Clinical Audit: Assessing the quality of ECG monitoring in DR-TB patients

FINAL DEGREE PROJECT

Infectious Diseases department
University College London Hospitals, London
January, 2019

Author: Antía Garcia Fernández
Clinical tutor: Dr. Michael Brown
Methodological tutor: Dra. Carme Carrion Ribas
I would like to thank the entire clinical team from the Whittington Hospital and UCLH for making me feel like part of the team.

My sincere thanks to Carme and Mike for believing in me, giving the chance to do what I really wanted and for always being there to resolve my doubts. Thanks to Phil for letting me be his shadow.

Quero, tamén, dedicarlle este proxecto a miña familia de Galiza. Graza por mimarme e apoiarme sempre e, por suposto, por confiar en min dende cativa.

Finalment, però no menys important, agrair a les meves companyes i companys pels increïbles sis anys al seu costat i per convertir-se en la meva família a Catalunya.

“Science and everyday life cannot and should not be separated.”

Rosalind Franklin.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>aDSM</td>
<td>active TB drug safety monitoring and management</td>
</tr>
<tr>
<td>AEs</td>
<td>adverse effects</td>
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<tr>
<td>ARVs</td>
<td>antiretrovirals</td>
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<tr>
<td>BCG</td>
<td>Bacille Calmette-Guérin</td>
</tr>
<tr>
<td>BDQ</td>
<td>bedaquiline</td>
</tr>
<tr>
<td>BNF</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>CDC</td>
<td>United States Centers for Disease Control and Prevention</td>
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<tr>
<td>CFZ</td>
<td>clofazimine</td>
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<tr>
<td>cLQT</td>
<td>congenital long QT</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CPG</td>
<td>clinical practice guideline</td>
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<tr>
<td>DLM</td>
<td>delamanid</td>
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<tr>
<td>DR-TB</td>
<td>drug-resistant TB</td>
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<tr>
<td>DST</td>
<td>drug susceptibility testing</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<td>ESTC</td>
<td>European Union Standards for TB Care</td>
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<tr>
<td>FQs</td>
<td>fluoroquinolones</td>
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<tr>
<td>GDG</td>
<td>Guideline Development Group</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>IGRA</td>
<td>interferon-gamma release assay</td>
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<tr>
<td>LTBI</td>
<td>latent TB infection</td>
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<tr>
<td>LVX</td>
<td>levofloxacin</td>
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<tr>
<td>MDR-TB</td>
<td>multidrug-resistant tuberculosis</td>
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<tr>
<td>MTBC</td>
<td>Mycobacterium TB complex</td>
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<tr>
<td>MXF</td>
<td>moxifloxacin</td>
</tr>
<tr>
<td>NAAT</td>
<td>nucleic acid amplification technology</td>
</tr>
<tr>
<td>NCLSH</td>
<td>North Central London South Hub TB clinic</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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<tr>
<td>NTM</td>
<td>non-tuberculous mycobacteria</td>
</tr>
<tr>
<td>PAS</td>
<td>para-aminosalicylic acid</td>
</tr>
<tr>
<td>QTc</td>
<td>corrected QT interval</td>
</tr>
<tr>
<td>RR-TB</td>
<td>rifampicin-resistant TB</td>
</tr>
<tr>
<td>SCD</td>
<td>sudden cardiac death</td>
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<tr>
<td>SDG</td>
<td>Sustainable Development Goals</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
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<tr>
<td>TdP</td>
<td>Torsade de Pointes</td>
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<tr>
<td>TST</td>
<td>tuberculin skin test</td>
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<td>UCLH</td>
<td>University College London Hospital</td>
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<td>WGS</td>
<td>Whole Genome Sequencing</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>XDR-TB</td>
<td>extensively drug-resistant tuberculosis</td>
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ABSTRACT

INTRODUCTION: multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are diseases of global concerns which require treatments with complex combinations of drugs. These drugs are associated with several adverse effects (AEs). QTc prolongation is one of those AEs, and it is considered as a risk factor for developing Torsades de Pointe (TdP), an arrhythmia that can lead to sudden cardiac death (SCD). In order to prevent cardiac events, ECG monitoring is recommended in patients treated with QTc-prolonging drugs.

DATA/METHODS: four of the main guidelines for ECG monitoring in drug-resistant tuberculosis (DR-TB) patients were reviewed to define the range of recommendations. We reviewed the case records of 10 DR-TB patients managed in the North Central London TB service between 2016 and 2018. We analysed the data to assess the quality of health care provided, including ECG monitoring, and interviewed clinical staff to determine possible barriers to ECG monitoring in daily clinical practice.

RESULTS: the recommendations for ECG monitoring in the case of Bedaquiline (BDQ) and Delamanid (DLM) were similar in all four guidelines analysed, while recommendations for Clofazimine (CFZ) and Fluoroquinolones (FQs) were only considered in one of the four guidelines. The care provided at the clinic largely adhered to the recommended guidelines. However, sometimes the results and actions taken were not clearly accessible. For example, we found that only 79.23% of the ECGs performed were compiled in the clinical records. There were not found remarkable barriers in the daily clinical practice, and there is a good team work between nurses and doctors at the clinic.

CONCLUSIONS: there is a lack of guidance for the frequency for ECG monitoring in patients on CFZ, FQs or more than one QTc-prolonging drug. There is a quality health care imparted by the clinical staff at the TB service assessed. Due to the complexity of adverse event-monitoring in patients with DR-TB, we propose a standard proforma to record these data during clinic visits. This measure could simplify the work of the clinical staff by providing easy access to previous results. Finally, we also propose to standardize the way ECGs should be storage, either in the patient’s folder or scanned into NHS platform.

KEY WORDS: Tuberculosis; Drug-Resistant TB; QTc prolongation; ECG monitoring; clinical audit.
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INTRODUCTION

1. TUBERCULOSIS

Tuberculosis is an infectious disease caused by a bacillus from the Mycobacterium tuberculosis complex (MTBC). MTBC is made up of seven phylogenetic lineages, of which *M. tuberculosis* (*Mt*) is the most common and important agent of human disease. Although this bacillus was discovered by Dr Robert Koch in 1882, many studies have shown that it has been affecting humans for thousands of years. It is transmitted through the respiratory route by inhaling small droplets. For this reason, TB mostly affects the lungs and is known as Pulmonary TB. It can also cause extra-pulmonary disease affecting lymph nodes, meninges, brain, kidneys and many other organs and tissues.  

1.1 EPIDEMIOLOGY

TB is one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent. It is estimated that 10 million people developed TB in 2017, from which 2/3 were in eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). Only 3% of global cases were in the WHO European Region. Even though TB incidence has been decreasing in recent years, and most people who developed the disease can be cured, TB remains a major public health concern. As a result, the WHO has developed the End TB Strategy. This has the target of reducing TB deaths by 95% and incidence by 90% compared with 2015 levels by 2035. The strategy is contained within the Sustainable Development Goals (SDG) along with targets for HIV, malaria and neglected tropical diseases.  

Figure 1 Estimated TB incidence rates, 2017

*Figure 1* Estimated TB incidence rates in 2017. WHO.
Drug-resistant TB: Worldwide, the best estimate is that in 2017, 558,000 people developed Rifampicin Resistant-TB (RR-TB), and of these, 82% had MDR-TB. Almost half of RR-TB/MDR-TB cases were reported in three countries: India (24%), China (13%) and the Russian Federation (10%). Globally, 3.5% of new TB cases and 18% of previously treated cases had MDR/RR-TB. In 2017, 8.5% among MDR-TB cases were estimated to have XDR-TB. This is a slight decrease from the 660,000 estimated cases of MDR and RR-TB in 2016. However, the number of deaths was 230,000 which is similar to 2016. Based on the data available from 22 out of the 40 countries with a high TB and/or MDR-TB burden, there is a trend for MDR-TB cases to increase as a proportion of all TB cases in these countries. This can be the result of a faster increase or a slow decrease of MDR-TB than the overall TB burden. The global cure rates for MDR-TB and XDR-TB are 54% and 30% respectively; hence new anti-TB drugs and regimens are critical to improving these outcomes. Because of that, drug-resistant TB is still a major public health concern in many countries.  

A. ENGLAND - LONDON CONTEXT

WHO defines low TB incidence countries as those with an incidence rate under 10 per 100,000 population. According to this definition, England became, for its first time, a low TB incidence country having an incidence rate of 9.2 per 100,000 population in 2017. In addition, 5102 people were notified with TB across England, which is the lowest rate since 1990. However, it remains a public health concern. Whilst 71% of TB notifications were in people born overseas, between 2016 and 2017 there was a decrease in the number of cases, and rate of TB, by 13% and 17% respectively, in non-UK born people, whilst there was no change among people born in the UK.

Figure 2 Three-year average TB rate in England and London (box) by clinical commissioning group, 2015-2017
The main burden of TB remains in large urban areas. London, known as the TB capital of Western Europe, is at the top of the list with a rate of 21.7 per 100,000 population, which is 37.6% of all notifications in the country. However, this proportion has been decreasing since the 2011 peak in incidence when it was 42.2% of notifications. As we can see in Figure 2, TB rates differ between London boroughs and wards. The London boroughs of Newham in the East and Brent in the West have the highest TB rates. In 2015 the Health Committee of the London Assembly published a report stating that the incidence in some boroughs was even higher than countries such as Rwanda or Iraq.

The proportion of UK people diagnosed with MDR/RR-TB was similar in 2016 and 2017 (1.7% vs 1.8% respectively), although the number of people decreased slightly from 60 to 55. Moreover, the proportion of people with Isoniazid resistance without MDR/RR-TB has remained around 6% over the last decade. There has been an improvement in the proportion of patients with drug-resistant TB who completed treatment by 24 months: from 52% in 2014 to 58% in 2015. In addition, there has been an improvement in the proportion of patients lost to follow-up: from 19% in 2014 to 8% in 2015. Yorkshire had the highest proportion of DR-TB cases in the UK between 2013 and 2017.

There were 61 patients with initial drug-resistant TB confirmed by Drug Susceptibility Testing (DST) or Whole Genome Sequencing (WGS) in 2017, 10 people had RR-TB and 51 had MDR-TB. 46 out of the 51 MDR-TB cases had confirmed resistance (one of them was actually acquired), and 5 were treated with a 2nd line regimen without confirmation, 4 of which were in fact contacts of people with confirmed MDR/RR-TB. Furthermore, the proportion of females diagnosed with drug-resistant TB was higher than males (2.5% versus 1.3%). There was a variation by country of birth with the highest proportion (23.7%) coming from Lithuania. Surprisingly the proportion of patients with drug-resistant TB was similar among the UK born and non-UK born population (1.7% vs. 1.9%). It is important to note the high proportion of patients with a previous diagnosis of TB (6.6% versus 1.5%) as well as a higher proportion of MDR/RR-TB cases among people with at least one social risk factor such as: “...current alcohol misuse that would impact on the patient’s ability to take treatment, current or history of drug misuse, homelessness and/or imprisonment”.

![Figure 3 Estimated TB incidence rate in London between 2000-2017, UK born - Non-UK born](image-url)
In 2017, 54 out of the 55 people had confirmed resistance to all 1st line drugs, and 23 were actually resistant to all four. Furthermore, 7/51 were resistant to at least one injectable agent and 18/53 were resistant to at least one FQ. These resistance patterns seem to be strongly related to the country of birth. Only three patients had confirmed XDR-TB (four less than in 2016) and only one of them have had a previous history of TB treatment. From 2013 to 2017, the highest numbers of people with XDR-TB were born in Lithuania (10), UK (6), India (3) and Romania (2). 

1.2 PATHOPHYSIOLOGY

TB is mainly transmitted through the inhalation of tiny drops after someone infected coughs or sneezes. These drops can remain suspended in the air for several hours. The TB bacillus is deposited at the alveolar site, where it triggers an inflammatory reaction. Some of these bacilli may not be destroyed by alveolar macrophages and multiply intracellularly. *Mtb* spreads via pulmonary lymphatics to the hilar lymph nodes and thoracic duct, from where it spreads to the systemic venous circulation. The TB bacillus may pass in to the systemic arterial circulation and become deposited in any organ of the body, leading to the development of extra-pulmonary TB. In 90% of patients *Mtb* remains dormant and is known as Latent TB Infection (LTBI). TB may reactive many years after primary infection and cause active disease when bacilli overcome immune control. 

Following initial infection, it takes two to eight weeks to develop a cellular immune response. Tuberculin is recognised by specific CD4-T lymphocytes. The CD4-T cells activate the macrophage that is trying to destroy *Mtb* through the liberation of IFN-γ, TNF-α and IL-12, giving place to granulomas. LTBI can be detected by using the tuberculin skin test (TST) or an interferon-gamma release assay (IGRA), but these tests will be negative during the window period while the cellular immune response is developed.
1.3 TB RISK FACTORS AND COMORBIDITIES

In general, persons at high risk for developing active TB fall into two categories: 2,7,8

a. People who have been Recently Infected with TB:
   - Close contacts of a person with infectious TB disease.
   - Persons who have immigrated from areas of the world with high rates of TB.
   - Children less than 5 years of age who have a positive TB test.
   - Groups with high rates of TB transmission, such as homeless persons, injection drug users, and persons with HIV infection.
   - People who work or reside with people who are at high risk for TB in facilities or institutions such as hospitals, homeless shelters, correctional facilities, nursing homes. And residential homes for those with HIV.

b. People with Medical Conditions that weaken the immune system:

Young children often have an under-developed immune system. Other people can have weak immune systems too, especially people with any of these conditions:

   - Substance abuse. Some studies have found that harmful use of alcohol increases the risk of TB 2-3 fold and is associated with poor TB treatment results. 6
   - Diabetes mellitus triples the risk of TB.
   - Tobacco smoking increases the risk of TB 2-3 fold and is associated with poor TB treatment results.
   - HIV infection.
   - Silicosis.
   - Severe Kidney Disease.
   - Malnutrition.
   - Organ transplants.
   - Head and neck cancer.
   - Treatment with corticosteroids and other immunosuppressive drugs or organ transplantation; and immunomodulatory drugs for rheumatoid arthritis and Crohn’s disease. 2,7,8
1.4 DIAGNOSIS

According to the last updated WHO guidelines, two sputum samples are enough in order to reduce time to diagnosis and accelerate initiation of treatment. On the other hand, European guidelines, including NICE, and the US CDC guideline recommend collecting three sputum samples.

The available genotypic tests are nucleic acid amplification technology (NAAT) (such as GeneXpert, that can detect both Mtb and rifampicin resistance) and line probe assays (which can be used to detect Mtb, rifampicin and/or isoniazid resistance). In some countries, Whole Genome Sequencing (WGS) tools are available for the identification of Mtb and of drug resistant variants.
1.5 STANDARD TB TREATMENT

The 1948 MRC Streptomycin trial heralded the start of effective chemotherapy for TB. For the next 25 years, TB treatment consisted three drugs taken for 2 – 3 years with the first year given in TB sanitoria. With the synthesis of Rifampicin in 1963, and its combination with isoniazid, pyrazinamide and ethambutol / streptomycin in subsequent trials in East Africa, short course chemotherapy was introduced in the 1970s and consisted of the following two phases:

- **Initial phase**: Isoniazid with pyridoxine, Rifampicin, Pyrazinamide and Ethambutol for 2 months. (H-R-Z-E)
- **Continuation**: Isoniazid with pyridoxine plus Rifampicin for a further 4 months.

In the case of CNS involvement or spinal TB with CNS involvement, the second treatment phase should last 10 months instead of 4. Very little changed in TB therapy for the next 30 years.

1.6 PREVENTION

INFECTION CONTROL

\[\text{Figure 5 Infection control according to NICE guideline}\]
It is important to identify patients with pulmonary TB promptly in order to reduce the risk of transmission. It takes time for effective treatment to reduce a patient’s infectiousness and so the number and duration of visits to clinic should be minimised.

(1) In cases of pulmonary TB, whether suspected or confirmed, patients should only be admitted if there is a clear public health need, such as homelessness. Nevertheless, their risk of DR-TB should be assessed and admitted to a single room if low risk, and a negative-pressure room if high risk. Sputum samples should be sent for rapid diagnostic tests.

(2) It is important to ensure that patients with suspected or confirmed pulmonary TB should not be admitted to a ward with immunocompromised patients.

(3) In the case of patients with suspected or confirmed DR-TB, a negative-pressure room should be provided until DR-TB is excluded, or if confirmed until they have three negative smears at weekly intervals and a negative six-week culture.

(4) In order to reduce the risk of transmitting TB to others, it is important to know when to do contact tracing. In particular, a risk assessment should be performed for patients admitted to hospital. It should take into account the degree of infectivity of the index case, the length of time before the infectious patient was isolated, whether other patients are particularly susceptible to infection, and the proximity of contact.9

LATENT TB

Latent TB Infection (LTBI) is the condition whereby TB bacilli remain inactive in the body without causing disease. These patients are not ill and cannot transmit TB. HIV-negative patients with LTBI have a 5 to 10% lifetime risk of developing active disease whereas for HIV-positive patients this is closer to a 5 to 10% annual risk. LTBI is a complex and poorly understood phenomenon. It is diagnosed in asymptomatic patients with a positive skin or IGRA and normal chest X-ray. These patients may receive a modified version of TB treatment in order to prevent active disease.2

VACCINATION

There is currently only one licenced vaccine against TB, Bacille Calmette-Guérin (BCG), which was created in 1921. BCG has variable protective efficacy, providing protection against severe extra-pulmonary TB but variable protection against pulmonary TB. Nevertheless, WHO recommends vaccinating HIV-negative babies to prevent the complications of extra-pulmonary TB. There are a number of studies underway in order to develop a new and more effective vaccine.36
2. DRUG-RESISTANT TUBERCULOSIS

Multidrug-Resistant TB is the disease caused by the TB that is resistant to at least isoniazid and rifampicin, two main drugs used in first line regimen. Thus, short course regimens cannot be used and other, often more toxic drugs are needed.\(^2\) It is important to mention the possibility of being sensitive to Isoniazid but resistant to Rifampicin, the most effective first-line anti-TB drug, known as **Rifampicin Resistant TB** (RR-TB). RR-TB is increasingly considered equivalent to MDR-TB. Drug resistance was first documented back in the MRC Streptomycin trial and although MDR-TB was recognised shortly after the introduction of Rifampicin, MDR-TB really took off in the 1990s. Twenty years later the WHO Assembly passed a resolution to take stronger measures to prevent and control the spread of resistance.\(^1,3\)

Extensively Drug-resistant TB (XDR-TB): was first describe in 2006 as a type of MDR-TB with additional resistance to any fluoroquinolone and at least one of the three injectable second-line drugs (i.e. amikacin, kanamycin or capreomycin); further compromising treatment options available to these patients.\(^19\) Pre-XDR-TB is when the isolate is resistant to isoniazid, rifampicin and either a fluoroquinolone or one injectable second-line drug\(^2\). It is therefore possible to see how inadequate treatment of MDR-TB can lead to a further selection of mutations and result in XDR-TB.\(^20\)

Drug-resistant TB can be developed according to two different pathways:

- **Primary drug resistance**: this is the result of direct transmission form one patient to another where the recipient has no previous TB treatment history. Communities with high prevalence of drug-resistant TB have an increased risk of transmission.
- **Acquired or Secondary drug resistance**: this is the result of de-novo mutations in patients previously treated with TB first line regimen.\(^20\) It means that mutant resistant strains have been selected after inadequate or incomplete treatment courses. The most consistent factor associated with MDR-TB is a previous history of anti-TB treatment over a period of 1 month or more.\(^1\) Hence it can be prevented by ensuring that the correct drugs are used from the beginning and patients are supported to adhere to therapy.

2.1 DR-TB TREATMENT

According to NICE latest TB guideline, MDR-TB treatment should be offered in the following situations:

- **Rifampicin resistance detected with rapid diagnostic NAAT.** Testing for resistance to 2\(^{nd}\) line drugs is required, as well as offering treatment with at least 6 drugs to which it is likely to be sensitive. In the case of no Rifampicin-resistance detected, the patient should be treated as drug-susceptible TB with the standard regimen.
- **In a person with high risk of MDR-TB but negative rapid diagnostic NAAT, it is recommended to obtain further specimens for NAAT and culture, as well as using rapid Rifampicin resistance detection on cultures that become positive for the MTBC.** If the
person is feeling well and stable, consider waiting for the results before starting treatment; if not, consider managing as MDR-TB until sensitivity results are available.

The treatment can be modified after definitive phenotypic susceptibility results are available.

**a. SECOND AND THIRD LINE DRUGS**

The most recent WHO guideline for MDR-TB treatment was published in 2016. However, an updated interim guideline was published after a meeting of the Guideline Development Group (GDG) in July 2018.

In the 2018 WHO report one of the main changes has been the redistribution of 2nd and 3rd line drugs into a hierarchy of three groups (A, B and C) instead of six (A, B, C, D1, D2 and D3). This is described in table 1. Furthermore, the use of Kanamycin and Capreomycin is no longer recommended due to the increased risk of treatment failure and relapse in longer regimens, and the use of amoxicillin-clavulanic acid is only recommended to accompany the carbapenems. 21

<table>
<thead>
<tr>
<th>GROUP</th>
<th>MEDICINE</th>
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| A: to be prioritised; include all three drugs. | Levofloxacin or Moxifloxacin (FQs)  
Bedaquiline  
Linezolid |
| B: to be added next; both can be added. | Clofazimine  
Cycloserine or Terizidone |
| C: to be included to complete the regimens when drugs from groups A and B cannot be used. | Ethambutol  
Delamanid  
Pyrazinamide  
Imipenem-Cilastatin  
Meropenem  
Amikacin or Streptomycin  
Ethionamide or Prothionamide  
p-aminosalicylic acid |

*Table 1 2nd and 3rd line TB drugs.*

**b. REGIMENS**

- **Longer MDR-TB regimen:**

The longer regimen usually last between 18 to 20 months. It usually includes at least five drugs to which the isolate is thought to be susceptible, and it is designed by adding them sequentially going down the three groups. This involves a balance of effectiveness against harm, but also by a preference for oral over injectable agents, the results of DST, population drug resistance patterns, medication history, drug tolerability and potential drug-drug interactions. 37

- **Shorter MDR-TB regimen:**

The shorter regimen usually lasts between 9 to 12 months. There is some evidence for similar levels of success compared with longer regimens, with a lower risk of treatment interruption. Nevertheless, shorter regimens were associated with higher treatment failure and relapse, in
particular when there was resistance to key medicines in shorter regimen, or when longer
regimens included one or more of the group A medicines. 37

The most common short regimen is based on:

| 4 or 6 months if no sputum smear conversion with: Moxifloxacin + Kanamycin + Prothionamide + Clofazimine + high-dose Isoniazid + Pyrazinamide + Ethambutol | + |
| 5 months with: Moxifloxacin + Clofazimine + Pyrazinamide + Ethambutol |

**c. CHOICE OF LONGER OR SHORTER MDR-TB REGIMEN**

MDR-TB treatment is increasingly becoming more individualised because of innovations in
diagnostics and the knowledge of the molecular basis for drug resistance, as well as the
pharmacokinetics and pharmacodynamics of TB drugs.

According to WHO recommendations: “shorter MDR-TB regimen should be started in patients
who do not have any of the following conditions:

- Resistance or suspected ineffectiveness to medicine in the shorter MDR-TB regimen
  (except isoniazid resistance);
- Exposure to one or more 2nd line medicines in the regimen for >1 month (unless
  susceptibility these 2nd line medicines are confirmed);
- Intolerance to any medicine in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-
  drug interactions);
- Pregnancy;
- Disseminated, meningeal or central nervous system TB; or any extra-pulmonary disease
  in HIV patients.” 21

**d. SURGERY**

Surgery could be considered in patients who have unilateral pulmonary disease, particularly if
medical therapy under direct observation has not worked or is likely to fail because of XDR-
TB. 21,37

**2.2 MONITORING ADVERSE EFFECTS DURING MDR-TB TREATMENT**

MDR-TB can be deadly and it is associated with high comorbidity itself. Furthermore, it requires
complex and long treatment regimens, which are associated with a lot of side effects, some of
them life-threatening. Because of that, multidisciplinary teams consisting of nurses, TB physicians,
pharmacists and specialities such as ophthalmology or audiology, are needed in order to ensure
that these adverse effects are recognized and treated quickly.

Most of the adverse effects can be recognized by patients. However, some side effects need
further enquiry and thus good programmes involve regular monitoring and a good knowledge
of the drugs used and their specific adverse reactions.
a. **MOST COMMON ADVERSE EFFECTS OF MDR-TB THERAPY**

In this table the most common adverse effects are summarized:\(^{19,22,23}\)

<table>
<thead>
<tr>
<th>ADVERSE EFFECTS</th>
<th>ANTI-TB DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Ethambutol</td>
</tr>
<tr>
<td>Anorexia</td>
<td>CFZ</td>
</tr>
<tr>
<td>Gastritis</td>
<td>BDQ</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>DLM</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>FQs</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Linezolid</td>
</tr>
<tr>
<td><strong>OTORHINOLARYNGOLOGIC</strong></td>
<td>Injectable agents</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td></td>
</tr>
<tr>
<td>Hearing disturbances</td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td></td>
</tr>
<tr>
<td><strong>OPHTHALMOLOGIC</strong></td>
<td>Ethambutol</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>Linezolid</td>
</tr>
<tr>
<td><strong>NEUROLOGICAL</strong></td>
<td>BDQ</td>
</tr>
<tr>
<td>Headache</td>
<td>FQs</td>
</tr>
<tr>
<td>Seizures</td>
<td>Linezolid</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Linezolid</td>
</tr>
<tr>
<td><strong>PSYCHIATRIC</strong></td>
<td>CFZ</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>DLM</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td></td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td></td>
</tr>
<tr>
<td><strong>ENDOCRINE</strong></td>
<td>Injectable agents</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td></td>
</tr>
<tr>
<td>(mainly with potassium, magnesium and calcium)</td>
<td>FQs</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Ethionamide/Prothionamide</td>
</tr>
<tr>
<td><strong>RENAL</strong></td>
<td>Injectable agents</td>
</tr>
<tr>
<td>Nephrotoxicity: Renal failure</td>
<td></td>
</tr>
<tr>
<td><strong>HEPATIC</strong></td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td>Hepatotoxicity: Hepatitis</td>
<td>PAS</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>BDQ</td>
</tr>
<tr>
<td>QT interval prolongation</td>
<td>DLM</td>
</tr>
<tr>
<td><strong>SKIN DISORDERS</strong></td>
<td>CFZ</td>
</tr>
<tr>
<td>Rash</td>
<td>FQs</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>Linezolid</td>
</tr>
<tr>
<td><strong>HAEMATOLOGICAL</strong></td>
<td>DLM</td>
</tr>
<tr>
<td>Anaemia</td>
<td>FQs</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Linezolid</td>
</tr>
<tr>
<td>Lactoopenia</td>
<td></td>
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</tbody>
</table>

*Table 2 Most common TB drugs adverse effects*
WHO introduced “active TB drug-safety monitoring and management” (aDSM) as a term to define active and systematic clinical and laboratory assessment of patients while on treatment. aDSM applies to patients in treatment with new anti-TB drugs such as Bedaquiline or Delamanid; MDR-TB patients enrolled in novel regimens; all XDR-TB patients. It can be extended to other patients with conventional MDR-TB regimens.  

b. BASELINE AND ROUTINE MONITORING FOR PATIENTS ON MDR-TB REGIMENS

The following table summarizes recommendations from the UK TB Drug Monographs. These recommendations are based on consensus opinions, rather than evidence-based, from TB physicians, pharmacists, nursing staff and specialities like audiology and ophthalmology, along with drug advisory organisations including FDA and BNF. They were produced to provide advice on the frequency of monitoring.

<table>
<thead>
<tr>
<th>BLOOD TESTS</th>
<th>Full Blood Cell Count</th>
<th>Serum Creatinine Serum Potassium</th>
<th>Serum Magnesium and Calcium</th>
<th>Liver Function Test</th>
<th>Lipase</th>
<th>Lactic acid</th>
<th>Audiometry</th>
<th>Vision tests</th>
<th>Educational, psychological and social consultation</th>
<th>ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>If on Linezolid monitor weekly at first and then monthly or as needed based on symptoms. For HIV-infected patients on zidovudine, monitor monthly at first + if needed.</td>
<td>Baseline + monthly while receiving an injectable agent. Every 1-3 weeks in HIV patients, diabetics and other high-risk patients.</td>
<td>Check them when hypokalaemia is diagnosed. At baseline + monthly if on BDQ or DLM. Repeat if any ECG abnormalities develop.</td>
<td>Every 1 to 3 months in patients on Pyrazinamide for extended periods or for patients at risk for hepatitis. On BDQ monitor monthly. For patients with hepatitis monitor every 1-2 weeks the first month and then every 1-4 weeks.</td>
<td>In case of abdominal pain in patients on linezolid or BDQ.</td>
<td>In case of lactic acidosis in patients on linezolid or ARVs Treatment</td>
<td>Baseline + monthly while on an injectable agent.</td>
<td>Baseline for patients on ethambutol or linezolid. Repeat if changes.</td>
<td>Baseline + if needed.</td>
<td>Before initiation of treatment with BDQ or DLM, and at least 2, 4, 8, 12 and 24 weeks after starting treatment. Monitoring ECGs should be done monthly if taking other QT prolongation drugs.</td>
<td></td>
</tr>
</tbody>
</table>

*Table 3 Baseline and routine monitoring in DR-TB patients*
2.3 QT INTERVAL PROLONGATION DURING MDR-TB TREATMENT

The QT interval is an ECG measure which quantifies the flow of ion currents across protein channels in ventricular myocytes.

The QT interval assesses the duration from the beginning of the QRS complex to the end of T wave. This interval has to be corrected by heart rate, known as QTc. The optimal correction formula is Fridericia’s (QTcF). This is also the one recommended by WHO for use with DR-TB patients.25

- QT INTERVAL PROLONGATION AND CLINICAL SIGNIFICANCE

QT prolongation is the result of blocking the outward rapid potassium current, leading to extended repolarisation; several drugs interact with these channels delaying repolarisation and increasing QTc. This may trigger an early after-depolarisation, which in combination with a heterogeneous intra-cardiac repolarisation, is associated with the onset of Torsade de Pointes (TdP) and sudden cardiac death (SCD); although most of the patients with prolonged QTc do not develop TdP. Torsade de Pointes is a polymorphic ventricular tachycardia which appears as twisting QRS complexes in the ECG. The prevalence of SCD due to TdP by QTc-prolonging DR-TB drugs is likely less than 1%. In the few cases of TdP, it was usually associated with another risk factor apart from the drug. 25

QTc is considered prolonged when it measures ≥450ms in adult males and ≥470ms in adult females. A QTc ≥500ms is considered significantly prolonged and therefore a risk factor for cardiac arrhythmias. There is evidence that a change in the QTc interval of ≥20ms may also increase the risk of cardiac complications. 24 26 Besides, the QTc may vary up to 75 msec in the same individual during the day. 25

The main symptoms of patients with arrhythmia associated with QTc prolongation are dizziness, giddiness, palpitations or episodes of syncope; although most patients are asymptomatic. The presence of any of these symptoms should prompt an exhaustive clinical assessment, ECG monitoring and the determination of electrolyte levels. 24

- RISK FACTORS FOR DEVELOPING QTc PROLONGATION

In the last years, many studies have been performed in order to determine risk factors for developing acquired QTc prolongation. To make a proper estimation of the risk of QTc-prolongation, both the drug therapy and patient-specific risk factors should be taken into account. 27

A recent study of the relationship between QTc and anti-TB drugs was published in late 2018 by J. Monedero-Recuero, L. Hernando-Marrupe, A. Sánchez-Montalvá, V. Cox, M. Tommasi, J. Furin... A. Piubello. The paper reviewed the literature including WHO, CDC, EMA, and manufacturers’ guidelines. In these study, they performed a risk assessment with the propose of giving an idea of a clinical approach to achieve an optimal balance between access to life-saving drugs and patient safety. They divided the Risk factors for QTc prolongation and TdP as follows: 25
The use of ≥1 QTc-prolonging drug is also associated with high risk. This is particularly important in DR-TB patients because they are usually treated with many different drugs for long periods of time. Most of the DR-TB patients have other comorbidities and treatments that may induce changes in the QTc:

- Anti-TB drugs that can prolong the interval in an indirect way, like ethionamide/prothionamide and para-aminosalicylic acid, that may cause hypothyroidism, which is a risk factor for QTc prolongation, and the injectable agents can prolong the interval through hypopotassemia and/or renal dysfunction.
- Anti-emetics as commented above, like ondansetron and metoclopramide, can prolong the QT and are commonly used in DR-TB patients due to the common AEs of nausea and vomiting.25
- Psychiatric disorders can also be developed as an AE of TB drugs. Some drugs used to treat these disorders may prolong the QTc such as antidepressants (Tricyclic), and antipsychotics (Thioridazine, haloperidol, Chlorpromazine, Trifluoperazine, Percycline, Prochlorperazine, Fluphenazine, Sertindole, and Pimozide).21
- Hydrazides and loop diuretics like hydrochlorothiazide and furosemide, may cause hypopotassemia and increase the risk of QTc prolongation.
- HIV-infected patients have an increased prevalence of QTc prolongation. These patients present multiple clinical risk factors for this prolongation, and in addition ARVs and treatment for opportunistic infections that may increase the chance of QTc prolongation.
  - ARVs: Efavirenz and atazanavir were associated with QTc prolongation and TdP. Furthermore, these ARVs, as well as lopinavir/ritonavir and saquinavir, may increase the levels of other drugs due to strong CYP3A4 inhibition that may result in QTc prolongation.
  - Treatment of opportunistic infections: cases of QTc prolongation and TdP have been described with the following treatments: trimethoprim-sulfamethoxazole, intravenous pentamidine, pyrimethamine, macrolides given for chronic disease, several azole antifungals (like fluconazole and voriconazole) and some antimalarials (halofantrine).25
Plasma concentrations of these medicines are also associated with high risk; therefore, physicians must ensure correct dose adjustment in case of chronic kidney or liver disease to avoid QT prolonging drugs accumulation. Physicians may also take into account possible drug-drug interactions like the combination of QT-prolonging drugs that are metabolised via cytochrome P450 with a possible CYP450-inhibitor that can lead to plasma level increases.  

- **CAUSES OF QTc PROLONGATION**

QTc prolongation can be congenital (cLQT) or acquired. More than 20 different genetic forms have been described as cLQT; however, is far less common than acquired long QT.

The QT interval can be prolonged by a number of different drugs and, in addition, some people have a genetic predisposition to QT prolongation. MDR-TB drugs known to prolong QT interval are macrolides, fluoroquinolones, clofazimine and the most recent anti-TB drugs, bedaquiline and delamanid. Furthermore, as nausea and vomiting are some of the most common AEs of treatment, a lot of the patients are on anti-emetics while on MDR-TB treatment. There is some evidence of the QTc prolongation with the anti-emetics Ondansetron or Metoclopramide.  

The following source is useful to assess drug interactions and the risk of QTc-prolongation: [https://www.crediblemeds.org](https://www.crediblemeds.org)

- **PHARMACOKINETIC AND PHARMACODYNAMIC OF ANTI-TB QTc-PROLONGING DRUGS**

1. **BEDAQUILINE: (BDQ)**

*Pharmacodynamics: Mechanism of Action:* BDQ is a bactericidal drug that inhibits mycobacterial ATP synthesis that is essential for the generation of energy in *Mtb*. *Mechanism of Resistance:* the most common is the mutation of the *atpE* gen, but there is suggest to be other possible mechanisms. BDQ resistant bacilli are usually less sensitive to CFZ.  

*QTc prolongation:* its metabolite’s (M2) concentration seems to be correlated with QTc prolongation.  

*Pharmacokinetics: Absorption:* BDQ’s maximum plasma concentration is reached 5-hour post-administration. Higher BDQs bioavailability is acquired if administrated with food.  

*Distribution:* BDQ’s metabolite (M2) union to plasmatic proteins is of 99.8%. Because of this, it is extensively distributed among the most part of the tissues; however, its brain distribution is low.  

*Biotransformation:* BDQ is metabolised by CYP3A4 giving N-monodemetilo (M2) as its metabolite.  

*Elimination:* BDQ is mainly excreted in the stool. It has a long half-life of 5.5 months.

2. **DELAMANID: (DLM)**

*Pharmacodynamics: Mechanism of Action:* DLM acts inhibiting the synthesis of the mycobacterial cell wall components, such as methoxy- mycolic and keto- mycolic acid.  

*Mechanism of resistance:* the mutation of one of the co-enzyme F420 gens is suggested to be the main mechanism.  

*QTc-prolongation:* The formation of DM-6705 is regulated by plasma albumin, and its concentration is related with the QTc prolongation. It is important to highlight that CYP3A4 is related to DM-6705’s metabolism, and you should be aware of any drug that can interact with that enzyme.
**Pharmacokinetics:** Absorption: DLM’s administration with food rises its bioavailability. Distribution: DLM’s union to plasmatic proteins is of more than 99.5%. Biotransformation: DLM is a pro-drug, needing to be reduced to des-nitro metabolite to be active, and being DM-6705 the major DLM’s metabolite. DLM metabolite’s concentration increase progressively until they reach their stationary state after six to 10 weeks. Elimination: It has a half-life of 30 to 38 hours.

3. CLOFAZIMINE: (CFZ)

Clofazimine was originally introduced for the treatment of leprosy, although, nowadays is used for MDR-TB treatment.

**Pharmacodynamics:** Mechanism of action: Its mechanism of action against TB is not clearly defined. CFZ appears mainly bonded to mycobacterial DNA, inhibiting its growth.39

**Pharmacokinetics:** Absorption: maximum plasmatic concentration is reached 8 to 10-hours post-administration. Distribution: CFZ is mainly accumulated in adipose tissue, but, later, it reaches other tissues and organs (but brain). Biotransformation: CFZ metabolism information is limited.39 Elimination: CFZ is mainly excreted in the stool. Its half-life is estimated to be around 70 days.19

4. FLUOROQUINOLONES: LEVOFLOZACIN (LVX) AND MOXIFLOCIN (MXF)

Levofloxacin and moxifloxacin are the current fluoroquinolones recommended for MDR-TB treatment according to WHO update.19

**Pharmacodynamics:** Mechanism of action: Both of them are bactericidal, and they inhibit the DNA gyrase. Mechanism of resistance: It is most often acquired through a stepwise process by target site mutations in DNA gyrase and topoisomerase IV.38

- MANAGEMENT OF QTc PROLONGATION DURING TREATMENT

According to the recent evidence and recommendations, patients with normal baseline QTc that present QTc>500msec during follow-up; it is recommended to repeat the ECG due to the variability of these outcomes in the same patients during the same day.25 In case of persistent prolongation, it is recommended to check potassium levels and, if possible, calcium and magnesium levels too. In addition, it would be necessary to review all other medications and possible clinical circumstances that could explain or stimulate this prolongation and to test, at least, for renal and hepatic function and TSH levels. In case of confirmed QTc prolongation they recommend the following actions:

- Replace electrolytes if needed.
- Suspend all QTc-prolonging drugs until resolution. They recommend discontinuing ancillary medication at first, followed by anti-TB drugs with a shorter half-life, and CFZ, and BDQ at last.
- If symptomatic consider hospital admission for close monitoring and advanced life support.
- In the case of TdP, hospital admission is needed in order to start with magnesium infusion and have access to a phasing pacemaker and defibrillator.
QTc-prolonging drugs can be added back or substituted by others if possible, once the patient’s QTc interval is stable under 500 msec and with normal electrolytes. 25

3. CLINICAL PRACTICE GUIDELINES

Clinical practice guidelines (CPG) are evidence-based tools designed to help both professionals and patients make rational decisions about the most appropriate health care. They aid selection of the most accurate diagnostic and therapeutic options to deal with a specific health problem. Furthermore, CPG have the ability to reduce variability and improve clinical practice. 28

Regarding the choice of a CPG, it is important to look for the ones that are both up to date and address the specific issue in question. Not all recommendations need to be followed and the final decision depends on the resources available.

There are a number of guidelines for Tuberculosis. WHO is the most globally relevant, but there are others designed for specific populations. In this review we compare the CDC TB guideline for the USA, European Union Standards for TB Care (ESTC), and NICE TB guideline from the UK. These guidelines are focused on the whole spectrum of TB, including drug resistance TB, and all clinical settings, including epidemiology, diagnosis, treatment, monitoring and adverse effects, and prevention.

In our clinical audit we use TB Drugs Monograph’s as the reference guideline because is the main guideline used in the daily clinical practice in the TB clinic we assessed. This guideline focuses on monitoring for adverse effects during MDR-TB. It was developed in the UK with the aim of providing a guide for clinicians to negotiate the complex treatment regimens and comorbidities. Their recommendations are based on available evidence, and expert consensus when the information is limited. 23

3.1 IMPLEMENTING CPG

The publication of a CPG alone does not ensure its use: implementation plans are needed to facilitate its incorporation in to everyday practice. The main aim of an implementation plan is to ensure that recommendations are being followed, and so it is important to identify barriers to this process.

The implementation plan should be dynamic and individualised and take in to account the social and institutional context. The plan needs to identify possible barriers that may impact on clinical change and identify the most effective strategies to achieve successful implementation.

Once the CPG has been selected the objectives of the implementation plan should be clearly identified. This should take in to account the following factors: forming a team and describing the responsibility of each of its members, identifying the target population, describing current clinical practice, designing a timescale for implementation, identifying any costs associated with implementation, and designing a monitoring and evaluation system. Next one should analyse
the context, identify any barriers and opportunities, and design the strategy for intervention. Over time the implementation plan should take in to account any updates in the CPG.

There are different models that describe the phases physicians and health care teams go through during the implementation of CPG.

- Orientation:
  - Promote awareness of innovation
  - Stimulate interest and involvement
- Insight:
  - Create an understanding
  - Develop insight into own routines
- Acceptance:
  - Develop a positive attitude to change
  - Create positive intentions/decision to change
- Change:
  - Try out a change in practice
    - Perception of practical barriers (time, staff, money)
    - Opportunity to try to change on a small scale
  - Confirm the value of change
    - Whether first experiences positive or negative
    - The degree of cooperation experienced and the reaction of pat. and colleagues
    - Side effects (e.g. higher costs)
- Maintenance:
  - Integrate new practice into routines
  - Embed new practice in an organization
    - The degree of support from management

Clinical audit is useful to evaluate the introduction and ongoing use of a CPG.  

3.2 CLINICAL AUDIT

Clinical audit is a tool for measuring what has been done in clinical practice. It demonstrates whether effective healthcare is being provided and tells care providers and patients how well the service is doing and where there could be improvements.

It has been shown that clinical audit, if administrated correctly (i.e. when used to improve rather than punish) and regularly, can have a huge potential for promoting change.

Clinical audits may be national or local in scope. In our case, we performed a local clinical audit. It is necessary to locally evaluate and adapt the selected CPG. Recommendations should be selected and prioritized attending to: the health care issue that it is being tackled, the recommendation’s strength (the trust on their benefits for the patients), their impact and compatibility with other recommendations already implemented, and the resources needed for their implementation (humans, economics and of time).
JUSTIFICATIONS

Although the number of cases of DR-TB is slowly decreasing, cure rates remain low and the potential for transmission is high. DR-TB patients require long and complex treatment and are consequently at risk of multiple, potentially life-threatening, adverse effects. CPGs have been developed to recommend how physicians should monitor these patients.

We summarised the main guidelines used for ECG monitoring in DR-TB patients treated with QT-prolonging drugs. These came from WHO, CDC, NICE and the UK TB Drug Monographs. The aim was to compare the main differences between these guidelines. Recent studies have attempted to show a link between risk factors for QT-prolongation and cardiac events with the aim of predicting high risk patients who should receive more frequent ECG monitoring. Thus, we chose to review some of the recent evidence.

The aim of our clinical audit is to assess the quality of ECG monitoring in the North Central London (Whittington) TB clinic. Although the audit is only focussed on the Whittington TB clinic, it could be used as a reference for further clinical audits elsewhere. Even though the UK is considered a low TB incidence country, there are many areas of London with TB incidence rates similar to countries in south Asia; a number of these clinics look after patients with DR-TB and could therefore make use of the audit.
AIM

1. To define the range of guidance on ECG monitoring in patients treated with anti-TB drugs known to prolong the QT suggested among the main guides across the EU, UK, US and globally with the WHO’s
2. To assess the quality of ECG monitoring in a TB clinic using TB Drugs Monographs guide as the reference
3. To describe barriers to quality monitoring

OBJECTIVES

1. Review the literature addressed to the need for ECG monitoring in particular anti-TB drugs known to affect the QT interval
2. To collect data on the management of ECG monitoring in patients treated with anti-TB drugs known to prolong the QT, and to change practice if management is not in accordance with the guideline.
3. To improve the quality of service on a TB clinic looking for barriers that may interfere in the day to day clinical practice
This audit is focused on patients diagnosed with DR-TB who needed ECG monitoring at the Whittington TB clinic between the 1st of January of 2016 and the 31st of December of 2018. Monitoring included patients on treatment and with other risk factors. This audit was based at the North Central London South Hub TB clinic which, with the UCLH Hospital as the inpatient unit, is a specialised centre for management of MDR-TB.

Our sample was obtained through a consecutive non-probabilistic sampling. According to the clinic’s health records, there were 10 DR-TB patients attending to the TB clinic during this period that needed ECG monitoring. One of the patients was excluded due to her return to her country of birth, thus N=9.

**Inclusion criteria:**
- Patients diagnosed with DR-TB who needed ECG monitoring at the TB Clinic between 2016 and 2018 for at least one month
- Patients treated with anti-TB drugs that can prolong the QT for at least one month
- Patients that needed ECG monitoring due to being on treatment with BDQ or DLM, or due to risk factors such as being on treatment with more than one anti-TB drug known to prolong QT such as CFZ or FQs, or other drugs known to prolong QT interval e.g. anti-emetics

**Exclusion criteria:**
- DR-TB patients who did not need ECG monitoring.
- DR-TB patients who were not possible to follow-up for at least one month.

**CHARACTERISTICS OF THE SAMPLE**

- **DEPENDENT VARIABLE**
  Frequency of ECG monitoring.

- **INDEPENDENT VARIABLES**

  These include risk factors for developing DR-TB (such as high incidence rate in the country of birth, previous treatment for TB, immunosuppression); QT-prolonging drugs used for treating DR-TB (BDQ, DLM, CFZ, FQs), concomitant use of other QT-prolonging drugs (such as anti-emetics), risk factors of developing cardiac events (e.g. sex, age, history of heart disease, hypothyroidism, renal and/or liver failure, electrolyte disturbances, and low BMI).

  **Risk factors for developing DR-TB:** of the nine patients studied six were diagnosed with MDR-TB (66.66%), two with pre-XDR-TB (22.22%) and one with XDR-TB (11.11%).

  - **Previous TB treatment:** Four out of the nine patients had a previous history of TB.
  - **Comorbidities:** Three patients had other medical conditions which included type 2 diabetes mellitus, epilepsy and Crohn’s disease. The patient with Crohn’s Disease was
on immunosuppressive treatment with anti-TNF agents when he developed pre-XDR-TB. None of our patients was HIV-positive.

- **Country of Birth:** From the ten patients only one was born in the UK, the other patients were from India, Bangladesh, Singapore, Romania, Russia Federation, Nigeria (2), Somalia and Ethiopia/Eritrea. It is important to remark that India is the country where more DR-TB cases were reported worldwide in 2017 according to WHO’s estimation, and Russian Federation the third. The UK is the only country of the list considered as a low TB incidence rate country according to WHO’s definition (less than 10 cases per 100,000 population). ¹

**QTc-prolonging drugs used for DR-TB treatment or as concomitant treatment:** Table 5 summarises which patients were treated for at least one month with QT prolonging anti-TB drugs. Furthermore, as nausea and vomiting is one of the most common AEs in patients treated with an anti-TB drug, some of them needed anti-emetics while on treatment. Ondansetron and Metoclopramide are known to prolong QT interval and their concomitant use with other QT-prolonging drugs may increase the risk of arrhythmias.

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>BDQ</th>
<th>DLM</th>
<th>CZM</th>
<th>MXF</th>
<th>LVX</th>
<th>Anti-emetics¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>x</td>
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<td>x</td>
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<tr>
<td>9</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>7</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

*Table 5 QTc prolonging drugs used in patients’ treatment*  
*Origin: Patients’ clinical history.* ¹ Five patients used Ondansetron as anti-emetic, while one used Ondansetron and Metoclopramide.

**Risk factors for QTc prolongation:**

- **Sex and age at the time of diagnosis:** none of the patients was over 60 years old, which may be considered a non-modifiable risk factor for QTc prolongation and TdP. The mean age was 31 years old. See Table 6.
- **Low BMI:** although the patient’s weight was recorded in the TB clinic admission report and at each subsequent appointment, the height was not. It was therefore not possible to calculate the BMI for any patient.
- **Heart condition:** none of the patients presented had an existing heart condition.
- **Renal and/or liver failure:** only one patient presented renal impairment requiring adjustment to the anti-TB regimen. This patient did not have any electrolyte disturbances neither QTc prolongation.
- **Electrolyte disturbances:** there were no reports of hypomagnesaemia, hypokalaemia or hypocalcaemia at any point of the follow-up of these patients.

¹ Tuberculosis country profiles can be analysed at the WHO’s website  
https://www.who.int/tb/country/data/profiles/en/
- **Hypothyroidism**: two of the patients developed hypothyroidism, probably due to treatment with prothionamide, and required thyroxine replacement. However, they did not develop any electrolyte disturbance related with it.

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>FEMALE</th>
<th>MALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>18-29</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>30-50</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>4</strong></td>
<td><strong>5</strong></td>
</tr>
</tbody>
</table>

*Table 6 Age and Sex distribution Origin: Patients' clinical history*
METHODS

The data used for this clinical audit was drawn from the following sources:

- TB Drugs Monographs guideline.
- Medway-NHS clinical platform. It was used to collect patients’ data (demographic factors, comorbidities...), doctors’ letters and the scanned ECGs.
- Patients’ folders, which contain: the first admission form that should be filled for every person referred to the clinic; printed ECGs; some doctors’, nurses’ and pharmacists’ letters.
- Questionnaires to clinical staff, including nurses and doctors. (see Annex 2)

DATA COLLECTION METHODS:

To meet the first objective of our audit, we have reviewed the recommendations for ECG monitoring in patients treated with anti-TB drugs known to prolong QTc interval of the following guidelines: WHO, NICE, TB Drug Monograph, CDC and manufacturer’s recommendations in the case of BDQ and DLM.

For our second objective, we based our ECG monitoring data collection on the following items for each patient: (see Annex 1)

- Epidemiological data and previous medical condition;
- Date when treatment started and ended;
- Anti-TB drugs that were prescribed;
- Concomitant prescribed QT-prolonging drugs;
- Risk factors: previous and during treatment;
- Dates the ECGs were performed;
- QTc values if available;
- If the ECG was printed, digitized on Medway’s NHS platform and/or commented on doctors’ letters;
- Comments, i.e: if the QTc value was discordant between the letters and the printed ECGs, or if the ECG was done before or after the clinic and due to that not commented on the letters.

Epidemiological and previous medical condition data were taken from the TB clinic admission form. To assess whether concomitant treatment could prolonging the QTc drugs we used the following resource https://www.crediblemeds.org/. We used the TB Drugs Monographs guideline as reference because it is the main guideline used in the clinic. To analyse the quantitative data, we used MS Excel.

In order to detect opinions and/or barriers that may interfere in the day to day clinical practices of ECG monitoring in these patients, some interviews were performed to clinical staff. A representative sample of nurses (2/4) and doctors (2/4) were interview following the questionnaire, which may be found attached in Annex 2. Finally, issues in recording ECGs could be inferred from the patients’ clinical histories.
This report follows the format recommended by the Healthcare Quality Improvement Partnership and set out in the following paper: “Documenting local clinical audit: A guide to reporting and recording”.29

Data were obtained retrospectively from the TB clinic computer system, patients’ folders and through questionnaires performed to nurses and doctors. Any patient-identifiable data was transferred. One of the clinic consultants piloted the process of data collection and, following modification, the data were collected by a final year medical student attached to the clinic.
RESULTS

OBJECTIVE 1

- MDR-TB QTc INTERVAL-PROLONGING DRUGS

As mentioned above there are several different guidelines for ECG monitoring but in fact little difference in their recommendations. Here, we summarize some of the main guidelines (WHO, NICE and TB drug monographs in the UK and CDC in the USA), as well as the recommendations of the drug’s manufacturer in the case of BDQ and DLM.

BDQ and DLM are the most recently licenced anti-TB drugs. Both of them are known to prolong the QTc interval, as well as other anti-TB drugs such as FQ, macrolides and CFZ. They are not recommended in case of: clinically significant ventricular arrhythmia; a QTc of >500ms confirmed by repeated ECG before or during treatment, severe liver disease, abnormal electrolytes levels. If syncope occurs during treatment with any of these drugs an ECG should be performed to detect QT prolongation. If QT prolongation occurs it is recommended to check the serum calcium, magnesium and potassium levels.

1. BEDAQUILINE

QTc prolongation has been reported in patients using this drug, and even more commonly in the presence of hypokalaemia, pro-arrhythmic conditions, and in combination with other drugs that prolong the QT. Because of that, serial ECGs are recommended to monitor BDQ’s adverse effects. Some studies have found a mean QTc prolongation of 10 to 15 msec but this has not been associated with TdP or cardiac events. 25

According to WHO recommendations: BDQ has to be used with caution in the following situations: “Use with other QT prolong drugs; history of TdP; history of cLQT syndrome; history of hypothyroidism and bradyarrhythmias; history of uncompensated heart failure; serum calcium, magnesium or potassium levels below the lower limits of normal.” Hence, serum calcium, magnesium and potassium levels should be determined at baseline, with LFTs and ECG. 19
ECG monitoring recommendations:

<table>
<thead>
<tr>
<th>RESOURCE</th>
<th>FREQUENCY</th>
<th>MORE FREQUENTLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO¹⁹</td>
<td>Before treatment + at least 2, 4, 8, 12 and 24 weeks after starting treatment</td>
<td>Heart conditions, Hypothyroidism, Electrolyte disturbances¹</td>
</tr>
<tr>
<td>NICE⁵¹</td>
<td>Baseline + monthly</td>
<td>Concomitant use with other QT-prolonging drugs</td>
</tr>
<tr>
<td>TB Drugs Monographs²³</td>
<td>Baseline + after 2 weeks + monthly</td>
<td>ECG after the addition of any new QT-prolonging drug</td>
</tr>
<tr>
<td>CDC²²</td>
<td>Baseline + at least 2, 12 and 24 weeks after starting treatment</td>
<td>Weekly if BDQ + other QTc-prolonging drug / have a history of TdP/cLQT s / hypothyroidism and bradyarrhythmias/uncompensated heart failure/electrolyte disturbances</td>
</tr>
<tr>
<td>Manufacturer³³</td>
<td>More frequently if BDQ + other QTc-prolonging drug / have a history of TdP/cLQT s / hypothyroidism and bradyarrhythmias/uncompensated heart failure/electrolyte disturbances</td>
<td></td>
</tr>
</tbody>
</table>

¹Particularly hypokalaemia, hypocalcaemia or hypomagnesaeemia.

Due to Bedaquiline’s long half-life, some studies suggest the need for continuing the ECG monitoring once the treatment has stopped. ²⁴

Interactions have been described with other QT prolonging drugs such as anti-arrhythmics such as amiodarone, procainamide, quinidine; antidepressants; antipsychotics; chloroquine and hydroxychloroquine; clofazimine; fluoroquinolones; macrolids.²³

### 2. DELAMANID

It has been shown that DLM has the potential to increase the QTc by 5 to 15 msec. This prolongation increases slowly over time during the first 6 to 10 weeks, remaining stable thereafter. It is important to note that DLM is a new TB drug and, since its early studies, it has not been associated with significant cardiac adverse events. ²⁵

Delamanid’s manufacturers recommend discontinuing DLM if QTc is above 500ms before or after starting the treatment, but also if serum albumin is <2.8 g/dL.
**ECG monitoring recommendations** according to the main guidelines:

<table>
<thead>
<tr>
<th>RESOURCE</th>
<th>FREQUENCY</th>
<th>MORE FREQUENTLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO(^{19})</td>
<td>Baseline + at least 2, 4, 8, 12 and 24 weeks after starting treatment</td>
<td>Concomitant QT prolonging drugs</td>
</tr>
<tr>
<td>NICE(^{34})</td>
<td>Baseline + monthly throughout treatment</td>
<td>- If QTc is &gt;450ms in males or &gt;470ms in females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If Albumin levels are between 2.8 and 3.4g/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Concomitant use of potent CYP3A4 inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If risk factors for QT prolongation</td>
</tr>
<tr>
<td>TB Drugs Monographs(^{23})</td>
<td></td>
<td>- If QTc is &gt;450ms in males or &gt;470ms in females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If Albumin levels are between 2.8 and 3.4g/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Concomitant QT prolonging drugs do ECG at least fortnightly for the 1(^{st}) month and if QT remains normal to do ECG monthly</td>
</tr>
<tr>
<td>Manufacturer(^{30}) (their ECG monitoring recommendations were updated in late 2018)</td>
<td>Baseline + monthly throughout treatment</td>
<td>- If QTc is &gt;450ms in males or &gt;470ms in females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If serum albumin levels are &lt;3.4 g/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If the patient is on any other drug that can interact with CYP3A4</td>
</tr>
</tbody>
</table>

Table 8 DLM's ECG monitoring

Interactions described with other QTc prolongation drugs such as anti-arrhythmics (e.g. amiodarone, disopyramide, procainamide, quinidine and sotalol); ART (limited data but lopinavir/ritonavir increases exposure to DM-6705); antidepressants; antipsychotics (e.g. Thioridazine, haloperidol, chlorpromazine, trifluoperazine, pencycline, prochlorperazine, fluphenazine, sertrindole, and pimozide); antiemetics (e.g domperidone); azole antifungicals (e.g. Fluconazole, itraconazole, posaconazole, voriconazole); fluoroquinolones (moxifloxacin is not recommended for use in patients on delamanid); macrolides. \(^{23}\)
3. CLOFAZIMINE

Many different AEs has been described with this drug. Although the evidence is limited, it has been reported to prolong the QTc interval by 10 to 20 msec. \(^\text{25}\) Hence, it has to be used with caution in combination with other QT-prolonging drugs. \(^\text{19}\)

**ECG monitoring recommendations** according to main guidelines:

<table>
<thead>
<tr>
<th>RESOURCE</th>
<th>FREQUENCY</th>
<th>MORE FREQUENTLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO(^\text{19})</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TBDrugsMonographs(^\text{23})</td>
<td>Baseline + 2 weeks after starting treatment + every 3 months</td>
<td>After the addition of any new QT-prolonging drug</td>
</tr>
<tr>
<td>NICE</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CDC</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Table 9 CFZ’s ECG monitoring*

Increased risk of prolonged QTc with other drugs that prolong QTc including FQs and BDQ. \(^\text{23}\)

4. FLUOROQUINOLONES

FQ’s risk of TdP is small, and MFX has been reported at the FQ with the greatest risk. \(^\text{25}\)

- **LEVOFLOXACIN**

LVX is contraindicated in patients with prolonged QTc. It has many AEs: QTc prolongation is rare but it is more common in presence of hypokalaemia and predisposing cardiac conditions. \(^\text{19}\) LVX has been considered the FQ that should be used in patients already on BDQ. \(^\text{25}\)

**ECG monitoring recommendations** according to main guidelines:

<table>
<thead>
<tr>
<th>RESOURCE</th>
<th>FREQUENCY</th>
<th>MORE FREQUENTLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TBDrugsMonographs(^\text{23})</td>
<td>Baseline + 2 weeks after starting treatment + every 3 months</td>
<td>After the addition of any new QT-prolonging drug</td>
</tr>
<tr>
<td>NICE</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CDC</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Table 10 LVX’s ECG monitoring*

**Interactions** described with other QTc prolongation drugs such as class IA and III antiarrhythmics, tricyclic antidepressants, macrolide, antipsychotics, ondansetron. \(^\text{23}\)
- **MOXIFLOXACIN**

Moxifloxacin is also contraindicated in patients with prolonged QTc. QTc prolongation has been reported as a common and serious AE, more common in hypokalaemia, pro-arrhythmic conditions and in combination with other drugs that prolong the QT interval such as ondansetron.

**ECG monitoring recommendations** according to main guidelines:

<table>
<thead>
<tr>
<th>RESOURCE</th>
<th>FREQUENCY</th>
<th>MORE FREQUENTLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TBDrugsMonographs²³</td>
<td>Baseline + 2 weeks after starting treatment + every 3 months</td>
<td>After the addition of any new QT-prolonging drug</td>
</tr>
<tr>
<td>NICE</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CDC</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Table 11 MXF’s ECG monitoring*

Interactions described with other QTc prolongation drugs such as anti-arrhythmics; antidepressants; antimalarials (chloroquine, hydroxychloroquine, mefloquine, quinine); antipsychotics (benperidol, droperidol, haloperidol, phenothiazines, pimozide and zuvlophenithiol); antivirals (saquinavir); beta-blockers (sotalol); pentamidine; anti-emetics (ondansetron).²³

**OBJECTIVE 2**

Clinical staff at Whittington TB clinic use TB Drug Monographs to guide ECG monitoring. In order to assess adherence to the guideline and the quality of the health care support provided, we collected the data presented below.

To assess the adherence of the clinical staff to the TB Drugs Monographs’s guideline, we took the standard recommendations for ECG monitoring of any of the QTc-prolonging drugs used to treat our 9 patients as the reference. In the following table, we compile the main 6 recommendations, the number of patients to whom those recommendations were applied from the beginning of 2016 to the end of 2018, and the concordance between the daily clinical practice and these recommendations. It was not possible to assess the adherence to the recommendations of the guide in the case of baselines ECGs, because of the lack of a shared clinical history among the different hospitals of London.
To assess adherence to the guideline during daily clinical practice, we checked whether the minimum number of ECGs were performed, and whether the frequency of recording met the guideline recommendation. Patients whose treatment included DLM (100%) or LVX (100%) were monitored optimally both in the number and frequency of ECGs. Similar results were obtained for patients treated with BDQ, despite the fact that in one of them it was not possible to carry out monitoring during one of the months as the patient was unable to attend clinic. The results with CFZ and MXF were more mixed: whilst the majority were monitored according to the guideline, two patients who were treated with both drugs had periods without monitoring. In one case this delay occurred at the start of the treatment when there was neither baseline ECG or week 2 ECG; paradoxically subsequent ECGs were performed more frequently than recommended. In the other case there was a gap of four months without ECG monitoring. Only when the patient complained of chest discomfort and dizziness was an ECG performed and a QTc of 500 msec was noted. The ECG was repeated later that day and showed a decrease in QTc interval to normal. The next ECG was performed one month after the event, and no more ECGs were recorded again during the last three and a half months of treatment.

<table>
<thead>
<tr>
<th>No.</th>
<th>Standard</th>
<th>N 2016-2018</th>
<th>Adherence 2016-2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>All patients on BDQ should have a baseline ECG + 2 weeks after treatment was started + monthly until the end of treatment + if any other QTc-prolonging drug is added</td>
<td>2</td>
<td>92.86%</td>
</tr>
<tr>
<td>2</td>
<td>All patients on DLM should have a baseline ECG + monthly throughout treatment and if: - QTc is &gt;450ms in males or &gt;470ms in females - Albumin levels are between 2.8 and 3.4g/dL - Concomitant QT prolonging drugs do ECG at least fortnightly for the 1st month and if QT remains normal to do ECG monthly</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>All patients on CFM should have a baseline ECG + 2 weeks after starting treatment + every 3 months + if any other QTc-prolonging drug is added</td>
<td>8</td>
<td>96.35%</td>
</tr>
<tr>
<td>4</td>
<td>All patients on MXF should have a baseline ECG + 2 weeks after starting treatment + every 3 months + if any other QTc-prolonging drug is added</td>
<td>7</td>
<td>95.83%</td>
</tr>
<tr>
<td>5</td>
<td>All patients on LVX should have a baseline ECG + 2 weeks after starting treatment + every 3 months + if any other QTc-prolonging drug is added</td>
<td>2</td>
<td>100%</td>
</tr>
<tr>
<td>6</td>
<td>If the patient is treated with more than one QTc-prolonging drug, more frequent ECG monitoring is needed</td>
<td>9</td>
<td>77.77%</td>
</tr>
</tbody>
</table>

Table 12 Adherence of the clinical staff to guideline’s recommendations. Green adherence 100%; Yellow adherence 80%-99%; Red adherence ≤79%.

To assess adherence to the guideline during daily clinical practice, we checked whether the minimum number of ECGs were performed, and whether the frequency of recording met the guideline recommendation. Patients whose treatment included DLM (100%) or LVX (100%) were monitored optimally both in the number and frequency of ECGs. Similar results were obtained for patients treated with BDQ, despite the fact that in one of them it was not possible to carry out monitoring during one of the months as the patient was unable to attend clinic. The results with CFZ and MXF were more mixed: whilst the majority were monitored according to the guideline, two patients who were treated with both drugs had periods without monitoring. In one case this delay occurred at the start of the treatment when there was neither baseline ECG or week 2 ECG; paradoxically subsequent ECGs were performed more frequently than recommended. In the other case there was a gap of four months without ECG monitoring. Only when the patient complained of chest discomfort and dizziness was an ECG performed and a QTc of 500 msec was noted. The ECG was repeated later that day and showed a decrease in QTc interval to normal. The next ECG was performed one month after the event, and no more ECGs were recorded again during the last three and a half months of treatment.
There are no clear recommendations on the optimal frequency of ECG monitoring in patients treated with more than one QTc-prolonging drug. We therefore took as a reference drugs that require more basic monitoring, such as BDQ or DLM, and assessed whether ECGs were performed more frequently than established by the reference guideline. The only cases in which there was no increase in the frequency of monitoring, at least for a period of time during treatment, are the two patients discussed above receiving CFZ and MXF. It should be noted that the patient with QTc prolongation was also taking ondansetron and thus needed more frequent ECG monitoring as she was taking three QTc-prolonging drugs.

Three patients had QTc prolongation at some point during treatment. The patient noted above was a 39 years old woman on treatment with MXF, CFZ and ondansetron for 13 months. She presented with dizziness and chest discomfort nine months in to treatment. No change on treatment was needed as the QTc returned to normal the same day. The second patient was a 30 years old man who was on BDQ, LVX, CFZ and ondansetron for 12 months. BDQ was stopped for a couple of weeks after six months of treatment, but was reintroduced later. This produced a stepwise prolongation of the QTc from 483-491 msec in one month to 500 msec in the following month. An ECG performed 4 days later was not commented upon in the notes for a further 2-3 weeks. At these point, despite the QTc interval returning to normal, the clinician decided to stop LVX. The third patient was a 33 years old woman who has been on treatment with CFZ and MXF for 12 months. After two months of treatment the QTc rose to 499 msec. The patient presented with dizziness and chest pain and a result the doctor decided to reduce MXF from 600mg to 400mg per day. However, the patient subsequently returned to MXF 600mg. The QTc fluctuated for a couple of months, achieving 500 msec in August. The doctor requested a repeat ECG in two weeks but this was not done until a month later. Nevertheless, the patient has not presented with further symptoms or with a QTc>500 msec in the subsequent six months.

OBJECTIVE 3

Access to the previous ECGs results is a barrier to monitoring. However, if the doctor is able to find the results in the previous clinical appointment letter or digitized at the clinical history this is helpful. As not all the ECGs were printed and storage on each patient’s file, it was necessary to use other resources. Some of the ECGs were digitized into the NHS platform, and most of them were at least mentioned at the doctors’ letters during the appointments. Most baseline ECGs were performed during patients’ hospital admission; other patients were started treatment outside the UK. Consequently, it was not possible to collect information on baseline ECGs for any of the patients. Below is a table showing how many ECGs were accessible for each patient and where the information was stored.
We also reviewed whether the ECG was done before or after the appointment, and how often it was reported as being done or as requested in the doctors’ letters. The results are represented in the figure 6 below. We found that 68% (88/130) of the ECGs were performed (and therefore available) before clinic, whereas 32% were performed after the clinic appointment. The request for or result of an ECG was recorded in 79% (103/130) of doctors’ clinic letters.

![Figure 6 ECG's performed before or after clinical appointment, ECG's commented in doctors' letters](image)

After interviewing some of the clinical staff at the Whittington’s TB Clinic with the questionnaire attached in Annex 2, we collected the following answers:

Both nurses and doctors confirmed to follow TB Drug Monographs’ recommendations. Nurses ensure that doctors’ request does not differ much from the guideline. According to both nurses and doctors, ECG is usually performed before the clinical appointment, especially if it is not the first visit for the patient. However, it is not always possible due to nurses’ availability. Both teams agreed that most of the risk factors are recorded in the TB clinic admission form, but as well during the follow-up, making changes in monitoring’s frequency and treatment if needed.

The average time spent in each ECG monitoring appointment is about 5 to 10 minutes according to both nurses. Nurse A reported that patient’s waiting time could be around 30 minutes sometimes, as some days there are two nurses instead of three. Nurse B reported that...
sometimes could take more time to perform an ECG due to a delay on the electrodes’ availability.

Regarding any difficulty for following-up patients, nurses agreed that patients usually come to every appointment, if not, there is a protocol to contact the patient to book another appointment. Both doctors agreed, but noticed that sometimes is difficult to follow-up the patients correctly because they are living abroad or travelling often, as they are usually not from the UK. When this situation is presented, they discuss it at the weekly MDT meeting in order to change dosage or treatment.

In order to find any other difficulty, we asked the doctors if they find hard to check previous ECG’s results or to know when was the last ECG performed to the patient. Both agreed that each doctor reports it in their own way. Besides, as a complex monitoring for this patients is needed, there are many things to check at every visit and, thus, sometimes it is hard to find previous ECGs. They also think that scanning the ECGs could be useful, for instance if ECG was done a different day from the clinical appointment.

Finally, we asked the doctors their opinion about the guideline they were following and if they find any lack of information or improvements at some concrete points. Both of them find it quite complete, but doctor A thinks that it could be useful if they integrate a list of which anti-emetic is more QT-prolonging and a list of which ones are safer, as anti-emetics are widely commonly used in DR-TB patients. Doctor A proposes to extend it to other QT-prolonging drugs commonly use like antipsychotics or antiepileptics.
DISCUSSION

One of the main objectives of this Final Degree Project was to summarize the current recommendations for ECG monitoring in patients diagnosed with DR-TB who needed treatment with QTc-prolonging drugs. The most recent anti-TB drugs, BDQ and DLM, are known to prolong the QTc interval, but there is a lack of information about their side effects and interactions. Perhaps because of this, the main guidelines recommend frequent ECG monitoring. As we have observed, there are not many differences among guidelines in the case of these two drugs. There are other drugs for treating DR-TB which are also used to treat other diseases. This is the case with CFZ, which was originally licenced to treat leprosy, and the FQs, which are commonly used antimicrobials. These drugs are more studied than BDQ or DLM, and their common side effects are well-known. QTc prolongation with these drugs is a rare AE which could be the reason why most of the guidelines do not have ECG monitoring recommendations. Nevertheless, it is important to highlight that the TB Drugs Monographs guideline does give recommendations for ECG monitoring in patients treated with CFZ and/or FQs. The TB Drug Monographs are based on consensus opinion, rather than evidence, among TB physicians, pharmacists, nursing staff and specialties and drug advisory organisations including FDA and BNF.

QTc-prolonging drugs are big concerns among physicians, and a lot of trials have been developed in the last years to see the association between QTc-prolongation and the prevalence of cardiac events. A cohort study performed in 2017 in South Korea by H-Y. Yoon, K-W Jo, G. B. Nam, T.S Shim, assessed the effects of QT drugs on cardiac events in patients with MDR-TB or NTM disease. They reviewed 373 patients treated for more than one month with BDQ, DLM, CFZ or any FQs. Although, ECG abnormalities were documented in 17% of the patients, none had adverse cardiac effects. Hence, they concluded that the use of QT drugs, alone or in combination, in DR-TB patients is relatively safe. A meta-analysis of the short treatment regimen across nine African countries did not show clinically significant cardiac events in more than 1000 patients; nevertheless, an unexpected death occurred in an HIV-positive woman on ARVs and with previous prolonged QTc. Similar results were found in other studies in the recent years, showing a regularly incidence of QTc prolongation that has been described for many drugs, whilst TdP reports were limited and epidemiologically considered very uncommon. Furthermore, a literature review of 249 patients with TdP and non-cardiac QTc-prolonging drugs reported that 71% of the patients had at least two other risk factors apart from the drugs.

In the preliminary results of the STREAM (Short-course Treatment for MDR-TB) study, an international controlled trial in MDR-TB patients, there was not statistically significant difference of QTc prolongation between controls and study arm, and none of the patients presented clinical cardiac events. There was one SCD in the study arm, but the cause is not yet confirmed. Other studies among TB patients, have reported that the total number of QTc-prolonging drugs was associated with higher QTcF prolongation. Moreover, patients presenting several risk factors may not tolerate small increases in the QTc interval and that it may lead to TdP.
Our clinical audit has been able to demonstrate good adherence to the TB Drugs Monographs’ guideline by the clinical staff at the North Central London TB clinic. Although clinical staff do follow the main recommendations for ECG monitoring in patients treated with BDQ, DLM, CFZ and FQs, the frequency of monitoring is not always increased in patients receiving more than one QT-prolonging drug. This is an area for improvement. There is a lack of evidence for the frequency of ECG monitoring in these cases, and hence it is not possible to conclude whether the frequency used was the correct ones, just whether they adhered to consensus guidelines. The main times monitoring was not increased was with patients treated with a combination of CFZ and MXF. As mentioned, recommendations for these drugs are limited to only one guideline. Thus, we consider that in some cases the clinical judgement may have prevaled over consensus opinion. Although numbers are small, it should be noted that none of the patients developed cardiac events in relation to QT-prolongation and clinicians often responded to QTc prolongation by changing treatment.

It was sometimes difficult to access to ECGs because there is not a standardized practice on how they should be saved. Nearly 70% of the ECGs were storage in patients’ file, however not all of them appeared as reported or requested in the patients’ clinical history records. It also happened the other way around: sometimes an ECG was reported as requested in the doctor’s notes but it could not be found in either paper files or the NHS electronic platform. Furthermore, in some cases the paper QTc interval was not the same as the figure recorded in the doctor’s clinical notes. Something similar happened with the date of performing the ECG. There is not a standard protocol for recording the results of monitoring the various individualised treatments. It is important to highlight that each patient is seen by different TB doctors throughout the course of their treatment. Every doctor uses a different system and, from the perspective of the audit and presumably real life, this makes looking back through data more difficult.

The AEs monitoring needed in DR-TB patients is complex and some of the doctors use tables to summarize the patient’s treatment progress and all the different monitoring needed for each drug. This is a possible solution to improve access to results when reviewing a patient in clinic. Only 16% of the ECGs were digitized and in most of the occasions, it was done months after the ECG realization. Scanning ECGs could be useful in order to be more accessible to doctors’ during the different follow-up appointments.

There is a good team work between nurses and doctors, and there were not serious barriers noticed at the interviews.

- LIMITATIONS

The main limitation of this clinical audit is that it was performed only in a TB clinic. The results cannot be extrapolated to other clinics and hence we consider the conclusions preliminary. The audit will be shared with the multidisciplinary team for review and develop action plan to improve the quality of ECG monitoring. Following this the audit cycle needs a second round of data collection to see whether the changes lead to an improvement in monitoring.
CONCLUSIONS

All guidelines have similar recommendations for ECG monitoring when BDQ or DLM are used to treat DR-TB patients. However only one guideline makes recommendations for patients taking CFZ or FQs, and the frequency of ECG monitoring for patients taking more than one QT-prolonging drug is not well established. According to the results of the most recent trials about DR-TB and QTc-prolongation drugs, the prevalence of cardiac events is quite low and these drugs are relatively safe. Taking into account the amount of AEs associated with these anti-TB drugs and thus, the complexity of monitoring needed, ECG monitoring could not be a priority. Nevertheless, patients with several risk factors for QTc-prolongation need more frequency of ECG monitoring. Because of that, the presence of risk factors has to be promptly assessed.

The audit provides preliminary information on the quality of ECG monitoring in the Whittington TB clinic over the past two years. The results should not be extrapolated to all clinics in London and a similar audit could be done in each of these centres. We intend to present the findings to the Whittington clinical team and with their input produce an action plan to improving care.

The audit demonstrated that ECG monitoring in the clinic generally followed guidelines and we consider it an area of good practice. However, AE monitoring is a complex process and on some occasions not all tests or their results were presented in an optimal way, with some tests being prioritised over others. In order to improve this, we suggest that the clinic develops a standard form for record AE monitoring: this should reduce variation in the frequency of requesting tests and improve the ease of reviewing data. Annex 4 shows an AE monitoring table use by one of the doctors at the TB clinic, which we propose as a possible solution. In addition, we recommend that all ECGs are digitalized on the day of clinic to ensure a safe and comprehensive record.
PHASE 1 ➞ Preparation and coordination (November 2018)
- **Activity 1.** Coordination of the Collaboration Agreement between Universitat de Girona and Hospital for Tropical Diseases.
- **Activity 2.** Meeting with the Final Degree Project advisors (Carme Carrion and Michael Brown) to decide about the topic of the FDP.

PHASE 2 ➞ Field work and data collection (December 2018 and January 2019)
- **Activity 3.** Review of the literature about the main issue regarded in this FDP.
- **Activity 4.** Identify the cases that will be included in our project.
- **Activity 5.** Review of the available patient’s data related to the issue regarded in this FDP.
- **Activity 6.** Meeting with Jessica Potter, one of the developers of the TB Drugs Monographs guide, to give some advice about carrying out the data analysis.
- **Activity 7.** Interview of nurses and doctors to determine possible barriers and facilitators to the daily health care.

PHASE 3 ➞ Data analysis and final evaluation (January 2019)
- **Activity 8.** Summarize the review of the literature.
- **Activity 9.** Organize the data collected and establish a relationship.
- **Activity 10.** Assess the quality of the health care provided in relation with the guideline used by the clinical staff.

PHASE 4 ➞ Publication and dissemination of the results (February 2019)
- **Activity 11.** Publication of results and exposition of the FDP to the court.
### PHASE 1. RESEARCHERS: Carme Carrion, Michael Brown, Antía García

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### PHASE 4. RESEARCHERS: Carme Carrion, Michael Brown, Antía García

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*Table 14 Chronogram*
ETHICAL ASPECTS

This clinical audit was carried out in accordance to the ethical considerations and requirements set out in international and national standards. This project followed the four ethical principles of autonomy, beneficence, non-maleficence and justice, principles established by the World Medical Association in the “the Declaration of Helsinki, a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data”, last updated in October 2013.

This project was designed as a literature review and audit of practice; as per UK regulations this does not require formal ethical approval. The clinical audit has been approved by the Clinical Director for Infection at UCLH and MDR-TB Lead for NCL South Hub TB clinic. Information Governance has been maintained throughout, with no patient-identifiable data removed from the Trust.
CONFLICT OF INTEREST STATEMENT

All the people involved in this project report no conflict of interest.
All the data used for this final degree project was collected from published studies, guidelines, the patients’ database and briefly interviews to clinical staff. Thus, the budget of this final degree project has been 0£.

As this clinical audit present preliminary results, and it may need revisions, further investigations and other TB Clinics from London may be included in order to be more representative, we present the following budget as part of an optional project:

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<td>Reviewing patient’s health records</td>
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<td><strong>Total cost</strong></td>
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*Table 15 Budget*
REFERENCES


2. Gagneux S. Advances in Experimental Medicine and Biology 1019 Strain Variation in the Mycobacterium Tuberculosis Complex: Its Role in Biology, Epidemiology and Control. 2017


5. CDC. “Chapter 2 Transmission and Pathogenesis of Tuberculosis”, Introduction to the Core Curriculum of tuberculosis, pp19–44. 2013


18. Idcr A. Tuberculosis in. 2006;9(2).


35. Smith, M.; Fereday, S. Healthcare Quality Improvement Partnership *Guide to managing ethical issues in quality improvement or clinical audit projects.* (2016)


# ANNEX

## 1. PATIENT’S DATA COLLECTION

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<th>Epidemiological information</th>
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<td>-Letters</td>
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*Table 16 Patient’s data collection*
2. QUESTIONNAIRE

1. Do clinic staff follow the TB drug monograph guideline on frequency of ECG monitoring in patients on QT-prolonging drugs?

Q: - **Nurses**: From your point of view, in daily clinical practice, do doctors differ much from the guideline?

A:

Q: - **Doctor**: Do you usually check the guideline when you are initiating any QTc-prolonging drugs? Do you ensure the ECG monitoring frequency is correct whilst on treatment? Is there any guideline recommendation for ECG monitoring that you find hard to follow or lacking information at any point?

A:

2. When is the ECG usually performed, before or after the clinic appointment?

A: **Nurse**:

A: **Doctor**:

Q: - **Doctor**: Do you consider digitized ECGs a useful tool for your daily clinic?

A: **Doctor**:

3. In relation to the patient’s risk factors: are risk factors for QT prolongation documented? Is an ECG monitoring plan adjusted for these RFs?

A: **Nurse**:

A: **Doctor**:

4. Patient issues: how often do patients not come to follow-up clinics during treatment? What is the average time spent in each ECG monitoring appointment?

A: **Nurse**:

A: **Doctor**:

5. Do you find any difficulties or barriers to ECG monitoring in clinic? Do you consider ECG monitoring as priority in these patients? Is it difficult to check previous ECG’s results or when was the last ECG performed for the patient?

A: **Nurse**:

A: **Doctor**:
3. IMPROVEMENT PROPOSAL

<table>
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*Table 17 Standard monitoring data collection proposal*