 5 mm width on the ECG rhythm strip, as shown in the figure below. Vertically, the ECG graph measures the height (amplitude) of a given wave or deflection, as 10 mm (10 small boxes) equals 1 mV with standard calibration.

At standard calibration (paper speed = 25 mm/s): one small square represents 40 ms (or 0.04 s) time, and 0.1 amplitude.

Measurements in ECG strips from a calibrated ECG machine



If the paper recording speed of the ECG is adjusted to 50 mm/s, 1 mV calibration signal is expected to produce a perfect square with a 10 mm height and 10mm width. Adjusted calibrations to a paper speed of 50 mm/s will make the HR appear one-half of what is recorded at 25 mm/s paper speed and all the ECG intervals are twice as long.

At adjusted calibration (paper speed = 50 mm/s): one large square represents 20 ms (or 0.02 s) time and 0.5 mV amplitude.

On occasion, particularly when the waveforms are small, double standard is used (20 mm equals 1 mV). On the other hand, when the waveforms are very large, half standard may be used (5 mm equals 1 mV). The paper speed and voltage are usually printed at the bottom of the ECG rhythm strip.

Annex 4 – Electrolyte replacement therapy

Annex 4a - Potassium replacement therapy

Note: Patients on QT-prolonging agents should maintain a serum potassium level of **at least 4 mEq per L (4 mmol per L)**. Careful monitoring during treatment is essential because supplemental potassium can be a common cause of hyperkalemia.

If serum K is low, always check magnesium and ionized calcium and replete as necessary (Annex 4b and Annex 4c).

Potassium Level (mmol/L)	Dosing	Monitoring Frequency
3.3- 3.4	40 mmol PO in 2-3 divided doses daily	Daily or multiple times a day, as clinically indicated
2.9 - 3.2	60-80 mmol PO in 3 divided doses daily	
2.7 - 2.8	60 mmol PO every eight hours	
2.5 - 2.6	80 mmol PO every eight hours	
< 2.5	10 mmol/hour IV and 80 mmol PO every 6-8 hours	One hour after infusion, every 6 hours with IV replacement

Note: The normal preparation of a potassium chloride infusion is 40 mmol (3 ampoules) in 1L of NaCL 0.9% infused over 4 hours. Do not exceed an infusion rate of 10 mmol/hour (250mL/hour). Potassium chloride 10% (100mg/ml) ampoules = 1 g per ampoule = 13.4 mmol. Potassium chloride controlled release tablets of 600 mg = 8mmol/tablet.

Sources: WHO Companion Handbook to the Guidelines for the Programmatic Management of Drug-resistant TB, 2014; endTB consortium. endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs. Version 4.0; January 2018.

Annex 4b – Magnesium replacement therapy

Magnesium level	Total daily dose	Monitoring frequency*
2.0 or more	None	Monthly
1.5 - 1.9	1000 mg - 1200 mg	Monthly
1.0 - 1.4	2000 mg	One to seven days
< 1.0	3000 mg – 6000 mg	Daily

*More frequently, as clinically indicated

Note: Quantities greater than 2000 mg are usually given by IV or intramuscular (IM). The normal preparation is magnesium sulfate 2 g in 100 ml or 4 g in 250 ml of 5% dextrose or normal saline. Do not exceed an infusion rate of 150 mg/min (2 g in 100 ml administered over one to two hours, 4 g in 250 ml administered over two to four hours).

Source: WHO Companion Handbook to the Guidelines for the Programmatic Management of Drug-resistant TB, 2014

Annex 4c – Calcium replacement therapy

Calcium level (total non-ionized calcium value adjusted for low albumin**	Dosing	Monitoring frequency*
>8.5 mg/dl (>4.2 mEq/l)	None	
7.5 – 8.4	500 mg three times a day	Monthly
7.0 – 7.4	1000 mg three times a day	One to two weeks
<7.0	Consider IV and taper to 1000 m three times a day	One to four days

*More frequently, as clinically indicated

Note: Normal calcium is 8.5-10.3 mg/dl (2.12 – 2.57 mmol/l).
**To adjust for low albumin in non-ionized values of calcium, use this formula: Corrected calcium = 0.8 x (4.0 – measured albumin) + reported calcium. If ionized calcium is being tested, it does not need to be adjusted for low albumin and normal value is 4.5 – 5.6 mg/dl (1.11 – 1.30 mmol/l).

Source: WHO Companion Handbook to the Guidelines for the Programmatic Management of Drug-resistant TB, 2014

Annex 5 – Clinical management of hypothyroidism according to severity grading

Hypothyroidism
Possible anti-TB drugs: Eto/Pto/PAS

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Sub-clinical hypothyroidism (TSH 6- 10mIU/L, T4 free normal)	Simple hypothyroidism without complications. Treatment required (TSH > 10 mIU/L)	Severe hypothyroidism with clinical symptoms. Urgent treatment	Myxedematous coma

TSH Normal value: <5 mlU/L
Start treatment when **TSH > 10 mIU/L (Grade 2)**. However, for pregnant women and children it is advisable to start levothyroxine at **Grade 1-subclinical hypothyroidism (TSH 6 mlU/L - 10 mUI/)** to avoid cognitive impairment/cretinism. Children clear thyroxine faster than adults, so daily replacement doses are higher.

Levothyroxine sodium dosing guidelines

Children

Age	Dose
0-3 months	10-15 mcg/kg/day
3-6 months	8-10 mcg/kg/day
6-12 months	6-8 mcg/kg/day
1-5 years	5-6 mcg/kg/day
6-12 years	4-5 mcg/kg/day
>12 years but growth and puberty incomplete	2-3 mcg/kg/day
Growth and puberty complete	1.6 mcg/kg/day
Adjust the dose based on clinical response and laboratory parameters	

Adults

Status of hypothyroidism	Initial Dose	Adjustment
Mild hypothyroidism: 1.7 mcg/kg or 100-125 mcg PO/day; not to exceed 300 mcg/day		
>50 years (or <50 yr with CV disease)	25-50 mcg PO/day	May adjust dose by 12.5-25 mcg every 6-8 weeks
>50 years with CV disease	12.5-25 mcg PO/day	May adjust dose by 12.5-25 mcg every 4-6 weeks until patient becomes euthyroid and serum TSH concentration normalized; adjustments every 6-8 weeks also used Dose range: 100-125 mcg PO/day
Severe hypothyroidism	12.5-25 mcg PO/day	Adjust dose by 25 mcg/day every 2-4 weeks, prn
Subclinical hypothyroidism	1 mcg/kg PO/day, OR If replacement therapy not initiated, monitor patient annually for clinical status	

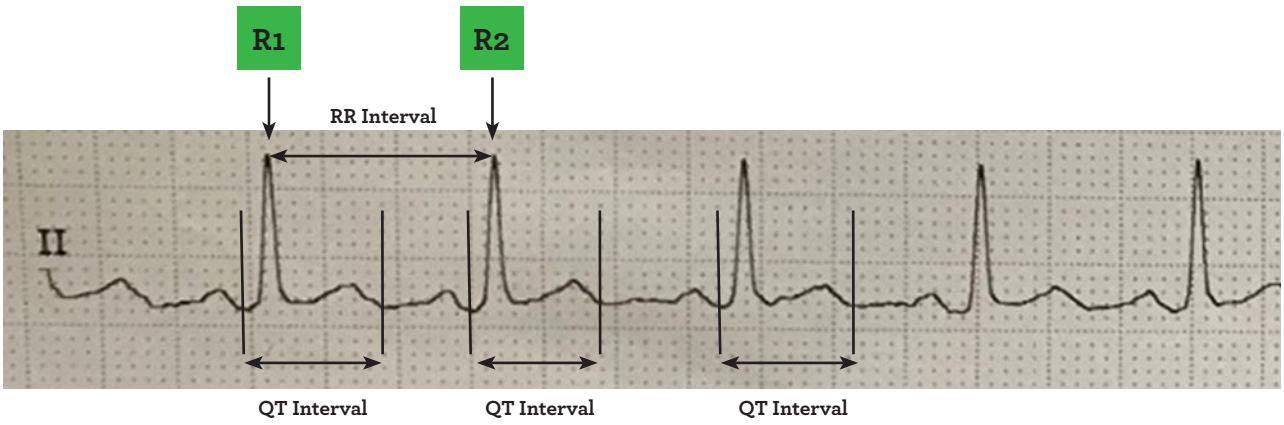
Source: https://reference.medscape.com/drug/synthroid-levoxyl-levothyroxine-342732

Monitor TSH every month and increase the dose by 25 mcg until TSH normalizes (TSH < 5 mIU/L). Adjust the dose more slowly in the elderly and in patients with cardiac conditions.

Thyroid dysfunction resolves upon discontinuation of the cause agent (Eto/Pto, PAS). Hormone replacement must continue for at least 2 to 3 months after DR-TB treatment is completed.

Annex 6 – Exercise on QTcF determination on an ECG rhythm strip (Calculator method and using the QTcF Nomogram)

Below is the ECG rhythm strip of a 45 year old male MDR-TB patient. Calculate the QTcF.



Step 1. Measure the QT interval.
QT = 9 small squares
= 9 X 0.04 = 0.36 s (360 ms)

Step 2. Measure the RR interval.
RR = 15 small squares
= 16 X 0.04 = 0.64 s (640 ms)

Measure the HR = 60/RR
= 60/0.64 = 93.75 or 94 bpm

Step 3: Determine the QTcF using different methods.

A. Manual Calculator

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

$$QT_{cF} = \frac{400}{\sqrt[3]{0.64}}$$

QT_{cF} = 417.7 or 418 ms

B. QTcF Nomogram

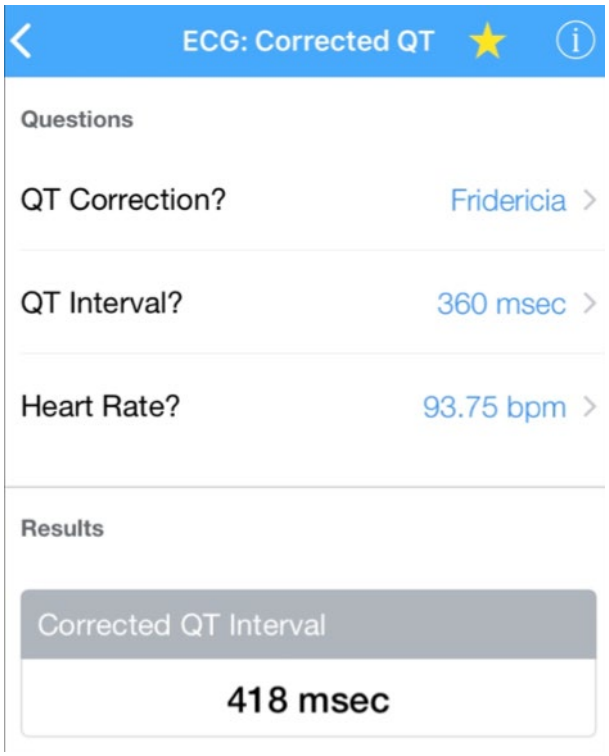
Using the QTcF Nomogram below, note that the resulting QTcF is not exactly on the given numbers in the Nomogram table. This is because the RR and HR fall in-between the given values. In this case,if the exact QTcF is desired, use the other methods described in this document, such as the smartphone application (QxMD), or the manual or electronic calculator via the website.

In other cases where the RR and the HR would fall exactly on the given numbers in the Nomogram, the resulting QTcF would be a value that is exactly on the table.

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

C. QxMD smartphone application



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