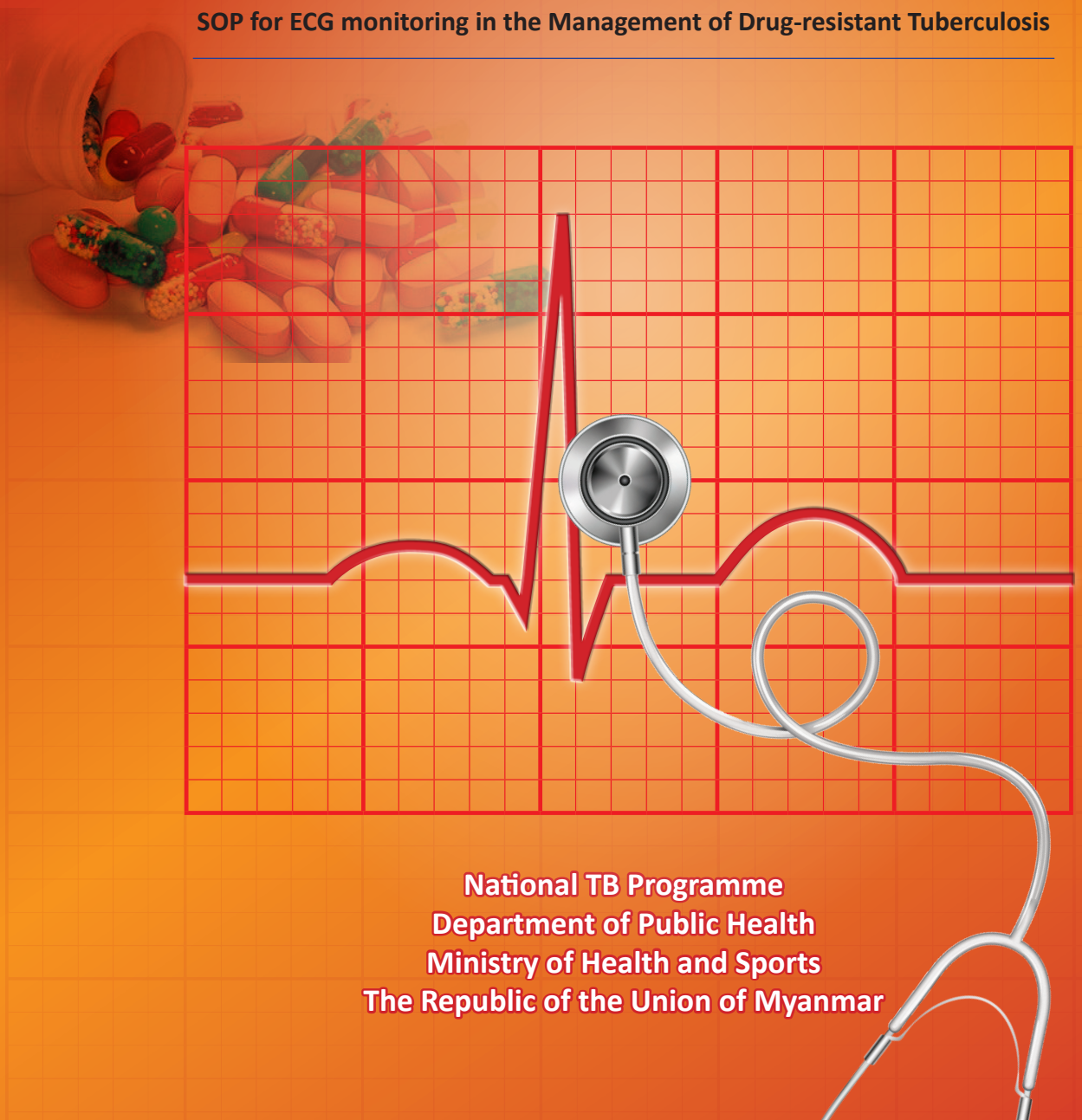
Guidance on QTc measurement for Monitoring and Management of Patients on QT-prolonging Agents

SOP for ECG monitoring in the Management of Drug-resistant Tuberculosis



National TB Programme
Department of Public Health
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The Republic of the Union of Myanmar

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August 2018

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 field guide 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.

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Acknowledgements

The National TB Programme, Department of Public Health, Ministry of Health and Sports, Myanmar would like to express its sincere thanks to Professor Nwe Nwe, Professor and Head, Department of Cardiology, University of Medicine 1, Yangon, Myanmar for the technical support and time in the development of this SOP and providing trainings to health care providers and to Dr. Mamel Quelapio, Senior Consultant from KNCV Tuberculosis Foundation for her technical support and guidance in the process of this SOP development. The National TB Programme also would like to thank Aung San TB Specialist Hospital for their collaboration and support in the development process of this SOP. The development of this SOP was undertaken in 2017 and 2018 with the support from the USAID-funded Challenge TB Project, FHI 360.

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1. Background

According to the Global Tuberculosis Report 2017, WHO estimated that there were approximately 9, 000 (CI 6,100 – 12,000) MDR/RR-TB cases among notified pulmonary TB cases in Myanmar in 2016. Recently, WHO has approved the use of new drug-resistant tuberculosis (DR-TB) medicines, Bedaquiline (Bdq) and Delamanid (Dlm) under certain conditions. Likewise, a shorter treatment regimen (STR) for MDR-TB that includes repurposed drugs, such as clofazimine (Cfz) and moxifloxacin (Mfx) were approved and recommended by WHO for eligible patients. However, these new and repurposed agents, including Levofloxacin (Lfx) to a lesser extent, may prolong the QTc interval in the electrocardiogram (ECG), which, if not addressed, leads to life-threatening arrhythmias such as torsades de pointes (TdP). Therefore, baseline and follow up ECG monitoring is recommended for patients started on TB treatment with QT-prolonging drugs.

2. Purpose and Scope of the SOP

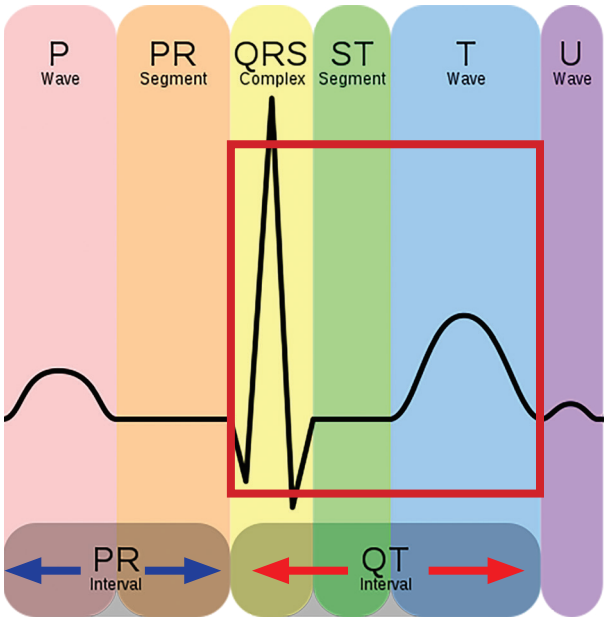
This Standard Operating Procedure (SOP) is intended to guide health care providers on the steps necessary to measure the corrected QT (QTc) interval from ECG monitoring of DR-TB patients treated with known QT-prolonging drugs, such as Bdq, Dlm, Mfx, Lfx and Cfz.

3. Basics of ECG

ECG is a non-invasive procedure that records the electrical activity of the heart over a period of time. The ECG detects 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 electro-physiologic cycle or one 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 electro-physiologic cycle or one heartbeat



**The QT interval is boxed in red.*

4. The QT interval

4.1. What is the QT interval?

The QT interval is the portion of the ECG that begins at the start of the QRS complex and ends at the end 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).

4.2. The QT interval needs to be corrected

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.

The normal QTc values

The QTc is considered normal at < 450 ms in males, and < 470 ms in females. It can vary by up to 75 ms in the same individual at different times during the same day. Because of the diurnal variation, it is recommended that during QT monitoring, the ECG be done at approximately the same time of the day.

Previous guidelines consider an increase of 60 ms from baseline QTc as prolonged. However, since the QT interval varies in the same subject within 24 hours, having a circadian profile with diurnal variability exhibiting a significant QT increase in the morning hours (when the QT is usually measured) and a consecutive decline to baseline levels, the increase of 60 ms from baseline may not be a reliable basis for QT prolongation. But an increase of 60 ms may flag closer follow up especially when the ECGs were done at approximately the same time of the day over different weeks or months.

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.

Causes of QTc prolongation

A prolonged QTc may be due to congenital defects, e.g. congenital long QT syndrome, electrolytes imbalance (hypokalemia, hypomagnesemia), hypothyroidism, or medications (anti-TB drugs like Bdq, Dlm, Mfx, Lfx and Cfz, and drugs for other conditions). A comprehensive list of medicines with known risk (KR), probable risk (PR) or conditional risk (CR) for TdP can be found at CredibleMeds.org. https://www.crediblemeds.org/healthcare-providers/.

Table 1. Causes of QTc Prolongation

Anti-TB drugs	• Bedaquiline (Bdq) • Delamanid (Dlm) • Moxifloxacin (Mfx)* • Levofloxacin (Lfx)* • Clofazimine (Cfz)
Other drugs	• Erythromycin,* Clarithromycin* • Quinidine* • Fluconazole,* Ketoconazole • Antipsychotics: haloperidol,* chlorpromazine,* amitriptyline, risperidone • Antiemetic drugs: Ondansetron*/ Domperidone, granisetron • Methadone* • Anti-retroviral: Atazanavir, Efavirenz, Saquinavir boosted with Ritonavir
Other causes	• Hypothyroidism • Hypothermia • Myocardial ischemia • Increased ICP • Electrolyte imbalance - Hypokalemia - Hypomagnesemia - Hypocalcemia
Congenital	• Congenital long QT syndrome

**Drugs with Known Risk (KR)*

Table 2. Possible ANTI-TB Drugs Causing QT Prolongation and Their Half-life

Drugs	Half -life
Bedaquiline (Bdq)	Approximately 4 - 5 months
Delamanid (Dlm)	38 hours
Clofazimine (Cfz)	Approximately 70 days (repeated oral doses)
Moxifloxacin (Mfx)	11.5 – 15.6 hours (single dose, oral)
Levofloxacin (Lfx)	6 - 8 hours

There is suggestive evidence that additional risk factors are present before drug-induced QT prolongation occurs. In most reported cases, at least one additional risk factor was present and in 70% of cases, two risk factors were present. Hence, it is important to thoroughly assess patients before attributing QT prolongation to anti-TB drugs. The table below shows unmodifiable and potentially modifiable risk factors for drug-induced QT prolongation. For a more comprehensive list of factors associated with TdP, visit https://crediblemeds.org/ndfa-list/.

Table 3. Risk Factors for Drug-induced QT Prolongation

Unmodifiable risk factors	Potentially modifiable risk factors
Female gender (present in 70% of cases)	Hypokalemia or severe hypomagnesemia
Increasing age	Absolute or relative bradycardia (including recent conversion from atrial fibrillation)
Genetic predisposition • Congenital long QT syndrome • Family history of sudden death • History of previous drug-induced QT prolongation	Drug interactions: • >1 QT-prolonging medicines* • Medicines that inhibit the metabolism of another QT-prolonging medicines • Medicines that cause electrolyte abnormalities** or may cause renal or hepatic dysfunction
Structural heart disease/LV dysfunction	Starvation or obesity
Impaired elimination due to renal or hepatic disease	High drug concentrations due to overdose or rapid IV administration

4.3. Determining the QTc value

The QTc can be determined either through automatic generation from the ECG machine, or by the manual method. However, before QT determination is done, the noise level of the ECG should be evaluated. Noise is manifested as artifacts on the ECG tracing that may be brought about by patient movement during the ECG procedure, chest hair, etc. If the artifact is significant, it is advised to repeat the ECG. Also, ECG machines must be calibrated to the proper paper speed to ensure that serial measurements of the electrical activity of the heart are consistently represented.

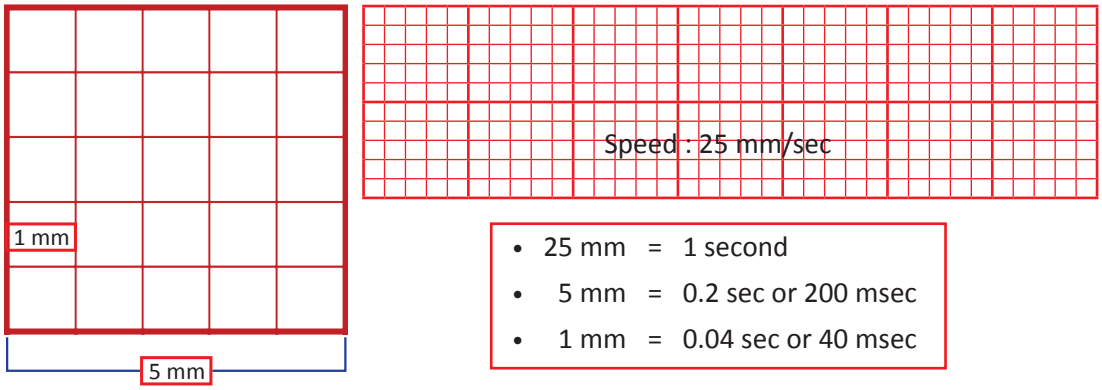
A. Automatic generation of the QTc

Most ECG machines nowadays automatically generate the QT and the QTc values. Automatic QTc generation saves staff time and effort; however, different machines use different formulae to arrive at the QTc. Fridericia (QTcF) and Framingham (QTcFr) formulae are considered to provide optimal correction although Fridericia is preferred as it was the formula applied during the phase II studies of Bdq and Dlm, as well during the STREAM trial.

Automatically generated QTc values have possible errors because of inconsistency between ECG manufacturers in the algorithm used for calculation, and the mechanical difficulty to identify the T and U waves when superimposed on each other. U waves are usually seen in hypokalemia which is frequent in M/XDR-TB patients. It is then crucial to recognize them and to know when they must be counted as part of the QT. For these reasons, it is recommended to supplement automatic QTc generation with manual reading when the QTc is prolonged.

At a calibrated paper speed of 25 mm per second, a small square (1mm) is equal to 0.04 sec or 40 ms as shown below. The calibrated speed is usually shown at the bottom of the ECG strip. See Annex for more details.

Figure 2. Standard calibrated paper speed of the ECG (25 mm/s)



At a paper speed of 50 mm/sec, 1 mm will be equal to 0.02 sec or 20 ms.

B. Manual determination of the QTc

To manually determine the QTc, 1) measure the QT interval, and 2) measure the RR interval (or the heart rate (HR) for some applications, as shown below); 3) determine the QTc using any of the methods described below.

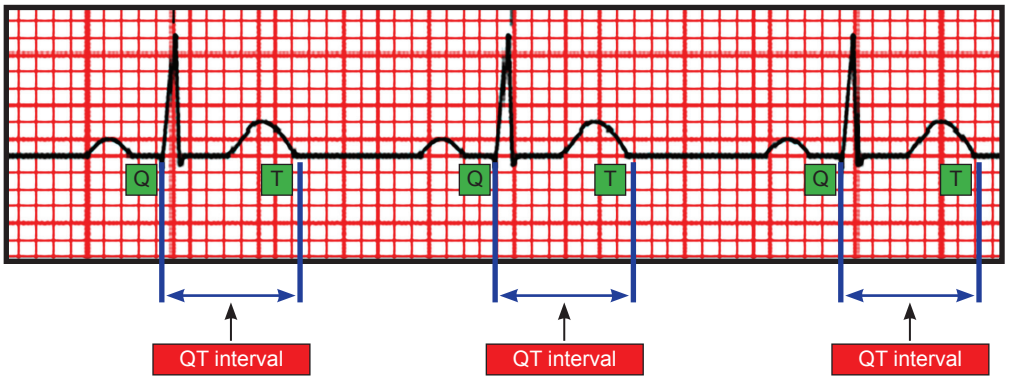
Steps in manual QTc determination:

1. Measure the uncorrected QT interval

From the 12-lead ECG tracing, choose Leads II, V5 or V6 as they usually best show the end of the T wave. Staff should, however, use their best judgment to assess which lead best shows the end of the T wave.

Measure the **QT interval** from the beginning of the QRS complex to the end of the T wave. Measure at least three successive beats, with the maximum interval taken, in case these three beats differ.

Figure 3. Sample ECG tracing showing QT intervals



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

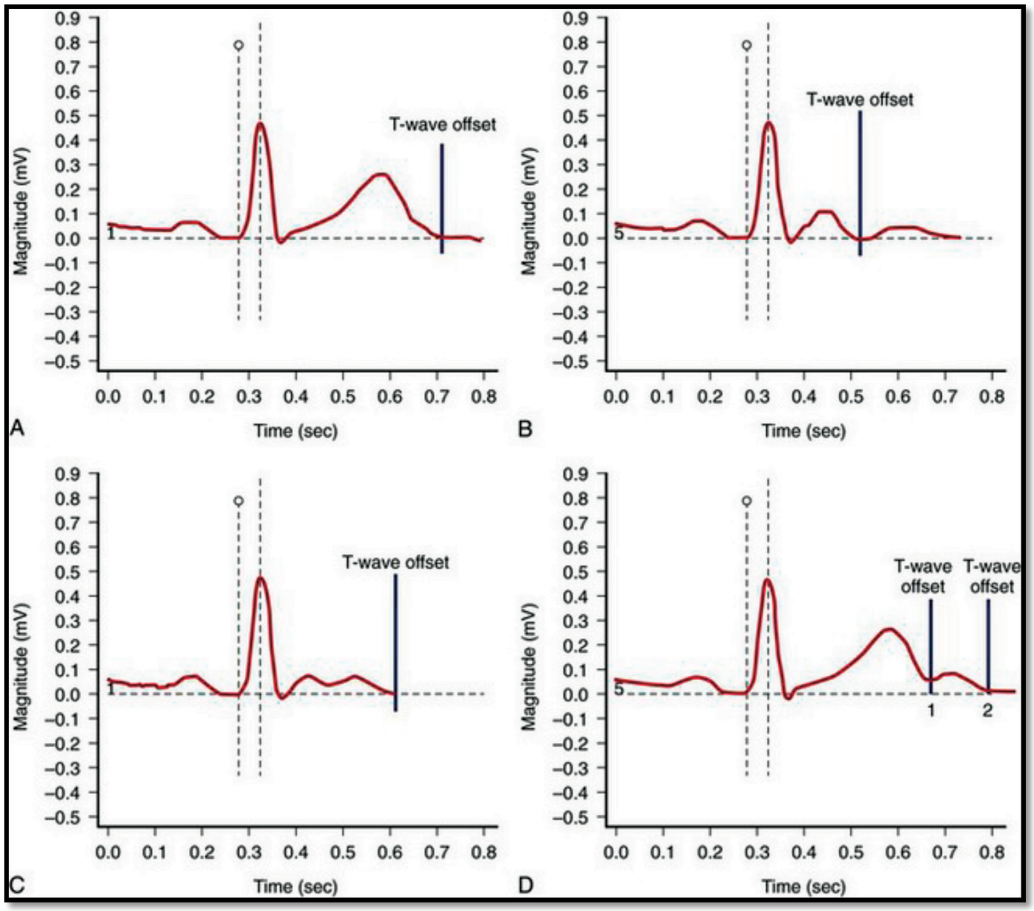
- In practice, make an imaginary line on Q and on T on the selected lead.
- Count the number of small squares between Q and T: 8 small squares (in the **figure 3** above).

  Multiply the number of small squares by the unit time per square (0.04).
- Hence: QT = 8 small squares X 0.04 sec = 0.32 s or 320 ms.
- Note: in case the speed is 50 mm/sec, QT = 8 X 0.02 = 0.16 or 160 ms.

The main difficulty lies in identifying correctly the point where the descending limb of the T wave intersects the isoelectric line, particularly when the T and U waves are close together.

- Large U waves (> 1mm) that are fused to the T wave are to be included in the measurement; and smaller U waves and those that are separate from the T wave are to be excluded **(Figure 4)**.

Figure 4. Illustrations of T wave and U wave morphology



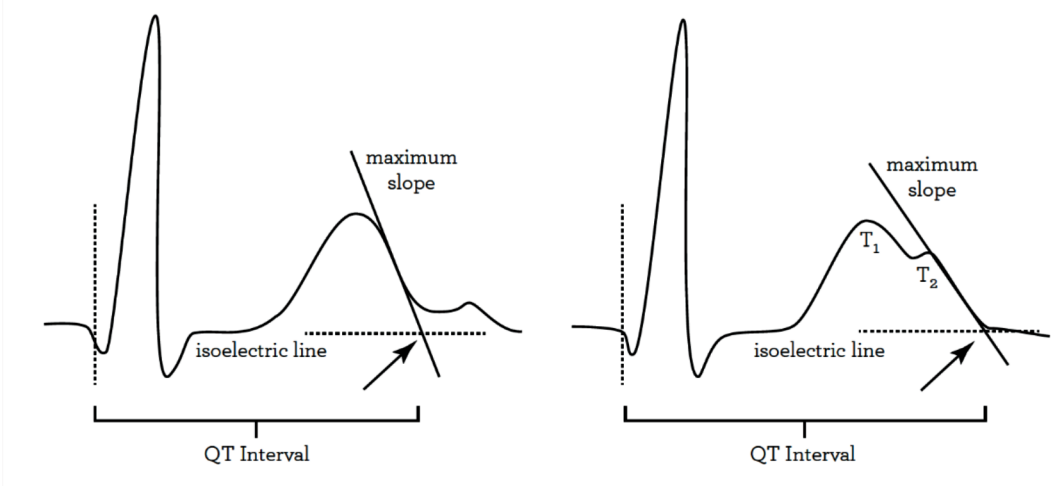
A. Normal T wave morphology: end of T wave is the point when the descending limb returns to baseline.

B. T wave is followed by a distinct U wave: end of 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): 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 5)**.

Figure 5. Defining the end of the T wave using the maximum slope intercept method



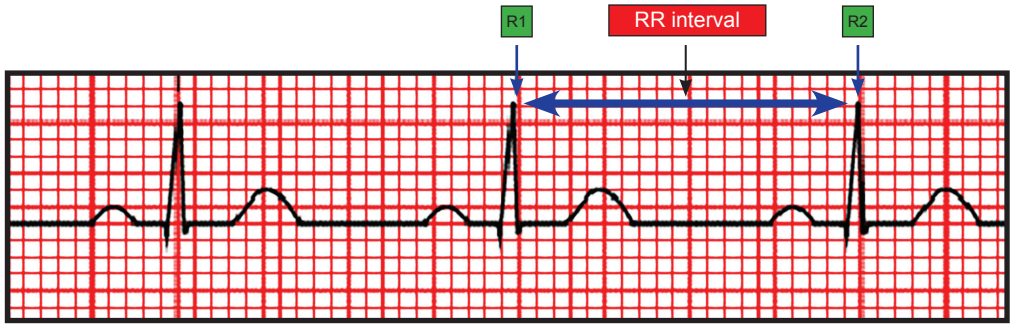
Left: *The maximum slope intercept method defines the end of the T wave as the intercept between the isoelectric line with the tangent drawn through the maximum down slope of the T wave.*

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.*

2. Measure the RR interval or heart rate

2a. Measure the RR interval:

Figure 6. Sample ECG tracing showing the RR interval



- The RR interval is the area between two consecutive Rs in the chosen lead, as shown in **Figure 6**. The two Rs are identified in the figure.
- Using the heartbeat with the longest QT interval **(Figure 3)**, and the succeeding heartbeat, measure the RR interval.
- Count the number of small squares between the two Rs. The RR interval in **Figure 6** spans 20 small squares.
- Multiply the number of small squares by the unit time per square (0.04 s).
- Hence: RR = 20 small squares X 0.04 = 0.80 s or 800 ms.

2b. Measure the Heart Rate

To measure the HR, use the formula:

HR = 60/RR interval

In **Figure 6**, the RR = 0.80 s

HR = 60/0.80 s

HR = 75 bpm

3. Determine the QTc (corrected QT)

Manual QTc determination can be done with any of the following methods: a) applying the Fridericia QT correction formula with a calculator, or b) downloading the smartphone application called QxMD, c) using the QTc nomogram, or d) using an electronic calculator at https://www.medcalc.org/clinicalc/corrected-qt-interval-qtc.php

a) Applying the Fridericia QT correction formula using a calculator:

The Fridericia formula is as follows:

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

Where:

QTcF = the corrected QT interval by Fridericia

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 Fridericia formula using the above example, where the calculated QT interval was 320 ms **(Figure 3)**, and the RR interval was 0.80s **(Figure 6)**, the QTcF value would be 345 ms.

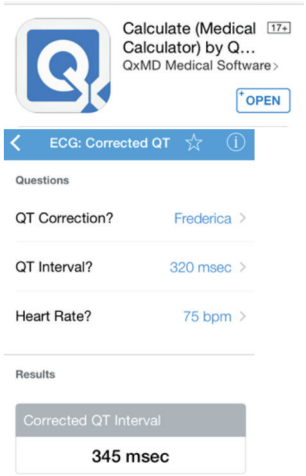
Note that the units used for the two variables were different (ms and s).

$$\text{QTcF} = \frac{320}{\sqrt[3]{0.80}}$$

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

b) Downloading the smartphone application QxMD

Figure 7. QTc determination using a smart phone application, QxMD (Medical Calculator)



This needs the QT interval and the HR.

- Open the QxMD application
- Under Cardiology, click ECG
  - Click Corrected QT
  - QT Correction?
    - Select Fredericia
    - Enter the manually counted QT interval (320 ms in **Figure 3**)
    - Enter the HR (75 bpm)
    - Click calculate
  - QTcF = 345 ms

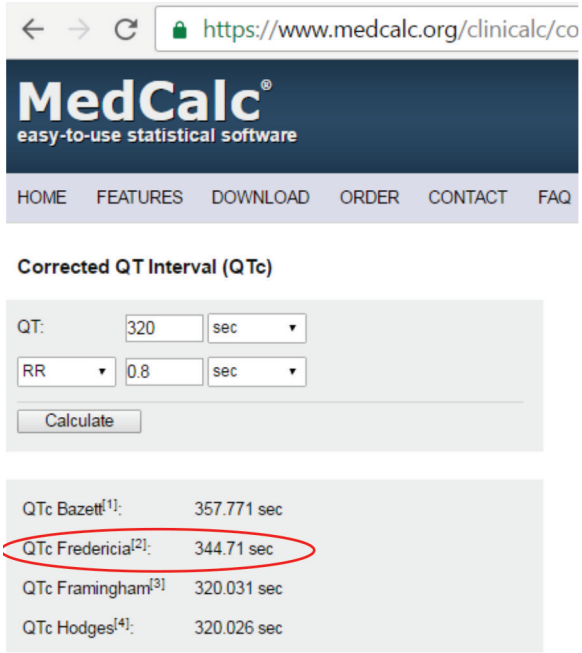
c) Using the QTc Nomogram

The vertical column of the nomogram shows the 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 3)**, and the RR interval of 0.80 s **(Figure 6)**, an intercept can be obtained in the QTcF nomogram. QTcF = 345 ms.

	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	519	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	627	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	538	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

d) Using an electronic calculator:

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



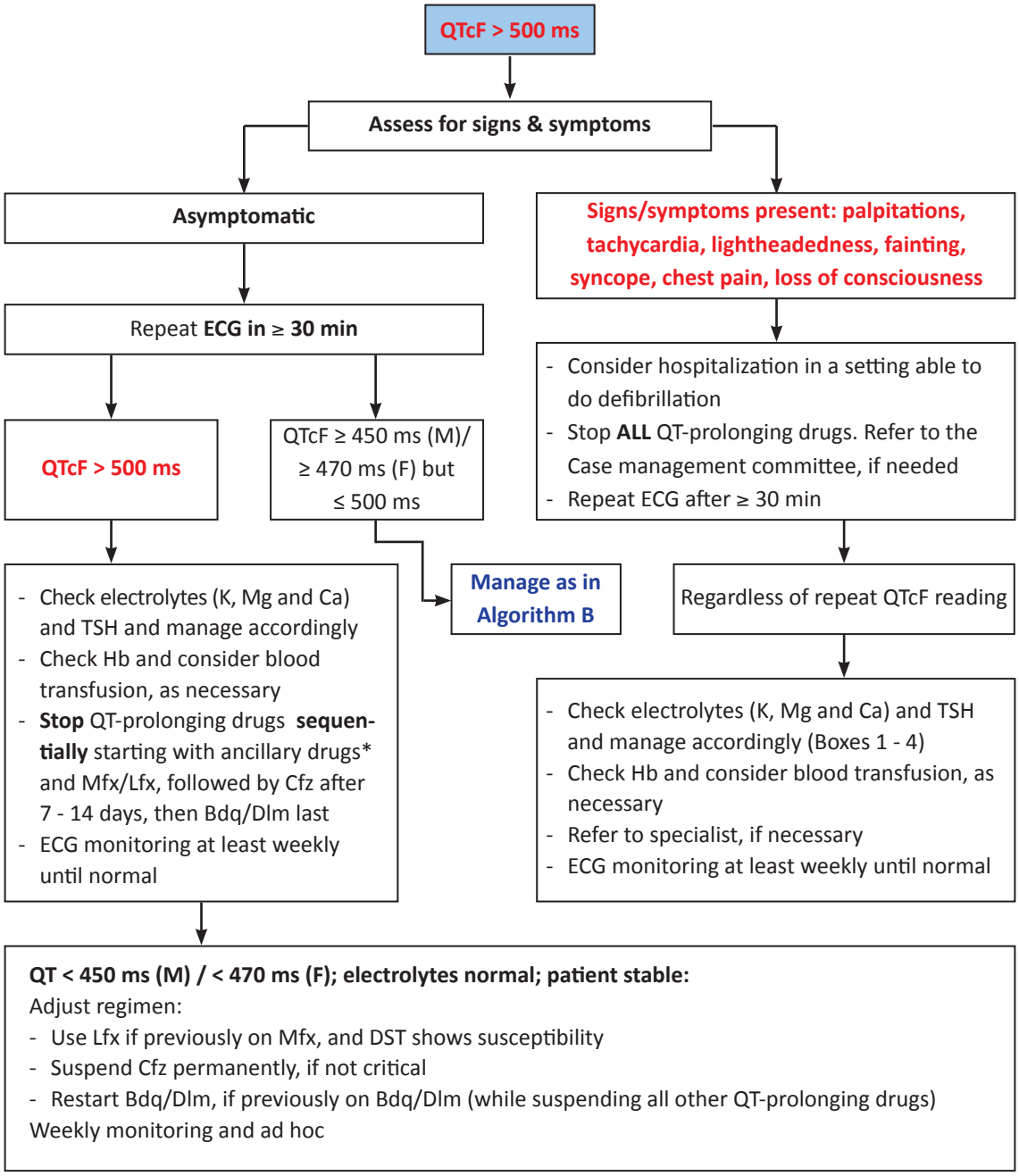
Note: Unit above should be in ms rather than sec

- Enter the manually counted QT interval **(Figure 3)**
- Enter the RR interval **(Figure 6)**
- Click on "calculate". Four QTc values will automatically appear using four different formulae
- **Choose QTc Fredericia. QTcF = 345 s (rounded off)**

5. The QTcF value and what action is recommended when it is prolonged

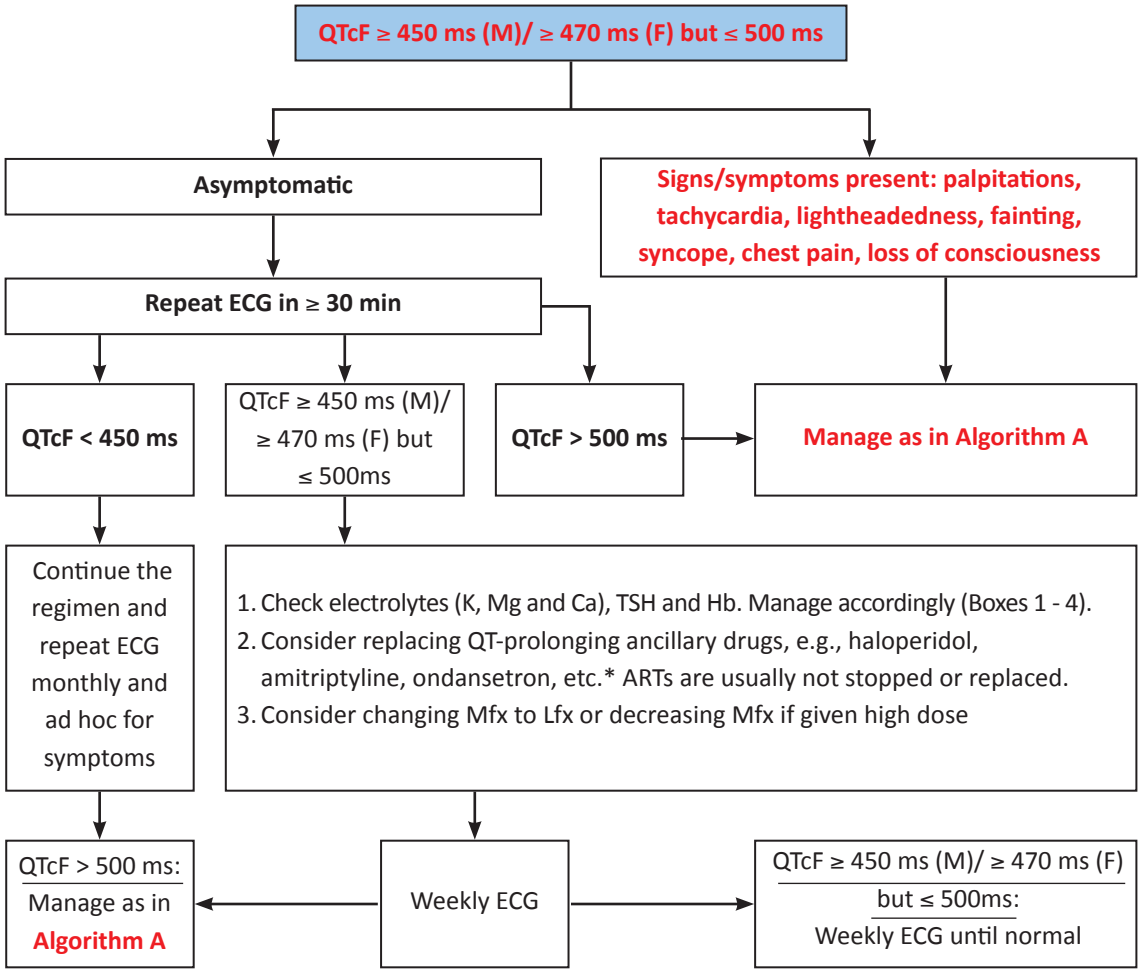
The QTcF is considered prolonged when it is ≥ 450 ms among males and ≥ 470 ms among females. It is considered dangerous when it is > 500 ms for both males and females. The recommended actions for these abnormal QTcF values are shown in the algorithms below, and a table with a severity grading scale and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

Algorithm A - Monitoring and managing QTcF prolongation among DR-TB patients (QTcF > 500 ms)



Note: Because of the long half-life of Bdq, if the QTcF is prolonged at week ≥ 24 and the patient is asymptomatic, weekly monitoring should continue until the QTcF normalizes (even though the drug is no longer being given).
*Website showing list of QT prolonging drugs: https://www.crediblemeds.org/ healthcare-providers/

Algorithm B- Monitoring and managing QTcF prolongation among DR-TB patients (QTcF ≥ 450 ms (male)/ ≥ 470 ms (female) but ≤ 500ms)



Adapted from Challenge TB Guide http://www.challengetb.org/library/pmdt

TABLE 4. SEVERITY GRADING SCALE OF QT PROLONGATION AND MANAGEMENT

Modified from endTB Clinical and Programmatic Guide ver 4.0

Prolonged QT interval **Possible anti-TB drug causes: Bdq, Dlm, Mfx, Cfz.** **Other causes: Hypokalaemia, hypothyroidism, other drugs** (E.g erythromycin, clarithromycin, quinidine, ketoconazole, fluconazole, furosemide, antipsychotics including haloperidol, chlorpromazine and risperidone, many anti-nausea drugs such as ondansetron and domperidone).				
Normal Values	**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)	> 500 ms and life-threatening consequences (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)
Action	• Monitor ECG more closely (weekly). • Check electrolytes and replete as necessary. • Check TSH and Hb and manage accordingly.	• Check electrolytes and replete as necessary. • Check TSH and Hb and manage accordingly. • Monitor ECG more closely; at least weekly until QTcF has returned to grade 1 or less.	• Hospitalize and replete electrolytes as necessary. • Stop the suspected causative drug in a phased manner. • Check TSH and Hb and manage accordingly.	• Hospitalize and replete electrolytes as necessary. • Stop all suspected causative drugs. • Check TSH and Hb and manage accordingly.

Box 1A – Severity grading and management of hypokalemia

Note: When on QT-prolonging drugs, always keep potassium > 4 meq/L.

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life- Threatening
Hypokalemia	3.4 - 3.0 mEq/L	2.9 - 2.5 mEq/L	2.4 - 2.0 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium with paresis, ileus or life-threatening arrhythmia
Action	Continue injectable. Start oral potassium replacement therapy. Check serum magnesium and replace if necessary.	Continue injectable. Start aggressive oral potassium replacement therapy. Replace magnesium empirically if unable to check serum magnesium.	Stop injectable temporarily. Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.	Stop injectable temporarily. Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.

* Reference : NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov - 2007.

Box 1B - Potassium replacement

Note: When on QT-prolonging drugs, always keep potassium > 4 meq/L.

Potassium level (mmol/L)	Dosing	Monitoring frequency
> 3.4	None	Monthly
3.3 - 3.4	40 mmol PO in 2-3 divided doses daily	Monthly
2.9 - 3.2	60 - 80 mmol PO in 3 divided doses daily	Weekly
2.7 - 2.8	60 mmol PO every eight hours	One to two days
2.5 - 2.6	80 mmol PO every eight hours	Daily
< 2.5	10 mmol/hour IV and 80 mmol PO every six to eight hours	One hour after infusion, every six hours with IV replacement

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

Box 2A – Severity grading and management of hypomagnesemia

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life- Threatening
Hypomagnesemia	0.60 - 0.70 mmol/L	0.45 - 0.59 mmol/L	0.30 - 0.44 mmol/L	< 0.30 mmol/L
Action	Start oral magnesium replacement therapy.	Start aggressive oral magnesium replacement therapy.	Start intravenous magnesium replacement therapy in addition to oral. Replace other electrolytes as necessary.	Start intravenous magnesium replacement therapy in addition to oral. Replace other electrolytes as necessary.

* Reference : NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov - 2007.

Box 2B - Magnesium replacement

Magnesium level (mmol/L)	Total daily dose	Monitoring frequency
> 0.70	None	Monthly
0.60 - 0.70	1,000 mg - 1,200 mg	Monthly
0.45 - 0.59	2,000 mg	One to Seven days
< 0.45	3,000 mg - 6,000 mg	Daily

Note :
Quantities greater than 2,000 mg are usually given IV or IM. The normal preparation is magnesium sulfate 2 g in 100 mL or 4 g in 250 mL of 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).

Box 3 - Calcium replacement

CALCIUM LEVEL (TOTAL NONIONIZED 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	1,000 mg three times a day	One to two weeks
< 7.0	Consider intravenous and taper to 1,000 mg three times a day	One to four days

Note :
Normal calcium is 8.5-10.3 mg/dl (2.12 - 2.57 mmol/l). To adjust for low albumin in nonionized 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).

Box 4 - Management of hypothyroidism

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

Management
TSH Normal value: < 5 mIU/L
Start treatment when TSH > 10 mIU/L
1. Most adults will require 100 – 150 mcg of levothyroxine daily. Start levothyroxine in the following manner:
• Young healthy adults can be started on 75 – 100 mcg daily
• Older patients should begin treatment with 50 mcg daily
• Patients with significant cardiovascular disease should start at 25 mcg daily.

2. 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.

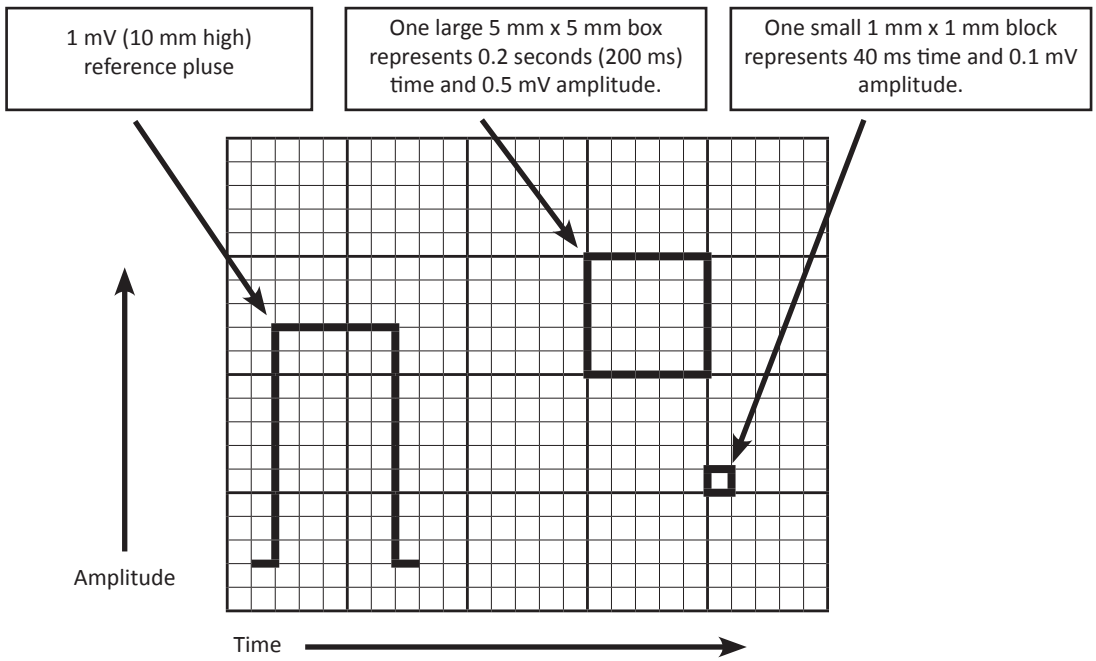
Note: it could be considered to start treatment with TSH > 6 mIU/L to 10 mUI/L with low dose of levothyroxine: 25 to 50 mcg.
Thyroid dysfunction resolves upon discontinuation of the causative agent. Hormone replacement must continue at least 2 to 3 months after completed DR-TB treatment.

Annex - Calibration of the ECG machine

The standard calibration of the ECG is 10 mm/milliVolt (mV) and a paper recording speed of 25 mm/sec, 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. If the speed of the ECG is adjusted to 50 mm/sec, 1 mV calibration signal is expected to produce a perfect square with a 10 mm height and 10 mm width. At standard calibration:

- one small square represents 40 ms (or 0.04 s) time, and 0.1 mV amplitude
- one large square (5 mm x 5 mm) represents 200 ms (or 0.2 s) time and 0.5 mV amplitude.

Measurements in ECG strips from a calibrated ECG machine



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