Assessing and comparing the effectiveness of treatment for multidrug resistant tuberculosis between specialized TB hospital in-patient and general outpatient clinic settings within the Western Cape Province, South Africa

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10 Ten Keywords:

- Tuberculosis (TB)
- Drug Resistant Tuberculosis (DR TB)
- Multi Drug Resistant Tuberculosis (MDR TB)
- Clinic initiated treatment
- Hospital initiated treatment
- Western Cape Province, South Africa
- Time to Treatment Initiation
- Treatment Outcomes
- Successfully Treated
- Defaulted Treatment

Definition of Key Terms:

Treatment of MDR TB: The medication that a patient with MDR TB is treated with.

Culture conversion: TB sputum culture is a laboratory test that looks for organisms/bacteria that causes infection in the lung, if no bacteria grow the culture is considered negative, hence to culture convert is having 2 consecutive negative sputum cultures taken 30 days apart, within the intensive phase of treatment. The specimen collection date of the first negative culture is used as the date of conversion.

Time to culture convert: The duration of treatment time before the patient develops 2 consecutive TB sputum culture test negatives, with sputum cultures taken 30 days apart.

Time to treatment initiation: the time taken from the initial sputum result of resistance to start of treatment

Intensive Phase of MDR TB treatment: Once the patient has 2 consecutive TB sputum culture negatives taken 30 days apart, to add an additional 4 months of treatment, this phase should be at least 6 months. This phase consists of daily injections and oral medication using a combination of medication.

Continuation Phase of MDR TB treatment: This phase consists of daily oral medication as treatment, using a combination of drugs, with the duration of the continuation phase being determined by adding 18 months to the date at which the patient's sputum culture 5 tests are negative (culture convert) for mycobacterium tuberculosis within the last 12 months of treatment.

Clinic initiated treatment: treatment initiated within the general (unspecialized) outpatient clinic setting, during which patients attend a clinic daily for MDR TB treatment within the intensive phase of treatment and will continue further treatment within the clinic for the continuation phase. Other

terms referred to are: community outpatient clinics, Primary Health Care facilities, ambulatory care and decentralized care.

Hospital initiated treatment: treatment initiated within a specialized TB hospital, during which the patients are admitted to the hospital where they are treated as in-patients until culture conversion and then discharged to the clinic or remains in hospital during the intensive phase of treatment (at least for 6 months) and discharged into the community for the continuation phase treatment. Other terms referred to are: specialized TB hospital in-patient and centralized care.

Appropriateness of TB medication regimen: The patient according to their recorded information of their treatment is shown to have culture converted, completed the intensive and continuation phase of treatment and has successfully completed treatment.

Treatment outcomes for MDR TB patients (Department of Health, 2011):

Cure Rates: A MDR TB patient who has converted (with 2 consecutive TB culture negatives taken 30 days apart) and has remained TB culture negative, has completed treatment and has been consistently sputum culture negative for five consecutive months in the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures, taken at least 30 days apart.

Treatment completed: An MDR TB patient who has completed treatment according to country protocol but does not meet the definition of cured; due to lack of bacteriologic results (ie. less than 5 cultures were done in the final 12 months of treatment).

Successfully treated: The combined treatment outcome of cured and treatment completed.

Failed treatment: Treatment will be considered to have failed if two or more of the five consecutive cultures recorded in the final 12 months are positive, or if any one of the final three cultures is positive. Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early, due to poor response to treatment after 6-8 months of effective treatment. Such patients will be put on a different treatment regimen after receiving an outcome of failure and be allocated to a new treatment cohort.

Death: An MDR TB patient who dies for any reason during the course of MDR TB treatment.

Defaulted treatment: An MDR TB patient whose MDR TB treatment was interrupted for 2 or more consecutive months for any reason.

Not Evaluated: The patient has not yet, been allocated a final treatment outcome.

XDR TB: an MDR TB and in vitro resistance to any of the fluoroquinolones and any injectable

Pre-XDR TB: TB with resistance to Isoniazid and Rifampicin, and either a fluoroquinolone or second-line injectable, but not both.

Decentralization: the process of re-distributing and dispersing the functions, power and people away from a more central setting (hospital) to the community setting (clinic)

EDRWeb: National Department of Health electronic database for the recording and reporting of DR TB data within South Africa

Xpert MTB/RIF (GeneXpert): The Xpert MTB/RIF is a cartridge based nucleic acid amplification test, automated diagnostic test that can identify Mycobacterium tuberculosis (MTB) DNA and resistance to rifampicin (RIF) by nucleic acid amplification test (WHO, 2011)

List of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral (ARV) Therapy
CI	Confidence Interval
DOT	Directly-Observed Treatment
DR TB	Drug Resistant Tuberculosis
DS TB	Drug Sensitive/Susceptible Tuberculosis
DST	Drug susceptibility testing
HAST	HIV, AIDS, STI, TB
HIV	Human Immunodeficiency Virus
HIV+	Human Immunodeficiency Virus positive
HIV-	Human Immunodeficiency Virus negative
MDR TB	Multidrug Resistant Tuberculosis
NHLS	National Health Laboratory Services
OPD	Outpatient Department
PHC	Primary Health Care
Pre-XDR	Pre extensively drug-resistant TB
TB	Tuberculosis
UWC	University of the Western Cape
WC	Western Cape
WHO	World Health Organization
XDR TB	Extensively drug-resistant TB
Xpert MTB/RIF	GeneXpert

Abstract

Background: Multidrug resistant tuberculosis (MDR TB) is a growing threat globally. The large increase in the incidence and prevalence of MDR TB in South Africa in recent years has impacted on the way in which MDR TB is managed within the health services. It became logistically difficult to manage MDR TB by treating all patients as in-patients in a specialized tuberculosis (TB) hospital. The clinics, which are run by nurses and/or general medical officers, are then required to manage this more complex form of TB, with limited resources, less experience and assumingly with less MDR TB knowledge. Of particular concern is that shifting of the patient management from specialized TB hospitals to Primary Health Care clinics which might worsen the already poor MDR TB treatment outcomes. There has been minimal assessment of the management of MDR TB at clinic level and hence the comparison of treatment outcomes for those patients initiated on treatment in clinics compared to in-patients in specialized TB hospitals is urgently needed.

Aim: To compare the treatment outcomes and the effectiveness of medication regimens provided to MDR TB patients initiated on treatment in specialized TB hospitals as inpatients, to that of MDR TB patients initiated on treatment as outpatients at community clinics within the Western Cape Province, South Africa.

Methodology

Study Design: A retrospective cohort study was undertaken, as the length of treatment for a MDR TB patient can be for 24 months or longer and this study was based on treatment outcome data.

Study Population and sample: The study population was uncomplicated MDR TB patients initiated on treatment in hospitals and clinics from January 2010 to December 2012. The sample comprised of 568 participants that were laboratory confirmed to have MDR TB and had the outcomes of their treatment recorded in an electronic database or a paper register.

Data Collection: The researcher collected MDR TB information from standardized MDR TB registers as well as an electronic MDR TB database.

Analysis: Data was analyzed comparing the exposed (clinic initiated) and

unexposed (hospital initiated) cohorts incidence of 4 key treatment outcomes, namely: successfully treated, failed treatment, died and defaulted treatment. Bivariate analysis (relative and absolute) was done to determine the cumulative incidence ratio and cumulative incidence difference and multivariate logistic regression analysis for the adjusted odds ratio to control for confounders and effect modifiers.

Ethics: Permission to conduct this research was obtained from the relevant authorities. The confidentiality of the participants as per the Department of Health policy and in adherence to general ethical guidelines was strictly maintained. The study proposal received ethical clearance and approval from the University of the Western Cape Research Committee.

Results: All participants within this study received the appropriate treatment as per the MDR TB guidelines. The incidence rate for the main outcomes of this study indicated that successfully treated for the clinic initiated participants was 41% and 31% for the hospital initiated participants. 'Defaulted' treatment was 39% and 41%, 'failed' treatment 7% and 13% and 'died' was 14% and 16%, respectively. The clinic initiated participants appeared to have better treatment outcomes on bivariate analysis, however on multivariate analysis, there was no difference in the treatment outcomes of the clinic initiated participants compared to the hospital initiated participants, and therefore the clinic initiated treatment is seen as effective. The time to treatment initiation for clinic and hospital initiated participants is excessively long for both cohorts, with a median of 29 days, and 37 days respectively. The key findings of note in the multivariate analysis is that the Human Immunodeficiency Virus positive (HIV+) participants provided with antiretrovirals therapy (ART) were, based on adjusted cumulative incidence ratios, 6.6 times more likely to have a successfully treated outcome (95% CI 1.48-29.84), and were 0.2 times less likely to die (95% CI 0.08-0.53). Having a previous cured history of TB and no previous history of TB were 2.9 times more likely to have a successfully treated outcome (95% CI 1.48-5.56) and were 0.1 times (0.04-0.38) less likely to fail treatment. An interesting finding was that participants living in the rural districts were 2.6 times more likely to die.

Conclusion: Clinic initiated treatment for uncomplicated MDR TB is as effective as hospital initiated treatment. Also, those provided with ART and those without previous TB or who had a previous bout of TB cured, had better outcomes.

Main Recommendations: The Western Cape health department should continue with the decentralization of MDR TB services to the clinics and could safely consider expanding the decentralization to include uncomplicated Pre-extensively drug-resistant TB and Extensively drug-resistant TB patients. Offering ART to HIV+ patients should be mandatory. The delays in the time to treatment initiation of MDR TB need to be further investigated.

Declaration

I declare that, ***'The effectiveness of treatment of multi-drug resistant tuberculosis at specialized TB hospitals and community clinics in the Western Cape Province, South Africa',*** is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Razia Vallie December 2016

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Dedication

This has been a journey of discovery ‘as within so without.’

The greater force shining within- is only with the grace of my Almighty, whose mercy and blessings is deeply ingrained, and sustains my connection with the universe.

To my family and friends, especially my Mother, who has been my pillar of strength as well as voice of reason throughout this process, it is your love that sees me through life.

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1.1 Background

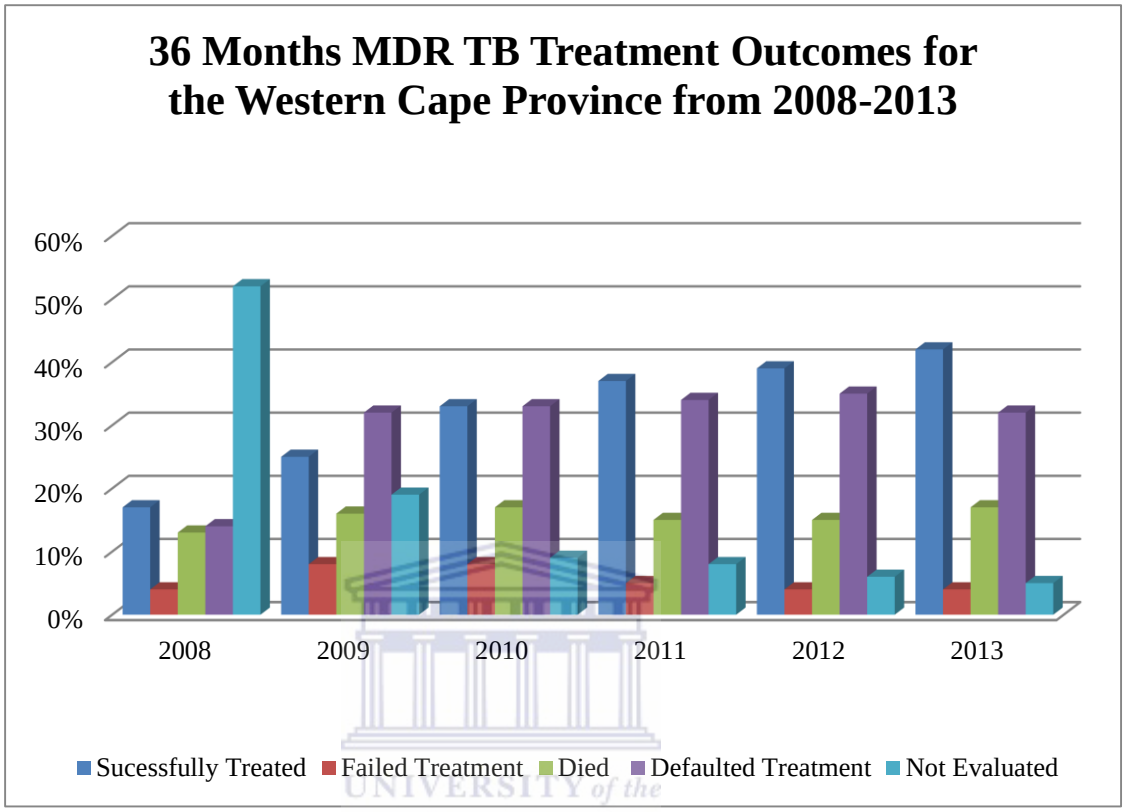
The World Health Organization (WHO) (2013) states that globally there are 8.6 million new cases (first time infections) of tuberculosis (TB) that are diagnosed annually. Africa represents 31% of these cases. TB is a curable disease but continues to kill nearly 1.3 million people across the globe annually.

The emergence of drug resistant tuberculosis (DR TB) is a major concern for TB control globally and within Africa and South Africa. TB is a disease, usually pulmonary, caused by the bacterium, *mycobacterium tuberculosis.* Multidrug resistant TB (MDR TB) is defined as, resistance to the two most potent first line (standard TB treatment) anti-TB drugs, namely isoniazid and rifampicin (WHO, 2008) (see appendix1, for a full list of first line anti-TB drugs). Hence the patients cannot be treated with the drugs they are resistant to, but must instead be given second and possibly third line drugs (see appendix 2 for a full list of second and third line anti-TB drugs), which are more expensive, less effective and have more side effects than the first line drugs (Loveday et al., 2015). The estimated cost of DR TB treatment accounts for half of the National TB programme expenditure in South Africa despite DR TB patients constituting only 7% of the TB patients (WHO, 2011).

MDR TB is a growing threat, according to the WHO (WHO, 2013), with approximately 480,000 MDR TB cases occurring globally every year, corresponding to approximately 5% of the world's incident TB cases, with an estimated 170 000 deaths from MDR TB. The WHO updated report, states that only 50% of globally detected MDR TB patients, in the 2012 cohort were successfully treated. The other outcomes of this cohort are, 10% failed treatment, 16% died, and 24% either defaulted treatment or did not have a treatment outcome recorded (WHO, 2015).

The South African statistics for the incidence of MDR TB patients as per laboratory diagnosis from the National Health Laboratory Services (NHLS) for 2010 is 7 386 cases which are 13.9 per 100 000 people, and the Western Cape (WC) Province had 1422 cases or 23.6 per 100 000 people (Department of Health, 2013). The Western Cape Province trend over time for MDR TB treatment outcomes (36 months report) as from 2008-2013, as illustrated in graph 1 below, shows that, 'successfully treated' which is essentially the indicator that monitors those believed cured of MDR TB has steadily improved from 17% to 42%, while 'failed treatment' has been consistent within this period ranging between 4% and 8%, with 'died' ranging between 13% to17%, whereas 'defaulted treatment' has significantly increased during this time period, from 14% to 32%. The above results are however extremely difficult to interpret as they were calculated including those for whom there was no outcome listed, and was therefore labeled as 'not evaluated'. This category as presented has decreased dramatically over time, which is probably why the anomaly of the 'successfully treated' proportion and the 'defaulted treatment' proportion both increasing with time, arose (Department of Health, 2009).

Graph 1: 36 Months MDR TB Treatment Outcomes for the Western Cape Province as from 2008-2013, sourced from the EDRWeb (EDRWeb, 2016).



DR TB is emerging as a major clinical and public health challenge in areas within the Western Cape Province and poses a great threat to the control of TB. The extent of the significant increase in incidence and prevalence of DR TB is further reinforced by Karim, Churchyard, Karim & Lawn (2009: 923) who cite that "Multidrug-resistant TB in South Africa is likely to represent an unrecognized and evolving epidemic rather than sporadic localized outbreaks."

The importance of addressing MDR TB is further amplified by reports, which state that Extensively Drug Resistant TB (XDR TB) represented 9% of MDR TB (WHO, 2013). XDR TB is defined as strains of MDR TB that are also resistant to fluoroquinolones and one or more of the three injectable drugs (amikacin, kanamycin or capreomycin). The National Department of Health report of 2013, indicates that in 2010, there were 741 XDR TB cases or 1.39

XDR TB cases per 100 000 people in South Africa and 112 XDR cases or 1.86 XDR TB per 100 000 people within the Western Cape Province.

In the Lancet, 'Health in South Africa' report (2009), it was reported that South Africa accounts for 17% of the world's Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS) cases, which equates to 5.4 million people and is the greatest HIV/AIDS burden in any country. They contend that the HIV/AIDS epidemic is intertwined with and indeed fueling the TB epidemic, that had by 2009 already "… more than doubled since 2001 with significant numbers of MDR TB cases and increasing XDR TB, a sure sign of a health system that cannot cope" (Mayosi et al., 2009:2031).

The National Department of Health in South Africa in response to this health system concern rolled out its 'decentralized and deinstitutionalized management of MDR TB Policy' in 2011. This policy was designed to provide guidance on various options of care for MDR TB patients, including the management of MDR TB ambulatory patients closer to their homes, by treating them in community outpatient clinics. This policy also enabled provinces to start MDR TB treatment as soon as a diagnosis was made thereby decreasing the risk of MDR TB transmission, and lessening the burden on the TB bed capacity of hospitals, while also decreasing nosocomial infections (Department of Health, 2011). The uptake of this policy was disproportionate within the Western Cape Province, where the initiation of treatment of ambulatory MDR TB patients was still undertaken exclusively at specialized TB hospitals rather than within a community clinic, in some areas.

MDR TB treatment overview

MDR TB treatment is more difficult for patients to tolerate than first line anti-tuberculosis treatment due to the long duration of treatment of roughly 18-24 months, frequent medication toxicities and the daily administration of an injectable medication (Loveday et al., 2015). The standard MDR TB treatment regimen is made up of an *intensive* phase during which time, 4 drugs and the injectable are administered to the patient on a daily basis. The duration of this

phase is usually 6 months or more, but it is variable in length and dependent on obtaining two consecutive sputum cultures, taken at least 30 days apart, that both test negative for TB. Adding 4 months to the first negative sputum result is the criterion for the cessation of the *intensive* phase. The *continuation* phase of treatment then commences and its treatment regime consists of the 4 oral medications, with the duration of this phase being 18 months (Department of Health, 2013). MDR TB is a laboratory diagnosis and thus monthly sputum specimens must be obtained and tested, as these results will determine the diagnosis, the duration of the *intensive* phase and the outcomes of treatment.

MDR TB is an infectious disease, and thus the need to lessen the time to treatment initiation is of great importance, to prevent the further transmission of this disease. The Xpert MTB/RIF (GeneXpert) machine was thus nationally implemented to be able to diagnose patients quicker and initiate treatment sooner, the rollout of this testing was sequentially introduced into the province as from 2011. The WHO policy on the GeneXpert explained that it is a screening test for all presumptive TB cases but has a high sensitivity of 80% and a high specificity of 98% (WHO, 2011). This machine is also able to detect rifampicin resistance and is, therefore, an indicator for the initiation of presumptive MDR TB treatment as per the South African National MDR TB guidelines, which allows the use of rifampicin resistance as a proxy for MDR TB diagnosis until sputum culture results are available (Department of Health, 2011; WHO, 2011). The scale-up of GeneXpert screening in South Africa, as discussed by Boehme et al. (2011), will allow for a more convenient and quicker diagnosis and may improve MDR TB treatment outcomes by shortening diagnostic delays and ineffective initial treatment.

The EDRWeb is the electronic database for DR TB within South Africa, which is used as a tool for surveillance, analysis and to monitor the performance of the DR TB programme, nationally and provincially. The main programmatic treatment outcomes (refer to the definition of key terms for a full explanation of these) for MDR TB is ‘successfully treated’, ‘failed treatment’, ‘died’,

'defaulted treatment' and 'not evaluated for an outcome' due to no data (Department of Health, 2009).

1.2. Study setting

The Western Cape Province has a population of roughly 5.8 million people, at a proportion of about 11% of South Africa's overall population (Statistics South Africa, 2012). This province presents with vast inequities in socio-economic indices and high prevalence of a variety of social determinants of health, such as overcrowding, inadequate housing structures, lack of water and sanitation, malnutrition, unemployment, gangsterism, substance abuse, and HIV, which influences the lives of its inhabitants. These circumstances resulted in a high prevalence and incidence of TB, especially amongst the lower socio-economic group.

In line with the National Health Act (No. 61 of 2003), six geographically contiguous health districts (one urban district and five rural districts were formally established in the province. In response to the high prevalence of TB specialized TB hospitals (see appendix 5 for details), which caters to the need of each district, were established in the province to be able to manage the burden of TB disease (National Health Act, 2003). Two TB hospitals are situated in the urban district and 5 TB hospitals in the rural districts. Primary Health Care (PHC) services are also provided by a combination of 284 clinics and health centres within the province, which treat drug sensitive TB (DS TB), and which historically did not treat MDR TB, until recently (Department of Health, 2013).

The initial treatment of MDR TB in the Western Cape Province mirrored the WHO guidelines, where patients were admitted for prolonged hospitalization of two years or more covering the full duration of their treatment, to a specialized TB hospital (WHO, 2006). This was easily manageable then due to the relatively small numbers of MDR TB. However, as the MDR TB incidence and prevalence raised this became increasingly difficult. In 2007 the numbers of

people with MDR TB initiated on treatment in the Western Cape Province was 439, but by 2010 this had increased dramatically to 1034 cases (Department of Health, 2013).

With the increasing numbers of MDR TB patients, the specialized TB hospitals were swamped and were hence forced to change the way in which treatment was delivered as there were insufficient beds to hospitalize every patient with MDR TB for the entire duration of their treatment. Hence a hybrid model of treatment whereby patients were admitted to the TB hospital for their *intensive phase* of treatment, which allowed easy administration of their daily injectable medication and allowed monitoring of the side effects of this highly toxic medication that can cause irreversible damage as well as preventing the further spread of MDR TB by limiting their contact with others, was implemented (Wells et al., 2007). These patients were then discharged to the clinics in the *continuation* phase of treatment, but had monthly outpatient Department (OPD) appointments to the hospital, so that the TB hospital doctors were still able to monitor and make clinical decisions regarding their treatment. Due to the complexities of MDR TB treatment, it was at that point deemed to require specialist doctor input and therefore the continued TB hospital interventions proceeded even after the patient was discharged. The assumption was that the clinics lacked sufficient trained staff, resources, knowledge and experience to be able to manage this complex condition successfully by themselves without active support from the specialist hospitals.

However despite the hybrid system of MDR TB management, the overwhelming numbers of MDR TB patients impacted severely on specialized TB hospital bed capacity, which resulted in pressured waiting lists for admission to the hospital, where the time to treatment initiation was often delayed by 2-3 months. This raised the public health concern, that these patients were delayed in being admitted to the hospital, which thus delayed the patient being initiated on MDR TB treatment and resulted in these patients ambulating within their communities in a highly infectious state, adding to the spread of MDR TB within the community. This was further exacerbated by the

emergence of Pre-extensively drug-resistant TB (Pre-XDR TB) and XDR TB. In 2008 the Western Cape Province started 34 XDR TB patients on treatment and this doubled to 61 in 2010 (Department of Health, 2013).

The increasing number of MDR TB was intensified by the already known large numbers of HIV immunocompromised cases admitted to the hospitals. This was significantly worsened by the lack of the provision of Highly Active Antiretroviral therapy (HAART), due to the high co-infection between HIV and TB, which further added to the fuel of MDR TB. The rise in MDR TB cases resulted in hospitals being overwhelmed by the high burden of TB and HIV. As ART became more affordable and available the management of HIV became more integrated within the clinic settings. The National Department of Health then responded to this, by reviewing its criteria for the provision of ART to include all TB patients who are HIV+ (Department of Health, 2013) as well as recommending the integration of HIV and TB services, to be able to better manage these patients (Farley et al., 2010).

However, despite the provision of ART the escalating numbers of MDR TB, Pre-XDR TB, XDR TB, resulted in an extreme lack of hospital bed space, and hence an inability to continue to manage these patients as inpatients even for the *intensive phase* of treatment. An added problem was that the ill DS TB, MDR TB, Pre-XDR and XDR TB were also predisposed to cross infection, as these infectious patients were often placed in mixed congregate wards which further increased the risk of nosocomial infections within the hospitals (Loveday et al., 2012).

Another treatment approach implemented to curtail the MDR TB hospital admissions was that patients were admitted to the hospital until at least one sputum culture was negative and were then discharged and referred to their closest clinic for further management. This approach thus limited hospital initiated treatment to 2-3 months, rather than the full duration of the *intensive phase*. The hospital admission was until the patient was deemed non-infectious and would not transmit MDR TB within the community. It further allowed the

clinic staff to start managing MDR TB patients within the intensive phase of treatment, albeit that they were initiated on this treatment in the specialized TB hospital.

In order for the clinics to now manage MDR TB during the *intensive phase* of treatment, their existing systems needed to be strengthened to ensure that their staff was capacitated through the appropriate training and mentoring to be able to manage this complex condition. The necessary resources such as the appropriateness of the provision of medication, monitoring side effects especially with the injectable administered in this phase, laboratory services, relevant stationery and recording and reporting tools also had to be in place to be able to manage MDR TB within the clinic (Villarino, Geiter & Simone, 1992). Given that patients were already being managed within the clinic after the first two months of hospital treatment, this then triggered the discussion as to whether clinics could potentially initiate patients on MDR TB treatment from day one. This would thus ensure that the patient had easier access to health services, by being initiated quicker on treatment while still maintaining their social identity within their communities and without requiring a hospital admission (Horter et al., 2014).

The staff within an area of the urban district in the Western Cape Province, who were already managing patients at the clinic within the intensive phase of MDR TB treatment, initiated a pilot project in 2009 whereby they initiated MDR TB patients on treatment in the clinic, themselves from the first day of treatment. The pilot project hoped to demonstrate the feasibility of the full decentralization of the management of MDR TB patients at the clinics thereby ensuring that effective treatment is accessible to the patient by being closer to their homes. The success of this pilot resulted in the province wide decentralization of MDR TB services in 2011, whereby uncomplicated MDR TB patients usually initiated on treatment within the hospital, were now initiated on treatment within the clinics (Hughes & Osman, 2014). The South African National Department of Health subsequently endorsed a policy recommending decentralization of MDR TB services to clinics with MDR TB treatment

initiation at the clinics, provided that clinic staff received appropriate training and support (Department of Health, 2013).

The Western Cape Province health department trained and mentored clinic staff on the clinical management of MDR TB by adhering to the South African National MDR TB guideline. MDR TB coordinators were employed in each district, to be able to follow up on these MDR TB patients and their close contacts and to ensure that the quality of management of MDR TB is maintained within the clinics. This cadre of staff is also responsible for the data capturing from the MDR TB register into the MDR TB electronic database, where variables such as patient demographic history, treatment regimens, treatment outcomes, previous TB history, HIV and ART history are recorded. This information is also retrieved for national and global reporting for the country. MDR TB counsellors or community health workers were trained on contact tracing and were allocated to counsel, screen and educate the patients and their close contacts about MDR TB and its management, through regular home visits. There are however differing approaches of managing MDR TB within this province which is unique to the context of each district and these differences are outlined below.

The urban district was the first to initiate the rollout of the decentralization of MDR TB to clinics, which entailed a specialized TB hospital admission for an MDR TB patient only when it was clinically indicated. The general outpatient clinic medical officer initiated treatment for uncomplicated MDR TB patients and reviewed these patients monthly. The patients attended the clinics daily for their oral medications and their daily injection within the *intensive phase* and then continued their oral medications within the *continuation* phase, under the supervision of the TB nurse. The general outpatient clinic services are either integrated (provide ART in addition to TB treatment services) or else to refer the patients who are HIV positive to facilities where ART is provided. Additional services provided to MDR TB patients are audiometry screening, patient and family counselling, home visits follow-up visits and social worker

support. These patients progress are also discussed at a standard clinical forum attended by the team managing the patient, to further inform the management.

Within the rural districts, different management strategies for MDR TB were adopted, where some MDR TB patients are treated within the specialized TB in-patient setting until one sputum culture is negative for TB and then they are discharged to their local clinic. Another rural district approach is that patients are admitted until the intensive phase is completed, so that the patient receives their injections within a specialized TB hospital, before they are discharged back to their clinic. This is mainly done as there are many seasonal workers within this area and due to the expanded distances of travel; patients are hospitalized to better monitor the patient's adherence and response to any side effects. The decision to hospitalize a patient is usually undertaken by the clinical team at these hospitals.

The decentralization of the treatment of MDR TB to the clinics within this province resulted in an expansion of MDR TB services, as described, and has thus created a creep of MDR TB treatment provision to the point where clinics are now initiating the majority of the uncomplicated MDR TB patients on treatment. There has however not been a study conducted to compare the effectiveness of the treatment within the hospital and clinic settings, to be able to evaluate whether clinics are providing as effective care to patients as they would receive at specialized TB hospitals.

Despite these efforts undertaken by the health services to improve and expand the management of MDR TB, as discussed above, the Western Cape Province still presents with poor MDR TB treatment outcomes, and thus other factors influencing the outcome of MDR TB such as socio-demographic and socio-economic factors are also operative. Shina, Furin, Bayona, Mate, Yong Kim and Farmer (2004) reported that many of the factors that determine MDR TB treatment outcome are not biological, but rather socioeconomic and psychosocial. Thus whether these social factors such as poverty, unemployment, overcrowded living conditions, depression,

age, gender, has any association on MDR TB also needs to be further explored.

1.3. Research Problem

The significant increase in the incidence and prevalence of MDR TB in South Africa underscores the complexities within the management of MDR TB. It is increasingly becoming more difficult with regards to logistics to manage MDR TB, by initiating treatment as in-patients in a specialized TB hospital, under the care of specialized TB physicians, due to the prolonged time to treatment initiation, the limited bed capacity, the risk of nosocomial infection as well as isolating the patient from their social environment. However, whether the general outpatient clinics, which are essentially, managed by nurses with general medical officer support, are ready to manage this more complex form of TB, with limited staff, less experience and assumingly with less MDR TB knowledge, is unclear.

Of particular concern is that the shifting of management from specialized TB hospital in-patients to a general outpatient clinic might worsen the already poor MDR TB treatment outcomes. Hence although expanding access to MDR TB therapy is urgently needed, yet expanding access by treating patients in general outpatients clinics might not be effective and hence an assessment of treatment outcomes for those patients initiated on treatment at general outpatient clinics, compared to those initiated on treatment at specialist TB hospital as in-patients, is urgently needed. Ideally one should also assess if treatment outcomes are related to additional factors such as age, gender, HIV status, provision of ART, a previous history of TB and where the patient resides, as these are factors that could potentially impact on the management of MDR TB and hence its treatment outcomes.

There is also the concern that inappropriate treatment will be administered to the patients, and would result in severe irreversible side effects. There is the argument that if, in fact, the clinic services are more accessible to the patients then this change in management practice might actually prove more effective

than the hospital inpatient treatment option. Despite the urgency, an assessment of the above issues has not yet been done in the Western Cape Province, even though some general outpatient clinics have been initiating MDR TB cases on treatment for the past few years.

1.4. Purpose of study

The findings of this study would be able to assist operational strategies for improved implementation of both the management of MDR TB patients within specialized TB hospitals and in general outpatient clinics. This study should provide policy makers with information that will assist them to take crucial decisions on the management of MDR TB patients by for instance, either advocating for acceleration of clinic based treatment of MDR TB, or for curtailment of it, or for modification of it.

The findings of this study will be presented at the provincial AIDS and TB management meeting, and the report will be made available to the attendees. Many key stakeholders involved in the management of MDR TB attend this meeting, hence providing a presentation to and tabling a report at this meeting ensures widespread dissemination of the study results to an appropriate audience. Other stakeholders to whom the report will be made available to the MDR TB coordinators and supervisors, as well as the health department senior line managers, health facility managers and staff of the specialized TB hospitals and the facility managers and staff of the community clinics.

Chapter 2: Literature Review

2.1 Introduction

The literature review below provides a comprehensive insight into the management of MDR TB patients initiated on treatment in hospital and clinic settings. It also covers details of the many factors associated with the management of MDR TB, which contribute to the understanding of this complex condition. These factors include appropriate medication offered to the patients, the time to treatment initiation, previous TB history and its potential influence on MDR TB, as well as the impact of HIV and ART provision on MDR TB, due to the known high TB/HIV co-infection rates. To deepen and enhance this contextualized appreciation of the dynamics of the management of people infected with MDR TB, the demographics related to MDR TB such as age, gender, and location are also further explored.

2.2 MDR TB treatment and adherence to treatment guidelines

Johnston, Shahidi, Sadatvi and Fitzgerald (2009), stated that guidelines are available for the management of MDR TB, however there still remains a lack of evidence based approaches from randomized controlled trials to support these guidelines.

The WHO in 2008, recommended that the MDR TB regimen should ideally consist of a combination of ethambutol and pyrazinamide, an injectable agent, a fluoroquinolone and a bacteriostatic drug, to which resistance had not yet been found, to give a total of at least five drugs during the intensive phase (WHO, 2008). Receiving the daily injectable medication is onerous and the medication has a high risk of serious irreversible side effects, which require close monitoring to detect early, in the hope of minimizing its impact. This treatment for the intensive phase has thus been adopted by the South African National Department of Health (Appendix 3).

The continuation phase includes 4 drugs, moxifloxacin, ethionamide, terizidone or cycloserine and pyrazinamide (Appendix 4). This standardized regimen can be modified based on the history of drug usage and drug susceptibility testing (DST). This is also further supported by Caminero (2006), who states that there is also an option to individualize the patient's regimens, with DST, or to standardize treatment based on the surveillance of anti-TB drug resistance. This is also reinforced by the WHO (2006). The MDR TB treatment should ideally last at least 20 months (WHO, 2011).

A WHO review of the DR TB programme of South Africa in 2009 stated that given the overwhelming burden of MDR TB, it is not surprising that MDR TB patients are not treated in accordance with the present South African Department of Health guidelines, but where treatment substantially differed from the guidelines was however not substantiated in this article (WHO, 2009). A study conducted in KwaZulu-Natal, South Africa, by Loveday et al. (2015), which comprised of 4 decentralized sites that treated a total of 736 MDR TB patients, found that each site presented with variations in health service provision. The variations were primarily dependent on the type of site, the motivation and knowledge of staff, as well as how the facility and the TB room were managed. The variations with regards to each specific site were not however further clarified. The above does however illustrate the different interpretations and implementation of the guidelines within the various health facilities, emphasizing the importance of support and regular monitoring at decentralized sites.

Villarino, Geiter and Simone (1992) in the early 90's, stated that policies and practice guidelines are in place to manage MDR TB, however they highlighted that it is important to evaluate health care workers knowledge on how to and attitudes towards managing this crisis condition. Ghebrehiwet (2009) in his study discussing the role of nurses in TB management, further adds that nurses working in primary health care (PHC) facilities usually identify and treat MDR TB patients and states that strengthening management should not only be isolated to nurses working in TB hospitals, but also include nurses working in

the clinics. He further added that especially in an era of TB/HIV co-infection, where the nurses' usually manage the treatment of HIV, competence in the arena of MDR TB is paramount. This study also highlighted the importance of the full clinical team inclusive of doctors, nurses, community health workers and even administrative staff in the effective management of the MDR TB patient.

Wells et al. (2007:99) in their study reinforced the need to understand the drug interactions between the anti-TB drugs as well as ART, as this has the potential to complicate the patients overall management, due to the 'overlapping of toxicities' which impacts treatment, due to the severe side effects of both, in addition to drug interactions which might occur. Common side effects listed were peripheral neuropathy, hepatoxicity, rash and ocular effects. This study then further discussed the potential risks of the use of an injectable agent during the *intensive phase* of treatment and highlighted that staff needs to adhere to the guidelines for the use of safe injection practices and universal precautions.

The view that programme failure, and specifically non-adherence to medication, is a predominant reason for resistance to anti-TB treatment, is supported by Sharma & Mohan (2004), who reiterate that the most important factor that causes MDR TB is incomplete and inadequate treatment. Johnston et al. (2009) also stated that drug resistant TB ultimately develops from the inadequate treatment of active pulmonary TB. There are multiple reasons for inadequate therapy which includes poor prescribing practices, insufficient treatment duration and poor drug selection, which are well recognized contributors.

Holtz, Lancaster, Laserson, Wells, Thorpe and Weyer (2006) found that treatment regimens amongst hospital inpatients in five provinces in South Africa were changed in 71(82%) patients due to severe side effects or drug resistance. Noting that 82% of patients had to change their regimens within the hospital setting, it is likely that a large percentage of regimen changes would be required in the general outpatient clinic setting as well, and the concern is that staff might not have sufficient knowledge of the treatment of MDR TB, to

effect appropriate treatment regimen changes. This therefore highlights that the appropriateness of treatment is essential when managing MDR TB patients, and that in addition to adhering to guidelines staff need to be trained to be able to provide adequate treatment regimens and contextualized management.

2.3 Time to treatment initiation

A prospective cohort study of 860 patients undertaken in, KwaZulu-Natal province in South Africa in 2008-2009, by Loveday et al. (2012), reported that in order to curb the MDR TB epidemic, early commencement of appropriate treatment is essential, as it limits transmission of MDR TB. The median time to treatment in their study was 72 days and 93 days for the clinics and hospital sites respectively. The shorter time to treatment for clinics, despite it being relatively long, suggests that treatment in clinic settings is more accessible to patient's, probably because it is closer to their homes and hence treatment delays can be minimized. In another study by the same primary author, Loveday et al. (2015), states that the increase in MDR TB patients and the consequent over-burdened bed capacity, as well as pressured waiting lists, resulted in an average delay of 111 days for hospital admission and treatment initiation.

Dlamini-Mvelase, Werner, Phili, Cele and Mlisana (2014), in a study at a memorial hospital laboratory in one of the highest burdened districts in KwaZulu- Natal, South Africa, found that for a year period between March 2011 and April 2012, a total of 34 444 patients were tested for TB, of which 637 were rifampicin resistant during this period, using the GeneXpert machine. A GeneXpert rifampicin resistant result suggests that the patient might have MDR TB and hence is a spur to pragmatic temporary commencement on MDR TB treatment, with a review of this decision once the resistance status is confirmed or refuted via culture tests. There was a reduced time to treatment initiation in MDR TB from 56 days to 5 days, noted in this study. Given that it is advocated by the South African National department of Health and reinforced in the National MDR TB guidelines, that all newly diagnosed MDR TB patients

should be started on MDR TB treatment within 5 days (Department of Health, 2013), it is commendable that this study achieved this.

Stagg et al. (2016) found in Latvia during 2009-2012, that with the introduction of the GeneXpert test, treatment initiation was decreased from 40 days to 27 days for 398 MDR TB patients who were rifampicin resistant. The delays in treatment were dependent on the setting, such as the diagnostic pathways, appropriate algorithms and the available resources. Naidoo et al. (2014) in a study undertaken in Cape Town, on 541 patients in 2011, found that there was a mean decrease of 25 days with the use of GeneXpert. This study concluded that the health systems and patient factors are the main contributors to the delays in treatment initiation. Farley et al. (2010), in their study conducted between 2000-2004, of 8 provincial programmes within South Africa, inclusive of the Western Cape Province, further supports other study findings, by citing that the time to treatment initiation is a systems issue, which further contributes to the poor MDR TB treatment outcomes in South Africa and they also emphasized that treatment delay is the main reason for this. The average delay in time to treatment initiation across the 8 provinces was 2 months.

There are additional factors that can also influence the delay in initiating treatment, especially with a condition such as MDR TB, which is associated with many social factors. Cramm, Finkenflugel, Moller & Nieboer (2010), in their study conducted in the Eastern Cape province in South Africa, showed that of the 1020 households of 4245 people, that health seeking behavior and non-adherence to treatment are the primary barriers to controlling MDR TB. This study also advocates that there is a need to achieve a high level of TB awareness which is crucial in the prevention and treatment programmes in this high risk population. It also appeared as if the perceptions of TB and HIV still requires more education within the communities, as stigma still appeared to impact case findings and case holding. The stigma of managing MDR TB was also identified in a study in Uganda (Horter et al., 2014). There are therefore many factors associated with delaying the time to treatment initiation and these delays influence the overall treatment outcomes for the MDR TB patient.

2.4 Treatment Outcomes for MDR TB

The WHO (2015) updated report, states that only 50% of the globally managed MDR TB patients, in the 2012 cohort, were successfully treated. This poses a significant concern as only half of the patients within the world who have MDR TB are being successfully treated. The South African MDR TB treatment success rate, between 2010 and 2012, improved from 40% to 50% (EDRWeb, 2016). The Western Cape Province presents with even lower treatment success rates, from 31%-38%, for the same period of 2010-2012. Despite the improvement seen over time, this province is still performing significantly lower than the national achievement. The available literature on treatment outcomes supports the current statistics within South Africa, as the data reported for most of the studies indicates relatively poor treatment outcomes for MDR TB. Brust, Gandhi, Carrara, Osburn & Padayatchi (2010) indicated that of the 1209 MDR TB patients admitted to the Provincial TB hospital in KwaZulu-Natal, with documented treatment outcomes, 491 (41%) were cured, 35 (3%) completed treatment, 208 (17%) failed treatment, 223 (18%) died and 252 (21%) defaulted. These high levels of treatment failed, treatment defaulted and the low cure rates (below 50%) are aligned to the South African and global statistics.

Goble, Iseman, Madesan, Waite, Ackerson & Horsburgh (1995) in their study in America, of MDR TB patients admitted into a hospital from 1973-1983, found that of the 171 MDR TB patients, 63 (37%) died, 47 (27%) patients were treatment failures, 20 (12%) were cured and 41 (24%) defaulted treatment. These treatment outcomes are significantly poorer than current global and South African cure rates and reflect the time frame of this earlier study, which took place during the emergence of MDR TB when grossly high death and failure rates and extremely poor success rates were the norm. While MDR TB still presents with poor treatment outcomes, improvement, has been shown over time.

Holtz et al. (2006) described the treatment process and outcomes for the first cohort of patients enrolled in the hospital programme in five provinces in South Africa, between October 2003 and January 2005. Of the 108 MDR TB patients, 87 were started on treatment during the study period. Treatment was successful for 54 (62%) patients, with 13 (15%) dying during treatment, 12 (14%) defaulting and 8 (8%) failing treatment. Poor clinical conditions and baseline second-line resistance contributed to treatment failure or death.

Johnston et al. (2009), performed a systematic search and found 36 articles representing 31 treatment programmes across 21 countries, the pooled findings of a total of 4959 patients reported treatment outcomes of 62% cured (95% CI 57-67) and showed that 11% of patients died and 8% failed treatment with a 13% defaulter rate in this study. These findings indicated that defaulting on treatment appears to be a global phenomenon with rates over 15% in several countries including Korea (32%), Taiwan (29%), Russia (20%), Italy (17%), Spain (16%), South Africa **(29%),** Argentina (20%) and Peru (19%). South Africa hence appears to have one of the highest defaulter rates globally.

In a study undertaken by Anderson et al. (2013) the authors stated that some of the reasons cited for non-adherence were patient's choice, pregnancy, side effects and strangely even 'spontaneous recovery'. Chan et al. (2013) within a hospital setting in Taiwan however attributed the high default rate to programmatic failure in the control of MDR TB. A study in the Hlabisa health sub-district in KwaZulu-Natal undertaken by Heller et al. (2010) on community treatment cited that there are economic and social costs involved in keeping patients isolated in hospitals, often far from their homes, which could lead to a default in treatment. Thus despite hospitals having a 'captive' audience of inpatients, they still grapple with patients who default treatment.

2.5 Hospital treatment of MDR TB vs. clinic treatment of MDR TB: The different models of care

"Home is where the patient is" (Horter et al., 2014:81). This qualitative study in Uganda of 9 MDR TB patients, reiterates that clinic and community based treatment, where patients are followed up by the nurse and health care teams, has been found to be effective with high cure rates. These cure rates were however not stipulated in the article.

Mitnick et al. (2003) in their retrospective study of 75 MDR TB patients in Lima, Peru, who were treated within their community, reinforced the view that by moving treatment into the clinic, 83% of patients were cured hence highlighting that good results can be obtained, however 8% of the patients died. They report that community treatment at the clinic, does not compromise the quality of therapy, it lowers the cost and it reduces the risk of nosocomial spread of MDR TB.

Loveday et al. (2015) in support of a community based care model for the management of MDR TB, reiterates that this model makes treatment more accessible by being available closer to the patients home, thus enhancing support for patients and their families, and also prevents the patients from having to undertake lengthy visits to the hospital, requiring money for travel. This study however also found that the survival rates at the community sites were lower than in the hospitals with death rates of 18% and 14% in community and hospitals sites respectively. The community setting were however more likely to be cured at 51% as compared to the hospital setting at 34%.

Horter et al. (2014), further supports that treatment within the community setting is a safe and feasible option which usually addresses wider health influencing factors, such as it is three to four times cheaper than hospital based approaches. A qualitative study of interviews with 30 participants, inclusive of patients and their families, noted the perceptions that a hospital setting has a greater risk of infection as compared to their home environment, and that persons recover faster within their homes. However, none mentioned a lack of

acceptance of having patients within their community being treated for MDR TB and this was therefore seen as safe, conducive to recovery and enables patients to spend more time with their family, as the family members would not have to travel to visit the patient in the hospital. Twenty percent of the participants however, preferred hospital treatment due to the perception that treatment will be given on time.

A retrospective study by Mitnick et al. (2003) in Lima, Peru from August 1996-November 1998 who described 75 MDR TB patients, further established that patients with MDR TB can be treated successfully within a clinic setting in a poorer socio-economic setting. This study motivated for the expansion of MDR TB management within clinic settings, noting that the cost per patient ranging from 504 USD to 32 383 USD, at a mean of 15 681 USD per patient and that it had much better treatment outcomes with an 83% cure rate. Sharma & Mohan (2004) however reported that management of MDR TB is a challenge and requires experienced clinicians at centres equipped with reliable laboratory services, as well as resources. This hence highlights that although the clinic appears to be cost effective, support systems needs to be in place and strengthened to be able to manage MDR TB.

An operational prospective cohort study conducted in KwaZulu-Natal, by Loveday et al. (2012), found that amongst 860 MDR TB patients (with 419 treated at decentralized clinic sites and 441 treated at a central hospital) care for MDR TB patients was slightly more effective at the clinics than the centralized hospital setting, with patients successfully treated being 58%, as compared to 54%, respectively. This study also further gave possible reasons for the better outcomes in the decentralized services, stating that they tend to initiate vigorous programmes, where the clinic staff are trained on administering the injectable, they educate the patients and their families and they introduce follow up strategies for patients who miss appointments. The study also explained that the central hospital patients are often discharged to the clinics prior to completion of their injectable medication and since they lack the intensive educational

curriculum provided at the clinic they are often uncertain and irregular in their clinic attendance and thus the receipt of the daily injectable.

2.6 Hospital initiated MDR TB treatment: a hybrid model of care

The management of MDR TB was initially seen as a hospital based condition however with the rapid escalation in incidence and prevalence of this condition, the need to expedite decentralization was stressed. Brust, Gandhi, Carrara, Osburn & Padayatchi (2010) in their retrospective study in KwaZulu- Natal, South Africa, traced 1209 MDR TB patients, this cohort were admitted to hospital, until the intensive phase of treatment was completed and were then followed up via monthly outpatient (OPD) appointments in the hospital during the continuation phase of treatment. This article noted that a centralized treatment programme, or hospital management, was unable to monitor and trace defaulters, or even provide Directly Observed Therapy (DOTS) in the continuation phase of treatment, as patients' homes were often very far from the hospital. The defaulter rate was 21%, hence indicative that a significant amount of patients were not followed up. This study thus recommended that to reduce the number of persons that default treatment, decentralization of MDR TB treatment should be considered, either by creating community-based treatment programmes, or initiating patients on treatment within the clinic.

This finding was also supported by, Loveday et al. (2015), who predominantly focused on the most effective care models for MDR TB and found that the management of MDR TB in a specialized TB hospital for the intensive phase of treatment for the injectable, was to allow for close monitoring of side effects and adherence. However once the patient was discharged back into the community for the continuation phase of treatment (18 months or longer), these patients were still expected to attend monthly OPD appointments. Some of these patients were expected to travel 500km for their OPD appointment, which had a large impact on reducing successful treatment outcomes. This study also explains that patients that are discharged from the hospital before the end of the

injectable phase, to be followed up for treatment by the clinics, are often unfamiliar with their management. Thus the assumption is that the clinic settings appear to be providing the patients with more information regarding their condition. Both these studies hence highlight the logistical and systemic challenges patients faced when hospitalized for the intensive phase of treatment and then subsequently discharged to the clinic with monthly OPD hospital appointments.

Bassili, Fitzpatrick, Qadeer, Fatima, Floyd and Jaramillo (2013) in a systematic review of 35 studies undertaken globally, noted that where MDR TB patient receives the intensive phase of treatment (whether hospital or clinic), is not associated with the treatment outcome, giving further support to the WHO guidelines (2011) to introduce ambulatory care to MDR TB patients. This study also reiterated that the main barriers to expanding access to the diagnosis and treatment of MDR TB are the limited availability of MDR TB drugs, limited resources available to provide treatment and the lack of quality assurance in laboratories.

Most of the articles perused for the purpose of this study emphasized the benefits of clinic initiated treatment for uncomplicated MDR TB patients (Horter et al., 2014; Loveday., et al, 2013; Mitnick et al., 2003; Loveday et al., 2015). This approach is favoured, as it makes care more accessible to the patients, it is more cost effective and allows the patients to socialize within their home environment and thus maintain their personal and social identities. This management aligns with the South African MDR TB decentralization guidelines, thus emphasizing that decentralized care is seen as being effective and feasible within the South African setting.

2.7 MDR TB with HIV and ART

Being infected with tuberculosis (TB) remains the leading cause of mortality among HIV-infected people worldwide (Reid et al. 2006). The findings from the South African National DR TB survey by Weyer, Van Der Walt, Brand, Lancaster and Levin (2003), informs that 40% of patients with MDR TB

were identified as being co-infected with HIV, equating to 4000 new HIV positive cases of MDR TB annually.

The South African Antiretroviral Treatment Guidelines (2013), in response to the high TB/HIV co-infection rate, amended the ART eligibility criteria, to allow ART to all TB patients. A study by Farley et al. (2010) who evaluated the outcomes by HIV status for MDR TB patients enrolled between 2000-2004, prior to ART access, provided useful information in that the study indicated that the 757 MDR TB patients with a known HIV status, were less likely to have a successfully treated outcome (40.0% vs. 49.6%; $P<0.05$) and were more likely to die (35.2% vs. 16.2%; $P = 0.0001$). This study hence indicated the need to provide ART during MDR TB treatment, as well as the need to integrate ART and TB services, as co-infection complicates TB treatment, yielding poorer treatment outcomes.

Another study by Wells et al. (2007) explained that hospital outbreaks of MDR TB have primarily affected HIV infected persons and that this is probably due to the delayed diagnosis, inadequate initial treatment, prolonged infectiousness and increased mortality among HIV infected persons. However, whether this follows a similar sequence within the community was unclear. This study also reinforces that HIV infected patients with MDR TB have significantly higher mortality rates and hence provision of ART is necessary. The authors recommend that in order to curtail the MDR and HIV epidemics, there is a need to scale up the program capacity to provide effective treatment, intensified case finding and infection prevention control.

Andrew, Shah, Gandhi, Moll and Friedland (2007), state that HIV infection and the development MDR TB have not been fully clarified and the authors therefore, question whether HIV infection is an independent risk factor for MDR TB development. This study then argues that regardless of whether HIV is a risk factor at an individual level, it is at a population level; as the increased pool of immunocompromised patients is certain to increase the overall burden of MDR TB, and thus the authors conclude that HIV infection is indirectly a

risk factor for the development of MDR TB. Hom et al. (2012) negate this by stating that HIV-infected patients not previously treated for TB, are at risk for primary infection with drug-resistant mycobacteria and thus HIV infection is a risk factor at an individual level. Several studies have shown increased rates of drug resistant TB in HIV infected person (Campos, Suarez, Sanchez, 2003). These studies thus affirm that HIV infection is a risk factor at an individual and population level for the development of MDR TB.

The global expansion of access to ART over the past decade has also impacted on the TB programme, as most patients still present with TB and HIV co-infection. Friedland, Karim & Karim, (2004) inform that ART has been shown to reduce TB incidence, and this will in all likelihood be seen with MDR TB and XDR TB as well. Loveday et al. (2015) found that among their study population of 1549 patients tested for HIV, there were high co-infection rates in both the clinic and hospital settings (76% vs 73%), however 91% of the HIV infected clinic patients were receiving ART compared to 82% at the hospital settings. These clinic patients on ART were also more likely to have a successfully treated outcome of their MDR TB.

2.8 MDR TB and Previous TB

WHO (2013) states that 4% of new TB cases in the world have MDR TB, however the levels are much higher in those previously treated for TB, at about 20%. Sharma & Mohan (2004) state that the proportion of MDR TB is higher in patients who have previously had anti-tuberculosis treatment and further emphasized that this is as a result of the failure of TB programmes to ensure complete cure of the patients with DS)TB. This is further supported by Brust et al. (2010), who reported that MDR TB is a marker of the TB control programs inability to adequately manage DS TB, as seen in the South African TB program that has been severely under-resourced and unable to handle the 3-fold rise in TB caseload that occurred over the past 15 years.

Chan et al. (2013) reiterated that a previous anti-TB treatment was a strong influence on the prognosis of MDR TB, and highlighted the importance of

recording and reporting of this history, to be able to ensure optimal treatment as well as monitoring of the patient. Goble et al. (1995) found that an unsuccessful response to therapy within the hospital setting was strongly associated with a previous history of TB.

Andrew, Gandhi, Moodley, Shah and Bohlken (2008) in a study in Tugela Ferry in South Africa, observed that a substantial proportion of patients with no prior history of TB, had evidence of drug resistance to standard anti-tuberculosis therapy. Of the 13 patients with MDR TB, 5 (38%) had no prior history of TB and were not on TB treatment at enrolment. This is perhaps indicative that primary MDR TB, which is the first episode of MDR TB, is also an area of concern.

Other factors are also related to the development of all forms of TB, Karim et al. (2009) states that the social, economic and environmental conditions created by apartheid in South Africa resulted in overcrowded squatter settlements, migrant labour and deliberately underdeveloped health services for blacks which created the milieu for TB and HIV to flourish and now contributes to the development of MDR TB.

2.9 MDR TB: Age and Gender

Johnston et al. (2009) in a systematic review covering 30 studies found that the overall mean age for MDR TB was 40 and also noted that a factor related to poor outcomes were male gender with a 0.61 Odds Ratio (OR) for successfully treated (95% CI 0.46-0.82), while having no previous TB increased the success rate with an OR of 1.42 (95% CI 1.05-1.94). Farley et al. (2010) illustrated that of their cohort of 1023 patients the mean age was 36.5 years. Khan (2010) in her findings stated that a disproportionate number of older adults are affected by all forms of TB. Espinal et al. (2001) in their analysis of 11 countries incorporating 9615 patients found that the mean age of the patients was 38 years. They found that patients aged 35-44 and 55-64 years were more likely to have MDR TB compared to the 0-14 year old category.

Another study by Goble et al. (1995) cited that poor outcomes were strongly associated with male sex. The study further reasoned that this could be due to behavioural and biological factors. This is also supported by Mulu, Mckonnen, Yimmer, Admass and Abera (2015) who reported that being a male and having prior exposure to anti-TB treatment were factors significantly associated with MDR TB.

Most of the articles perused illustrated that the mean age of MDR TB was greater than 30 years old (Brust et al., 2010; Goble et al., 1995; Farley et al., 2010; Espinal et al., 2001) and to a lesser extent it appears as if most of the articles related to gender indicated that the male gender has poorer treatment outcomes (Johnston et al., 2009; Mulu et al., 2015; Goble et al., 1995).

2.10 MDR TB in Urban and Rural settings

A survey undertaken by Casel & Vaquero (2005) found that the different risk factors for MDR TB identified were age, HIV infection and population mobility (immigration within Western European countries). Within the Western Cape Province, more so within the rural districts, there is significant population mobility, due to the seasonal nature of agriculture and agriculturally linked work. Almeida et al. (2003) in their study comparing urban and rural settings in India discussed that there was a high incidence of TB in the urban settings and worryingly doctors were prescribing the incorrect therapy to the patients in the urban areas. Regarding the marked rise of MDR TB within the urban areas, the explanation they provided was that rural services are free and supervised weekly. The rural patients also had less access to multiple doctors, the use of which is associated with poor prescribing habits.

2.11 MDR TB Recording and Reporting

Rose et al. (2013) conducted a retrospective cohort study and assessed the completeness and accuracy of the electronic recording of DR TB data in 77 children in Cape Town and found that only 64% were captured onto the electronic database. The authors also found that there were under-reporting and suggested that the clinicians at a facility level should be capturing the data in

the electronic database and not the MDR TB co-ordinators, who usually does the capturing of the MDR TB data into the electronic database for their designated districts. Additionally, they recommended that the data variables should be simplified and they also highlighted that the recording and reporting for DR TB should be improved.

2.12 Summary of the Literature Review

In summary, it appears as if most of the articles reviewed support clinic initiated treatment, and there does not appear to be a significant difference in the treatment approaches between the clinic and hospital, even though they do operate differently. The need to decrease the time to treatment initiation to prevent the further spread of MDR TB was commonly found, however, all articles highlighted that this is greatly dependent on multiple factors such as patient related issues and health systems logistical delays.

The double burden of HIV and TB was predominant in all the literature perused and hence the need to offer ART is emphasized in most of the literature, there was however limited available literature specifically comparing the provision of ART with the MDR TB treatment outcomes. Another finding that was frequently presented was that a previous history of TB and being male appears to be significant factors associated with developing MDR TB. However, unanticipatedly, there was also limited literature found comparing MDR TB treatment outcomes to a previous TB history. Additionally, the articles appraised found that the context, in which people live in, should be considered, however, there were no real conclusive findings to support any differences in management between urban and rural districts. An article on the recording and reporting of MDR TB emphasized the importance of accurate and complete data capturing to be able to better manage the MDR TB programme.

Chapter 3: Aim and Objectives

Aim

To compare the treatment outcomes and the effectiveness of medication regimens provided to MDR TB patients initiated on treatment in specialized TB hospitals as inpatients, to that of MDR TB patients initiated on treatment as outpatients at community clinics within the Western Cape Province, South Africa.

Objectives

- To compare the MDR TB final treatment outcomes: successfully treated rates, treatment failure rates, defaulted treatment rates and death rates, between participants initiated on treatment in specialized TB hospital in-patients and community clinic outpatients.
- To compare the effectiveness of the MDR TB medication regimens which patients are placed on between specialized TB hospital in-patients and community clinic outpatients.
- To compare the MDR TB treatment outcomes in specialized TB hospital in-patients and community clinic outpatients stratified by facilities located within urban and rural areas and other potential confounders.
- To compare the MDR TB time to treatment initiation between patients initiated on MDR TB treatment at specialized TB hospitals and community clinic outpatients.

Chapter 4: Research Methodology

4.1 Study Design

The study design used was a retrospective cohort study, as the duration of treatment for a MDR TB patient can be for 24 months or longer. This study design thus shortened the time needed to conduct a cohort study and made use of historically or previously compiled data. It was eminently possible to use this less time consuming and efficient study design in this setting, as detailed MDR TB records were available.

4.2 Study Population

The Study population comprised of laboratory confirmed MDR TB adults above 18 years of age who were initiated on treatment between 2010 and 2012. This time period was selected as 2010 was when most of the MDR TB patients were still managed according to the National Guidelines, by being admitted into specialized TB hospitals as in-patients and kept there until they 'culture converted'. These years were also additionally selected as the treatment duration for MDR TB is approximately 24 months long, therefore patients who started treatment in December 2012, would complete their treatment by December 2014 or early in 2015.

The exposed group was composed of those patients initiated on treatment entirely as outpatients in the community clinic setting for the full duration of the treatment course. The unexposed group was composed of those patients initiated on treatment as in-patients until sputum 'culture conversion' (typically from 4 to 8 months), in the specialized TB hospital setting and thereafter treated at the hospital outpatients section or at community clinics. Laboratory confirmed MDR TB, indicates that all relevant tests were undertaken and the participant was confirmed as having MDR TB.

Children (those under18 years of age) were excluded as the treatment regimens for them are different to those for adults and adherence to medication and clinic appointments follow different dynamics amongst teenagers and children than

among adults, as children are usually dependent on caregivers to take them to a clinic. Additionally, the inclusion of paediatric cases in this study would not be feasible as the vast majority of the MDR TB paediatric cases are still managed as in-patients.

The exclusion criteria for this study were XDR TB, Pre-XDR TB, extra pulmonary TB, TB Meningitis, TB with concomitant cancers or other serious illness, the terminally ill, ICU admissions, high care admissions and admissions for surgery. However, those with TB and HIV will not be excluded, as HIV is commonly seen in TB. XDR cases are excluded from this study since as per current policy, all these patients still require admission to the specialized TB hospitals and are treated with a different regimen of medication. Pre-XDR cases are also excluded as they too are treated with a different medication regimen to what the MDR TB patients receive. The terminally ill, those with cancers or other serious illnesses, ICU admissions, high care admissions, and those admitted for surgery are excluded as due to the nature and/or severity of their illness they would have received specialized care. Patients that are in correctional services facilities were also excluded, as their management received might have differed.

4.3 Sample Size

According to the MDR TB electronic database (EDRWeb), there were approximately 4000 MDR TB patients registered in the database during the 24 month period from 1 January 2010 until 31 December 2012. Using this time period has the advantage of assessing the very latest treatment cohort, as the last patient in the cohort should have completed the treatment course by December 2014 or soon thereafter.

The sample size was therefore based on an estimated population size of 4000 MDR TB patients and calculated using the statistical database EpiInfo7 (CDC, 2007). Based on a confidence interval of 95% a power of 80%, with the ratio of the unexposed to exposed set at 1:1, with a presumed cure rate in the unexposed group (treatment initiated in the hospital) of 20% and with the risk ratio at 0.60

comparing the hospital treatment initiated cohort to the clinic treatment initiated cohort. The sample size was calculated to be 660 participants (330 exposed comprising of 165 participants from the urban setting and 165 from the rural setting and similarly 330 unexposed with the same rural and urban breakdown).

4.4 Sampling Type and Procedures

The sampling type for this study was random sampling with participants being randomly selected from amongst those MDR TB patients in an electronic database who met all the inclusion and exclusion criteria. After permission to access the electronic database was obtained, the patients in the database were sorted into those who met the study criteria and those who didn't. Thereafter those who met the criteria were numbered and then selected using a random set of numbers.

4.5 Data Collection

Data was extracted from the electronic register via an excel export template. The data extracted included demographic data, facility treated at, time to treatment initiation, time to culture conversion, cure rates, treatment completed, failed treatment, died, defaulted treatment, and medication regimens that the patients were put on, HIV status, initiated on ART, previous TB history, gender, age, and district accessing treatment.

A pilot study was undertaken within urban and rural sites, two months prior to the implementation of this study in order to assess the follow through of information from the standardized MDR TB register into the electronic database, as well as to further assess whether the data extraction tool was appropriate, valid, correctly calibrated, easy to use and reliable. The necessary amendments were then made to the data extraction tool prior to data collection. The pilot study was also undertaken, to assess the likelihood of data missing from or incorrectly entered within the MDR TB register and to forewarn about any potential logistical challenges with accessing the data.

4.6 Analysis

Pre-analysis quality control checks were done to identify and correct any errors. There was a potential for an error to be made with the capturing of information from the standardized paper register into the electronic database, this was curtailed by cross-checking the information from the register to the database. If anything unusual was detected that required further clarity, the MDR TB co-ordinator was consulted to further cross-check. The researcher cross-checked every tenth entry captured on the standardized data extraction tool with the data in the electronic database.

The univariate descriptive analysis was conducted to assess the proportions for categorical variables, and the mean, median and distributional spread for the continuous variables. The univariate numerical data included the ages of the participants, the days taken to two consecutive culture negative results, the days to treatment initiation from the initial sputum result to the start of treatment as well as the days from the start of treatment to the discontinuation of treatment. The univariate categorical analysis included determining the cumulative incidence of the key treatment outcomes of successfully treated, failed treatment, died and defaulted treatment; and explanatory exposure variables such as previous TB, HIV, ART provision, and gender.

The bivariate analysis (relative and absolute) to determine the cumulative incidence ratio and the cumulative incidence difference for the 4 outcomes noted above was then conducted to determine the association of the exposure variables with each of the outcomes.

Multivariate logistic regression analysis was then done modeling all variables that were significantly associated with the outcomes on bivariate analysis, to control for confounders and effect modifiers. The final model included the key exposure variables of clinic and hospital initiated participants and the potential confounders of type treatment offered, location, previous TB, gender, HIV, ART provision, and age.

4.7 Validity

The sample size of this study was calculated from EpiInfo, and it was large enough to allow for a minimal chance to have occurred. This was also further noted in the narrow ranges of the 95% CI for most variables of this study, the wider 95% CI ranges noted in the study had reasonable explanations.

The information was collected from routine data in the MDR TB register; this register is the data source for the MDR TB electronic database. There was a possible information error, due to incomplete data captured into the register. This information error, however, was minimal as the variables within the register and the electronic database are standard and therefore allows for a more structured manner of capturing this data. There are also designated trained TB staff within the province that are capturing this data, for a relatively small cohort of MDR TB patients in a health system with comparatively much larger cohort conditions, and thus the data is more easily manageable and would allow for more time to capture and hence less information error. This data is also regularly captured and updated for reports that are required at a provincial and national level thus indicative that the data needs to be verified, accurate and more complete. MDR TB co-ordinators are based in each district within the province, to capture the data into the electronic database and monitor the DR TB data, these officials were contactable to advise if gaps were noted, and to ensure further accuracy and completeness of the data. The MDR TB co-ordinators also captures the data for both the hospital and clinic settings, thus limiting a potential measurement bias.

Treatment outcomes of all patients who do not die during the treatment period are based on attendance record and consecutive sputum results. The decision to allocate a particular treatment outcome is in practice made by the attending clinician (nurse or doctor) based on an attendance and sputum results algorithm. Since this is done by literally hundreds of clinicians the possibility of these decisions being applied in a non-standardized manner was high. Hence the researcher applied the attendance and sputum results algorithm to obtain an outcome for all the patients and then compared her outcome to that recorded by

the attending clinician. In the absence of sputum results being recorded, participants were classified as having defaulted, however this was only done in 7 cases.

The chance of confounding occurring in this study was minimized by further analyzing the data using multivariate logistic regression analysis.

4.8 Reliability

A pilot was conducted within the urban and rural areas, prior to the formal data collection. A proportion of 15% of the total study population, were included in the pilot. This was done, to be able to verify the appropriateness of the capturing template for the variables of this study within the different contexts; any gaps noted were amended accordingly. These included adding more variables to the template, such as, culture conversion date, the dates of the sputum, researcher outcome, and the stratification for previous TB history.

To ensure that reliability was facilitated, the data was extracted from the MDR TB registers only by the researcher, who has sufficient knowledge of the study inclusion/exclusion definitions and used a prepared data extraction tool which would ensure uniformity and standardization of data extraction.

4.9 Generalizability

The Western Cape Province MDR TB incidence and prevalence is one of the highest within the country and can thus be comparable with Kwazulu-Natal and the Eastern Cape provinces. However when assessing the different contexts of these provinces, the Western Cape province is better geared to treat and manage MDR TB due to its historical experience with TB control and management, and its long and efficient history of the management of TB not only in the specialized TB hospitals but also within the general outpatient clinic domain. Hence caution needs to be employed when attempting to generalize the study results beyond the Western Cape Province.

4.10 Ethical Considerations

The study proposal was submitted to the University of Western Cape (UWC) Research Committee, who perused the proposals ethical soundness and provided the necessary ethical clearance. The Department of Health and the City of Cape Town (Urban District) are the custodians of the health information records of patients accessing their services, hence permission to access the participants health records was sought through the Provincial Research Committee and the City of Cape Town Research Committee, who co-ordinate all the research requests within the Western Cape Province. The full research protocol was therefore submitted to both authorities. Permission was then also obtained from the relevant provincial and City of Cape Town managers at the sites where the data was accessed as well as the Provincial Director of the HAST (HIV, AIDS, STI, TB) unit with whom the MDR TB services and electronic information management responsibility resides.

The confidentiality of the participants was strictly maintained. The cohort's private identification data captured was and will not be disclosed or reported. All data extracted was stored in a password protected database accessible only to the researcher and supervisor. After the participant identifier data was used to verify the accuracy of the data all identifiers were removed and analysis was done on an anonymised set of data.

Chapter 5: Results

5.1 Sample Realization

The initial estimated study population size for this study as detailed under sampling above was 660 participants, equally split between the exposed and the unexposed and stratified by rural and urban. However when the sample was accessed, it was discovered that the TB hospitals in the urban district were no longer admitting all MDR TB patients during 2011 and 2012, but rather admitting only patients with complicated MDR TB or who were seriously ill. A consequence of this was that zero uncomplicated MDR TB patients were initiated on treatment as an inpatient within the urban hospitals since 2010 and hence all of these patients did not meet the study's inclusion/exclusion criteria. Instead all uncomplicated MDR TB patients in the urban district, had their treatment fully provided (initiated and completed) at the clinics as outpatients since 2011. Hence the only appropriate available urban hospital inpatient initiated treatment cohort was patients admitted in 2010 and preceding years.

The dilemma was that using this cohort would require that we compare cohorts who had been treated at different points in time and hence run the risk of introducing a selection bias, due to potential changes in treatment approaches or first line medication within these different time periods. However there were no changes in treatment approaches or first line medication in the province between 2010 and 2012. Therefore using these hospital cohorts, who were treated during a different time period, was a valid selection option, since omitting them would mean reducing the sample size and decreasing the generalizability, and as the hospital cohort would then be drawn entirely from rural facilities while the clinic cohort covered rural and urban areas, one would incur a much greater risk of selection bias by omitting them. Thus the risk of selection bias was smaller when selecting the 2010 urban hospital cohort than if the hospital cohort were composed of only rural hospital patients, while the clinic cohort were composed of rural and urban patients.

In the rural districts, the hospital still managed most of the MDR TB patients during 2012 (via inpatient initiated treatment), thus indicating that rural districts took slightly longer to initiate patients on treatment in the clinics. Considering these factors during the data collection phase and restricting the sample to all patients treated in 2012 for rural districts and urban clinics while using all patients treated in urban hospitals in 2010 the final study population was 644 participants. Urban hospitals contributed 165 participants; urban clinics contributed 174 participants; rural clinics contributed 149 participants and the rural hospitals contributed 161 participants.

From the 644 participants that were enrolled in the study, only 568 participants had a final outcome documented, and hence the bivariate analysis was restricted to this group. Having 76 (11.8%) of the MDR TB participants without a final documented outcome should be a concern for the TB programme as this hampers routine monitoring and evaluation of the programme.

5.2. Univariate Analysis

The results of the univariate analysis of both numerical and categorical data are shown below, followed by the bivariate results comparing the exposures measured to the outcomes of successful treated, failed, died and defaulted. The results of the multivariate analysis are then subsequently presented.

Table 1 below illustrates the univariate numerical analysis of this study. Each numerical variable is explored separately through its mean, median, standard deviation (SD) and interquartile range (IQR) and is further stratified between the clinic initiated and hospital initiated cohorts. The variables in this table included: the ages of all participants, the days to two consecutive sputum culture negative results, the days to treatment initiation from the initial sputum culture to the start of treatment and the days from start of treatment to discontinuation of treatment.

The overall age of participants within the exposed and unexposed cohorts indicates not much of a difference between these two groups. It was of interest to note that the average age of all persons initiated on MDR TB treatment was 34 years of age; this is aligned to the literature, where on average patients appear to develop MDR TB at this later age (Farley et al., 2010; Johnston et al., 2009; Espinal et al., 2001). This finding is however in contrast with DS TB where the average age is 25 years, as reported by a study conducted by Nyabadza & Winkler (2013), in the urban district in the Western Cape Province.

Clinic initiated participants culture converted earlier than hospital initiated participants at a median of 79 days and of 93 days respectively. The time that patients take to culture convert (no mycobacteria cultured from the sputum) is important, as a short time to conversion is a good predictor of a successful treatment outcome, this is further supported by Loveday et al. (2012).

The days to treatment initiation from the initial sputum collection to the start of treatment, as per the National Department of Health treatment guidelines, should be within 5 days as results are typically available using the GeneXpert

test within 1 to 2 days (Department of Health, 2013). However clinic and hospital initiated participants both had an excessively long time to treatment initiation within a median of 29 days, and 37 days respectively.

Table 1: Univariate Numerical Analysis of MDR TB participants initiated on treatment in the clinic and hospital settings

Variable	Combined n= 644				Clinic initiated n= 323				Hospital initiated n= 321			
	Mean	**Median**	**SD**	**IQR**	**Mean**	**Median**	**SD**	**IQR**	**Mean**	**Median**	**SD**	**IQR**
The ages of all participants	36	34	11	27 - 43	36	35	11	27 - 43	36	33	12	28 - 44
The days taken to two consecutive culture negative results	112	86	77	65 -123	102	79	73	62 - 110	122	93	80	68 - 143
The days to treatment initiation from the initial sputum to the start of treatment	39	34	30	18 - 49	33	29	28	10 - 43	44	37	31	25 - 58
The days from start of treatment to discontinuation of treatment	463	454	249	237 - 716	480	532	249	244 - 720	447	425	250	221 - 708

Table 2 illustrates the univariate categorical analysis by exploring the frequencies of the study explanatory variables separately, within all participants of the cohort and then stratified by the clinic initiated and hospital initiated cohorts.

Eighty percent were initiated on the standard MDR TB regimen and 20% were initiated on other effective alternative regimens. Eighty four percent of the clinic initiated participants were administered with the standard MDR TB regimen, whereas 77% were initiated on standard treatment within the hospital setting.

Sixty three percent of the participants had a previous TB episode. The previous TB history was then further analysed by history of previous TB with a cured outcome, defaulted on previous TB treatment and previous TB treatment failed. The participants initiated in the clinic setting were more likely to have no history of previous TB treatment, with 45 % having no previous TB treatment compared to the hospital initiated participants at 30%. The clinic initiated participants were also more likely to have being cured of a previous TB episode at 32% compared to the hospital setting of 20%. However of note is that only 1% of the clinic initiated patients had a previous history of failed TB treatment, whereas 22% of the hospital initiated participants had a previous failed TB treatment history.

A total of 610 participants had their HIV status recorded, with 46% being HIV+; there was little difference between the clinic and hospital cohorts. According to the National Department of Health ART and MDR TB policy all TB patients who are HIV+ qualify for ART (Department of Health, 2013). However 11%, of this studies HIV+ participants were not placed on ART, there was no difference in ART provision rates between the clinic and hospital initiated cohorts.

Table 2: Univariate Categorical Analysis of MDR TB participants initiated on treatment in clinic and hospital settings (for additional univariate analysis refer to Appendix 6)

Variable n=644	**Description of variable**	**All participants n= 644**		**Clinic treatment initiated participants n= 323**		**Hospital treatment initiated participants n=321**	
		Frequencies	**95% CI**	**Frequencies**	**95% CI**	**Frequencies**	**95% CI**
Treatment within the Intensive phase of treatment n= 644	Standard Treatment Received n= 517	517 (80.28%)	76.95% - 83.24%	271 (83.90%)	79.33% - 87.64%	246 (76.64%)	71.54% - 81.08%
	Other Effective treatment received n=127	127 (19.72%)	16.76% - 23.05%	52 (16.10%)	12.36% - 20.67%	75 (23.36%)	18.92% - 28.46%
Treatment within the Continuation Phase treatment n= 399	Standard Treatment Received n=279	279 (69.92%)	65.12% -74.34%	162 (77.88%)	71.63% - 83.33%	117 (61.26%)	53.95% - 68.20%
	Other Effective treatment received n=120	120 (30.08%)	25.66% - 34.88%	46 (22.12%)	16.67% - 28.37%	74 (38.74%)	31.80% - 46.05%
Previous TB history n=637	No previous TB n= 233	233 (36.58%)	32.85% - 40.47%	140 (44.30%)	38.77% - 49.97%	93 (28.97%)	24.14% - 34.32%
	Previous TB n= 404	404 (63.42%)	59.53% - 67.15%	176 (55.70%)	50.03% - 61.23%	228 (71.03%)	65.68% - 75.86%
Outcome of previous TB history n=622	No TB history n=233	233 (36.58%)	32.85% - 40.47%	140 (45.09%)	40.23% - 51.67%	93 (29.34%)	24.45% - 34.74%
	Previous TB Cured n=161	161 (25.88%)	22.52% - 29.55%	99 (32.46%)	27.30% - 38.07%	62 (19.56%)	15.42% - 24.45%
	Treatment default n=104	104 (16.72%)	13.92% - 19.94%	44 (14.43%)	10.78% - 18.99%	60 (18.93%)	14.85% - 23.77%
	Treatment failed for TB n=49	49 (7.88%)	5.94% - 10.35%	18 (5.90%)	3.64% - 9.33%	31 (9.78%)	6.84% - 13.73%
	Treatment failed for DR TB n=75	75 (12.06%)	9.66% - 14.94%	4 (1.31%)	0.42% - 3.55%	71 (22.40%)	18.01% - 27.47%

Variable n=644	**Description of variable**	**All participants n= 644**		**Clinic treatment initiated participants n= 323**		**Hospital treatment initiated participants n=321**	
		Frequencies	**95% CI**	**Frequencies**	**95% CI**	**Frequencies**	**95% CI**
Further breakdown of the outcomes of previous TB n=622	Combination of no previous TB and previous TB cured	394 (63.34%)	59.40% - 67.12%	239 (78.36%)	73.23% - 82.76%	155 (48.90%)	43.28% - 54.54%
	Combination of previous TB treatment defaulted and treatment failures	228 (36.66%)	32.88% - 40.60%	66 (21.64%)	17.24% - 26.77%	162 (51.10%)	45.46% - 56.72%
HIV status of participants n= 610	HIV + participants n=278	278 (45.57%)	41.58% - 49.62%	136 (45.33%)	39.60% - 51.16%	142 (45.81%)	40.19% - 51.53%
HIV + Participant is treated with ART n= 278	Treated with ART n=247	247 (88.85%)	84.55% - 92.30%	121 (88.97%)	82.46% - 93.69%	126 (88.73%)	82.35% - 93.42%
	Not treated with ART n=31	31 (11.15%)	7.70% - 15.45%	15 (11.03%)	6.31% - 17.54%	16 (11.27%)	6.58% - 17.65%
Gender of participants n=644	The number of female participants n= 270	270 (41.93%)	38.10% - 45.85%	125 (38.70%)	33.40% - 44.27%	145 (45.17%)	39.66% - 50.80%
	The number of male participants n=374	374 (58.07%)	54.15% - 61.90%	198 (61.30%)	55.73% - 66.60%	176 (54.83%)	49.20% - 60.34%

Table 3 shows the univariate categorical analysis of the frequencies of the 5 main treatment outcomes of the entire cohort as well as stratified by clinic initiated and hospital initiated cohorts. Successfully treated is a combination of the 2 outcomes of treatment cured (a cure was proven within the expected timeframe) and treatment completed (patient completed treatment, but did not meet cured definition due to lack of bacteriologic results), which were combined into the category of "successfully treated" indicating the total numbers considered to be cured of MDR TB and consolidating the outcomes into 4 categories instead of 5.

Participants initiated on treatment within the clinic setting appeared to have had better outcomes with regards to successful treatment at 41%, compared to the hospital initiations at 31%. Similarly clinic initiated participants were less likely to fail treatment than hospital initiated participants (6.6% versus 12.5%). However death and default rates were similar amongst clinic initiated participants and hospital initiated participants.

Table 3: Univariate Categorical Analysis of the main treatment outcomes of MDR TB participants initiated on treatment in clinics and hospitals

Variable n=644	**Description of variable**	**All participants n= 644**		**Clinic treatment initiated participants n= 323**		**Hospital treatment initiated participants n=321**	
		Frequencies	**95% CI**	**Frequencies**	**95% CI**	**Frequencies**	**95% CI**
Researcher assessed final treatment outcomes n=568	Cured n= 178	178 (31.34%)	27.57% - 35.36%	98 (36.16%)	30.44% - 42.19%	80 (26.94%)	21.97% - 32.36%
	Treatment Completed n=23	23 (4.05%)	2.64% - 6.11%	12 (4.43%)	2.31% - 7.61%	11 (3.70%)	1.86% - 6.53%
	Successfully treated: Treatment outcome of cured and treatment completed at the end of treatment n=201	201 (35.39%)	31.48% - 39.50%	110 (40.59%)	34.69% - 46.70%	91 (30.64%)	25.45% - 36.23%
	Defaulted n=228	228 (40.14%)	36.10% - 44.31%	106 (39.11%)	33.27% - 45.20%	122 (41.08%)	35.43% - 46.91%
	Treatment failure n=55	55 (9.68%)	7.44% - 12.49%	18 (6.64%)	3.98% - 10.29%	37 (12.46%)	8.93% - 16.76%
	Death n=84	84 (14.79%)	12.03% - 18.04%	37 (13.65%)	9.80% - 18.32%	47 (15.82%)	11.87% - 20.48%

5.3 Bivariate and Multivariate analysis

The bivariate results comparing the exposures measured to the outcomes of successful treated, failed, died and defaulted were computed and then the variables that were found to be statistically significantly associated with one or more of these outcomes on bivariate analysis were included in the multivariate analysis. Table 4 illustrates the absolute and relative differences between the clinic initiated participants compared to the hospital initiated participants, with regards to the consolidated 4 main outcomes. Also shown are the outcomes absolute and relative differences comparing HIV+ participants initiated on ART, to HIV+ participants not provide with ART. The cumulative incidence ratio was used to determine the potential causality of the variable and the cumulative incidence difference to identify the absolute effect of the exposure variables on the outcomes.

Table 4: The Cumulative Incidence Ratio and Cumulative Incidence Difference of various treatment outcomes

Variable	**Successfully treated**		**Failed**		**Died**		**Defaulted**	
	Cumulative Incidence Ratio	**95% CI**	**Cumulative Incidence Ratio**	**95% CI**	**Cumulative Incidence Ratio**	**95% CI**	**Cumulative Incidence Ratio**	**95% CI**
Clinic treatment initiated vs hospital initiated	1.32	1.06 - 1.66	0.53	0.31 - 0.91	0.86	0.58 - 1.28	0.95	0.78 - 1.16
HIV+ participant on ART vs HIV+ participant not on ART	3.28	1.12 - 9.63	1.35	0.34 - 5.39	0.34	0.19 - 0.61	0.92	0.57 - 1.48
Variable	**Successfully treated**		**Failed**		**Died**		**Defaulted**	
	Cumulative Incidence Difference	**95% CI**	**Cumulative Incidence Difference**	**95% CI**	**Cumulative Incidence Difference**	**95% CI**	**Cumulative Incidence Difference**	**95% CI**
Clinic treatment initiated vs hospital initiated	9.95	2.10 – (+ 17.80)	-5.82	-10.60 - (-1.03)	-2.17	-8.00 - (+3.65)	-1.96	-10.03 – (+6.10)
HIV+ participant on ART vs HIV+ participant not on ART	26.30	12.46 – (+ 40.14)	2.67	- 8.33 - (+13.67)	-25.40	-44.62 - (-6.18)	-3.57	-23.61 – (+16.47)

The findings in table 4 indicates that clinic initiated participants were 1.3 times more likely to be successfully treated compared to hospital initiated participants, and this was statistically significant (95% CI: 1.06-1.66). The clinic initiated participants were also 0.53 times less likely to have failed treatment and again this was statistically significant at (95% CI: 0.31-0.91). On cumulative incidence difference 10% more of the clinic initiated participants were successfully treated compared to the hospital initiated participants, which was statistically significant (95% CI: 2.10-17.80).

The HIV+ participants treated with ART were 3.3 times more likely to be successfully treated compared to the HIV+ participants not provided with ART, which was statistically significant (95% CI: 1.12- 9.63). The HIV + participants on ART were also 0.3 times less likely to have died (95% CI: 0.19-0.61). The absolute effect showed that 26% more of the HIV+ participants placed on ART were successfully treated compared to the HIV+ participant not treated with ART, which was statistically significant (95% CI: 12.46-40.14) and similarly for death with, 25% less likely to have died [95% CI: -44.62 - (-6.18)].

Table 5 shows the results of the bivariate analysis of the cumulative incidence ratios of the 4 main outcomes comparing various exposure variables. Age was also analysed via linear regression analysis, and found not to have any association with any of the outcomes, with the regression coefficients as follows: 'successfully treated' $r^2 = 0.00$; 'failed' $r^2 = 0.00$; 'died' $r^2 = 0.03$; 'defaulted; $r^2 = 0.02$. Age was further analysed as both a continuous variable and a categorical variable (18-34 years of age, compared to >35 years of age).

Similarly the 'time to treatment initiation' on linear regression analysis showed no association with any of the treatment outcomes, with a regression coefficient of $r^2 = 0.00$ for each of the outcomes. Time to treatment initiation was then also analysed as both a continuous variable and a categorical variable in logistic regression analysis comparing ≤14 days to treatment initiation versus > 15 days.

Table 6 shows the results of the variables which were statistically significant on bivariate analysis and the main exposure variables (hospital and clinic initiated treatment), after being analysed via multivariate logistic regression analysis, using a forward stepwise regression approach, with the final model shown. Earlier iterations of the multivariate logistic regression modelling are shown in the appendices (Refer to appendix 7).

Table 5: Bivariate Analysis of MDR TB participant Treatment Outcomes i.e. Successful treated, Failed treatment, Died and Defaulted treatment comparing various exposure variables

Variable	Successfully treated		Failed		Died		Defaulted	
	Cumulative Incidence Ratio	**95% CI**	**Cumulative Incidence Ratio**	**95% CI**	**Cumulative Incidence Ratio**	**95% CI**	**Cumulative Incidence Ratio**	**95% CI**
Clinic treatment initiated vs hospital initiated	1.32	1.06 - 1.66	0.53	0.31 - 0.91	0.86	0.58 - 1.28	0.95	0.78 - 1.16
Treatment within the Intensive phase of treatment Participant received standard treatment or Participant received other effective treatment	1.96	1.34 - 2.88	0.82	0.46 -1.48	0.46	0.31 - 0.68	0.93	0.73 - 1.18
Treatment within the Continuation Phase treatment Participant received standard treatment or Participant received other effective treatment	1.32	1.05-1.66	0.34	0.13 - 0.90	0.98	0.44 - 2.21	0.78	0.59 - 1.04
No TB history recorded vs previous TB history recorded	1.15	0.92 - 1.44	0.46	0.24 - 0.84	1.03	0.68 - 1.56	1.03	0.84 - 1.27
Previous TB cured vs previous TB Defaulted and failed TB	1.38	1.10 - 1.74	0.50	0.24 - 1.02	0.60	0.35 - 1.04	1.00	0.79 - 1.26
No previous TB and previous TB cured participants vs previous failed and defaulted TB	1.56	1.20 - 2.03	0.32	0.19 - 0.55	0.73	0.48 - 1.09	1.04	0.84 - 1.29

Variable	Successfully treated		Failed		Died		Defaulted	
	Cumulative Incidence Ratio	**95% CI**	**Cumulative Incidence Ratio**	**95% CI**	**Cumulative Incidence Ratio**	**95% CI**	**Cumulative Incidence Ratio**	**95% CI**
HIV positive status of participants vs HIV negative status participants	0.98	0.78 - 1.23	1.07	0.64 - 1.78	1.19	0.79 - 1.80	0.94	0.77 - 1.16
HIV + Participant is treated with ART vs HIV+ with no ART	3.28	1.12 - 9.63	1.35	0.34 - 5.39	0.34	0.19 - 0.61	0.92	0.57 - 1.48
HIV+ participant on ART vs not on ART and HIV- participants n=610	1.12	0.89 - 1.40	1.11	0.66 - 1.86	0.86	0.56 - 1.31	0.93	0.75 - 1.15
HIV+ participant on ART vs HIV- participant n=579	1.06	0.84 - 1.33	1.10	0.65 - 1.85	0.99	0.63 - 1.55	0.93	0.75 - 1.15
Year of enrolment 2012 vs 2010 of the participant	1.73	1.27 - 2.37	0.38	0.23 - 0.62	1.44	0.87 - 2.37	0.78	0.63 - 0.95
The 2012 hospital initiations vs 2010 hospital initiations n=321	1.68	1.18 - 2.39	0.389	0.19 - 0.77	1.845	1.07 - 3.21	0.70	0.53 - 0.93
Female participants vs male participants	1.29	1.03 - 1.60	0.94	0.56 - 1.57	0.87	0.58 - 1.30	0.85	0.69 - 1.05
Participant lives in rural areas vs Participant lives in urban areas	1.33	1.07 - 1.66	0.42	0.23 - 0.75	1.41	0.95 - 2.09	0.82	0.67 - 1.01
Ages of participants*	1.00	0.99 - 1.02	0.98	0.96 - 1.01	0.96	0.94 - 0.98	1.03	1.01 - 1.04
Ages 18-34 vs Age >35	1.02	0.81 - 1.27	0.66	0.39 - 1.10	0.70	0.47 - 1.05	1.24	1.01 - 1.52

Variable	Successfully treated		Failed		Died		Defaulted	
	Cumulative Incidence Ratio	**95% CI**	**Cumulative Incidence Ratio**	**95% CI**	**Cumulative Incidence Ratio**	**95% CI**	**Cumulative Incidence Ratio**	**95% CI**
Days to treatment initiation*	1.00	1.00 - 1.01	1.00	0.99 - 1.01	1.00	0.99 - 1.00	1.00	0.99 - 1.00
Time to treatment initiation in < = 14 days vs time to treatment initiation > 15 days	0.98	0.75 - 1.29	1.086	0.60 - 1.96	1.20	0.69 - 1.74	0.96	0.75 - 1.23

*Age and Time to Treatment initiation were analysed as numerical variables via logistic regression.

Table 6: Multivariate logistic regression analysis showing the final stepwise forward regression model comparing the main exposure variable (hospital and clinic initiated treatment) and other variables which were significant on bivariate analysis, with the 4 main treatment outcomes.

Model 6: Variable	Successfully treated		Failed		Died		Defaulted	
	Adjusted Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI
Clinic treatment initiated vs hospital initiated	1.05	0.57 - 1.96	1.25	0.44 - 3.61	0.63	0.27 - 1.45	1.16	0.64 - 2.10
Participant received standard treatment vs Participant received other effective treatment	1.94	0.94 - 4.02	0.51	0.19 - 1.36	0.75	0.32 - 1.75	0.87	0.46 - 1.63
Participant lives in the rural areas vs the urban areas	0.98	0.54 - 1.79	0.51	0.18 -1.44	2.58	1.20 - 5.55	0.75	0.43 - 1.33
No TB and previous TB cured participants vs failed and defaulted participants	2.87	1.48 - 5.56	0.12	0.04 - 0.38	0.70	0.31 - 1.57	1.06	0.59- 1.94
Female participants vs Males participants	1.70	0.95 - 3.05	0.88	0.35 - 2.18	1.19	0.56- 2.55	0.60	0.35- 1.03
HIV+ on ART vs HIV+ not on ART	6.63	1.48 - 29.84	1.30	0.26 - 6.55	0.20	0.08 - 0.53	0.96	0.39 - 2.33
Ages of participants	1.00	0.97 - 1.03	0.98	0.93 - 1.03	0.96	0.92 - 1.00	1.04	1.00 - 1.07

Clinic initiated treatment although having a statistically significant difference on bivariate analysis (tables 4 and 5) for the outcomes of cured and failed treatment, did not retain this statistically significant difference on multivariate analysis.

Those participants placed on the standard treatment regimen were 1.9 times more likely to be cured on bivariate analysis, which was statistically significant (95% CI: 1.3 -2.9), however on multivariate analysis there was no statistically significant difference.

Similarly on bivariate analysis participants living in the rural areas were 1.3 times more likely to be successfully treated, compared to the urban participants, and 0.4 times less likely to have failed treatment, but this was not statistically significant on multivariate analysis. However, participants living in the rural districts were 2.6 times more likely to die compared to participants living in the urban district and this was statistically significant (95% CI: 1.2 - 5.6) on multivariate analysis.

Those with no previous TB or had previous TB but it was cured, were compared to participants with previous TB but who had defaulted on their treatment, and their treatment had failed, were found to be 1.6 times more likely to have been significantly successfully treated, (95% CI: 1.2 - 2.0), as well as 0.3 times less likely to have failed treatment (95% CI: 0.2 - 0.5), the multivariate analysis indicates that participants with no TB and a cured previous TB as compared to defaulted and failed TB treatment, were 2.9 times more likely to have had been successfully treated, at a statistical significance of (95% CI: 1.5 - 5.6). These participants were also 0.1 times less likely to have failed treatment with a statistical significance of (95% CI: 0.0- 0.4).

HIV+ participants on ART were 6.6 times more likely to be successfully treated compared to HIV+ participants not on ART, which was statistically significant even though the range was broad (95% CI: 1.5 - 29.8), and they were also 0.2 times less likely to die, which again was statistically significant at (95% CI: 0.1 - 0.5).

Gender and age had no statistically significant effect on the treatment outcomes in the multivariate analysis.

Chapter 6: Discussion and Limitations

6.1. Discussion

The discussion section commences with commentary on the appropriateness of the medication supplied to MDR TB patients at clinics and hospitals, since whether patients were being provided with appropriate medication, especially at the clinics, was uncertain, and a serious concern of the MDR TB programme managers. Commentary on the incidence rates of the 4 main study outcomes follows on from this. The discussion then focusses on the main thrust of the study which is the comparison of the 4 main outcomes of participants managed via clinic initiated versus hospital initiated treatment. Thereafter other variables that could influence the treatment outcomes were deliberated on, commencing with those that were found to be statistically significantly associated with any of the 4 treatment outcomes investigated, followed by the variables that were found to not have an association with the treatment outcomes.

6.1.1 Appropriate vs. inappropriate medication regimen for clinic and hospital initiated participants

The findings of this study indicated that 100% of the participants, in the univariate analysis, either received the standard MDR TB regimen or an alternative effective regimen, amongst both the clinic and hospital initiated participants. This finding hence negated the fear that incorrect and hence inappropriate treatment would be given to participants by less experienced and non-specialist staff in clinics and importantly establishes that it is safe to decentralize MDR TB care to clinics, as staff at these clinics are indeed following the prescribed treatment protocol.

A further implication of this 100% appropriate and correct treatment provision, is that the logistics and supply of medication to clinics seems also to be very

resilient, thus further re-assuring managers that patients initiated on MDR TB treatment in the peripheral clinics throughout the province will receive the correct medication irrespective of the clinic location and associated logistical challenges with medication supply.

A further inference is that the MDR TB guidelines are being studiously adhered to by doctors and nurses working in the clinics. This finding is surprising as adherence to clinical guidelines and standardized treatment protocols is notoriously low amongst health staff (Kirkman, Williams, Caffrey, Marrero, 2002). Prompting the question, why is this so unique? One could probably reasonably conclude that this phenomenon is due to the lack of experience amongst clinic staff with treating MDR TB cases, prompting them to place greater reliance on the treatment guidelines, as their inexperience would inhibit any personal preference deviance in management of patients (Ershova, Podewils, Bronner, Stockwell, Dlamini and Mametja, 2014).

The opposite would usually apply in most other scenarios where clinical guidelines and standardized treatment protocols are provided to clinicians as they would usually be familiar with managing the conditions referred to in the guidelines and would have amassed a degree of experience and would already have developed certain personal preferences in their approach to the medical conditions which the guidelines/protocols refer to MDR TB being a relatively new phenomenon and having almost entirely been managed by sub-specialist physicians, is then an unusual scenario and hence the usual pattern of adherence to guidelines/protocols does not pertain (Ghebrehiwet, 2009; Kirkman, Williams, Caffrey, Marrero, 2002).

The presumption that the novelty of MDR TB treatment is the defining factor in explaining the 100% adherence to treatment guidelines is however undermined

by high adherence rates to DS TB guidelines, noting that many clinicians would be familiar with managing DS TB patients. In a South African study undertaken for the National TB programme, by Ershova, Podewils, Bronner, Stockwell, Dlamini and Mametja (2014) to evaluate adherence to national TB management guidelines for DS TB in three provinces, the authors reported that the majority of the DS TB patients received appropriate treatment, with 96% of new TB cases and 91% of retreatment TB cases receiving the recommended therapy according to the national TB guidelines. This finding both aligns to and makes the interpretation of the finding in our study more complex. It suggests that besides MDR TB being a novel condition, the very strict regimentation of the management of TB patients over many years would be a partial and complementary explanation of the 100% adherence to the MDR TB guidelines.

The 100% appropriateness of MDR TB medication received in both the clinic and hospital initiated participants, conveniently and advantageously provided a perfect setting in which to assess the effect of clinic and hospital initiated treatment, as the potential confounder or effect modifier of 'appropriate/correct treatment provision', was not operable, hence allowing the effect of the type of facility (and staff) providing the treatment to be more validly assessed.

6.1.2 Treatment outcomes incidence

A successfully treated outcome is an indication of the effectiveness of the MDR TB programme in curtailing this condition. In the univariate analysis, the percentage successfully treated, was 35% for both cohorts combined, with 41% for clinic initiated and 31% for hospital initiated participants, suggesting that the clinic initiated participants appeared to have a slightly better treatment outcome. When reviewing the global statistics, a systematic review of 35 studies conducted in 22 countries, by Bassili et al. (2013) concluded that the pooled treatment success rate for MDR TB was 66% (95% CI 61–71), with no statistical

difference between ambulatory (66%; 95% CI 55–75) and hospital-based models (67%; 95% CI 61–72). Of the 4 studies by South Africa included in this review, the overall treatment success rate was 56%. In another systematic review by Johnston et al. (2009) where 36 articles were reviewed presented with a 62% success rate (95% CI 57-67), the lowest result was from an Italian study, which was 39%, the pooled treatment success for the South African outcomes in this review was 44%,which is still higher than the findings of our study of 35%. Nardell & Dharmadhhikari (2010:1233) states that "cure rates in the best MDR TB treatment programs average about 60%." The Western Cape Province thus presents with a considerably lower success rate especially when comparing it to the global data, and even with the overall South African MDR TB treatment success rate.

When assessing the overall trend of MDR TB treatment outcomes in the 36 months report in the Western Cape Province (refer to Graph 1), (EDRWeb, 2016), The trend suggests that the treatment success has improved from 2008-2013 (from 17% - 42%), denoting that the health system is responding to this low treatment outcome, with a steady improvement noted, although it is unclear whether this is a real improvement or simply an artefact caused by a decrease in the proportion of patients who were classified as "not evaluated".

Hughes & Osman (2014) in their study in Khayelitsha equated the poor MDR TB outcomes (<45% of MDR TB cases reported as treatment success) to defaulting and side effects and recommended that there be reliable access to newer, more effective drugs with shorter more tolerable regimens needed to improve the chances of curing MDR TB patients.

The proportion that defaulted treatment within our study was high for both cohorts (47% clinic initiated and 54% for hospital initiated), with the overall defaulter rate at 40%, which is significantly higher than the global findings, as

reviewed by Bassili et al. (2013), where the pooled defaulter rate was 14%. Similarly in the systematic review by Johnston et al. (2009) the combined defaulter rate was 13% with the defaulter rate for South Africa representing 29%, the second highest in the review, highlighting that the Western Cape Province appears to have a significantly higher defaulter rate, even in comparison to the rest of the country. The adherence to treatment of MDR TB patients is often associated with the long duration of treatment which is about 18-24 months, as well as the drugs offered to patients which have high toxicity levels and hence severe side effects are experienced by them, contributing to their defaulting on treatment.

Social factors also plays a pivotal role in the adherence of patients to MDR TB treatment as reinforced by Shina, Furin, Bayona, Mate, Yong Kim, and Farmer (2004: 1530) who report that many of the factors that determine TB treatment outcome are not biological but rather socioeconomic and psychosocial, and that ‘‘Effective community-based TB control requires comprehensive initiatives that need to incorporate efforts to address the root causes of disease, notably poverty and its resultant ills’’. Poverty is a large risk factor for TB related non-adherence to treatment and mortality. Malnutrition, inability to work and social isolation all stem from the synergistic forces of TB and poverty. While poor to begin with, many patients who develop MDR TB become too sick to work and are often additionally burdened by the costs of medical attention.

Our study findings for the participants who failed treatment, within the hospital initiated cohort was 12%, compared to the clinic initiated participants at 7%, even though the ‘very sick’ were excluded from the study, this finding could reflect that the ‘sicker’ patients were hospital initiated preferentially, rather than initiated on treatment at the clinic. This finding is aligned to global statistics where the pooled treatment failure rate was 10% (7.3–12.4) (Bassili et al., 2013)

The univariate analysis for the participants who died within our study, showed that the hospital initiated cohort mortality was 16%, compared to the clinic initiated participants at 14%. This finding is aligned to the global statistics where the pooled death rate was 15% (Bassili et al., 2013) and 11% (Johnston et al., 2009).

6.1.3 Clinic initiated versus Hospital initiated treatment outcomes

The cumulative incidence ratio on bivariate analysis indicated that participants placed on clinic initiated treatment were 1.3 times more likely to have a successfully treated outcome, and 0.5 times less likely to fail treatment, which amounted to an absolute increase of 10% in the successfully treated proportion and an absolute reduction of 6% in those that failed treatment. However, on multivariate analysis, no association was seen with either of these outcomes, indicating that the bivariate effect was confounded by other variables. The 'died' and 'defaulted' treatment outcomes showed no association with the format of treatment.

These findings hence suggest that there is no difference in treatment outcome between the hospital and clinic initiated participants, indicating that clinic initiated treatment is as effective as hospital initiated treatment and hence it is safe to continue with and indeed expand on this decentralized clinic mode of MDR TB treatment within the province. A similar finding was reported by Bassili et al. (2013), where the MDR TB treatment outcomes in the hospital versus clinic setting showed no differences. This current study therefore adds to the available evidence supporting the World Health Organization's recommendation that patients be treated using mainly ambulatory care, conditional on adequate infection control measures in the home and clinic, the clinical condition of the patient, the availability of treatment support to facilitate adherence to treatment, and provisions for backup facilities to manage patients

who need inpatient treatment care (WHO, 2013). All of these are readily available within the Western Cape Province.

This finding also aligns to the South African National Department of Health's 'decentralized and deinstitutionalized management of MDR TB policy' and its recommendation to decentralize MDR TB services to clinics. The provision of decentralized clinic care for MDR TB patients also aligns very well with the Western Cape Province health care plan (Health Care 2030 Plan), of improving the 'patient centred experience', by making the services more accessible to the patients, which initiating care within the clinics should accomplish (Department of Health, 2013).

This result further suggests that with the effective treatment of MDR TB, the management and thus the initiation of treatment of stable Pre-XDR TB and XDR TB patients, could potentially also be expanded to the clinic. Since the guidelines regarding medication provision for MDR TB patients were 100% adhered to at both clinics and hospitals in this study, the assumption that the treatment guidelines for Pre-XDR TB and XDR TB will also be similarly adhered to at clinics is a reasonable one. According to an annual audit undertaken in the Western Cape Province, the management of all forms of TB at a clinic level (DS TB and MDR TB), is overseen by the same staff, within the same TB room, with the same resources, hence since the current MDR TB guidelines are well adhered to, the guidelines for Pre-XDR TB and XDR TB treatment should essentially also be well adhered to (HAST Audit Report, 2015). The assumption can thus then be made that if staff are provided with the appropriate training and guidelines, then clinics will be able to manage stable Pre-XDR and XDR TB patients effectively (Department of Health, 2015) .

Another benefit of decentralizing the stable Pre-XDR and XDR TB cases in addition to the MDR TB patients is related to the cost implications to the health

system, as discussed by, Pooran, Pieterson, Davids, Theron and Dheda (2013:1) in their South African study related to the budgetary implications of not responding appropriately to the DR TB challenge. The authors state that,

> "Assuming proper adherence to National DR TB management guidelines, the current per patient cost of XDR-TB is ZAR303 508 (USD26 392), four times greater than that of MDR-TB at ZAR77 878 (USD6 772). A decentralised XDRTB treatment programme could potentially reduce costs by ZAR79 695 (USD6 930) (26%) per case and reduce the total amount spent on DR-TB by 7%."

Decentralizing stable Pre-XDR TB and XDR TB patients, should however be implemented with caution due to the potentially increased risk of the spread of infection within the community, when ambulatory care is used. This however is not an absolute concern as the literature shows that most of the community spread of TB happens prior to the initiation of treatment. Heller et al. (2010:420) in their study in KwaZulu-Natal reiterates that it is "likely that most patients have been infectious for several months before hospitalization, given the delays in diagnosis and treatment under routine programme conditions."

6.1.4 Time to treatment initiation

Nardell & Dharmadhhikari (2010) state that the most important way to control transmission of MDR TB in the institutions as well as the community is, prompt diagnosis and effective treatment. The actual time to treatment initiation of MDR TB, from the time of sputum collection to the start of treatment, was on median 29 days for the clinic initiated patients and 37 days for hospital initiated patients. This is very long for both cohorts, as the MDR TB guideline stipulates that initiation of treatment should occur within 5 days of sputum collection (Department of Health, 2011). This prolonged initiation of treatment also raises

concern about the spread of this disease within the community, due to the infectious nature of the patient. A study by Narasimooloo & Ross (2012) in KwaZulu-Natal, similarly reports that, delaying treatment for patients who are actively coughing perpetuates the spread of MDR TB.

Both the bivariate and multivariate analysis, found that there was no association between any of the 4 treatment outcomes and time to initiation of treatment. However, the time to treatment initiation is critical to prevent further spread of the disease. Participants took too long to be initiated on treatment and theoretically could have infected more people; however, this was not investigated in this study.

The GeneXpert machine was introduced to initiate patients more rapidly on treatment as it facilitates rapid diagnosis of MDR TB, however, as per the literature, time to treatment initiation is governed by many other factors, such as health systems, logistics of treatment provision and socio-economic factors, all of which significantly impact on the participant's treatment being initiated. Hence the current existing systems within the clinics and hospitals need to be strengthened to support this process. This is supported by Dlamini-Mvelase, Werner, Phili, Cele and Mlisana (2014), who conducted a retrospective cohort study between 2011-2012 at a hospital in KwaZulu- Natal, and concluded that despite the rapidity of the GeneXpert provision of diagnostic results, only about 70% of patients were initiated on treatment within a month, and they further emphasized the need to improve the health systems in order to prevent these delays.

A study undertaken in the Western Cape Province by, Naidoo et al. (2014) reiterated that the health systems and patient factors are the main contributors to the delays in treatment initiation. This study also discussed that on the extended

Cox analysis there were no variation in treatment initiation times on any other strata such as: gender, age, HIV status, MDR TB risk profile and treatment initiation site

Added to late initiation is not finding cases early enough, which also increases the spread of infection. Nardell & Dharmadhhikari (2010:1233) states that "it is estimated that less than 10% of the estimated number of MDR TB cases worldwide are being treated, and as many as half of MDR TB cases occur in previously untreated cases, indicating transmission"

6.1.5 MDR TB and HIV

Ninety-five percent of our study participants had their HIV status recorded. Of the 610 participants that had their HIV status recorded, 46% were HIV+ supporting the vast literature on co-infection of TB and HIV as well as the need to continue with and strengthen the integration of TB and HIV services. Wells et al. (2007: 87) also reported that HIV infection is the strongest risk factor for the development of TB whether drug sensitive or drug resistant. They found, in a high burdened HIV rural community in KwaZulu-Natal, that 41% of MDR TB cases were HIV+. This finding is similar to our study findings of 46% of MDR TB patients being HIV+. However, a later study in KwaZulu-Natal assessing 1549 patients in centralized versus decentralized settings between 2008 and 2010; found that the rate of co-infection was even higher at both the clinic (76%) and the hospital (73%) (Loveday et al., 2015). Wells et al. (2007) further emphasized the need for governments to provide additional staff and budgets to adequately address TB/HIV integration.

Another study in KwaZulu- Natal documenting treatment outcomes for 1209 patients found that 52% of the patients were HIV+ (Brust et al., 2010). Lessels,

Swaminathan & Godfrey-Faussett (2015:439) states that "in 2013, only 48% of TB cases globally had a documented HIV test result". Another study in the Western Cape Province, inclusive of 70 clinics conducted from 2010-2014, found that 98% of patients had their HIV status recorded and 47% were HIV+ (Kaplan et al., 2016). It hence appears that South Africa is performing better than most countries on testing for HIV and this could be in response to the HIV epidemic within this country, and also due to the high burden of TB/HIV co-infection.

In our study, there were a similar proportion of HIV+ participants in both clinic and hospital initiated participants at roughly just below 50%, hence indicative of a balanced spread in both cohorts, and that HIV testing practices are adopted in both these settings. The HIV+ status of the participants compared to the HIV-status of the participant on bivariate analysis i showed no association with any of the treatment outcomes.

6.1.6 MDR TB and ART

In the univariate analysis, the proportion of HIV+ participants treated with ART was 89% for both cohorts, again, emphasizing that there is not much of a difference between the management practices between these two cohorts. Loveday et al. (2015) also showed that a high percentage of HIV+ patients were offered ART, however it was slightly better within the clinic setting (91%) as compared to the hospital (82%). The WHO (2011) guidelines recommend prompt initiation of ART for all HIV and TB co-infected patients, irrespective of their CD4 cell count. This was also adopted by the South African National ART guidelines, where the criteria for providing ART was amended to include all TB patients that are HIV+ (Department of Health, 2013).

The provision of ART is known to improve outcomes in drug DS TB, however, there is limited literature assessing the impact of ART on MDR TB treatment outcomes (Moyo et al., 2014). One of the few studies available was a case control study undertaken in one of the rural TB hospitals in the Western Cape Province, to determine if ART influences MDR TB treatment outcomes. It found that in the 363 participants selected between the 2004 - 2006 period, the group of HIV+ patients who received ART had a similar cure rate to the group of HIV+ patients who did not receive ART, with cure rates of 35% and 34% respectively. They also found that the provision of ART had no significant effect on the death rates (Mugabo, Adewumi, Theron, Burger and Van Zyl, 2015). However, treatment of both MDR TB and HIV has evolved and improved since then, and the Western Cape Province in particular has had many systems and policy changes within the TB and HIV programmes since then.

The cumulative incidence ratio of our study indicates that HIV+ participants on ART are 3 times more likely to have a successful treatment outcome and are 0.3 times less likely to die, however there was no significance with defaulted treatment or failed treatment. The findings of the absolute effect indicate that 26% more HIV+ participants on ART are successfully treated compared to HIV+ participants not on ART and 25 % of HIV+ participants on ART were less likely to die.

On multivariate analysis these associations strengthened to 7 times more likely to have a successfully treated outcome and 0.2 times less likely to die, thus emphasizing the importance of offering ART to MDR TB patients given its huge effect on successfully treating and reducing deaths in MDR TB. These findings provide clear evidence supporting the South African ART guideline that declares that all patients who are HIV+ and have TB should be offered ART. This co-treatment should be greatly encouraged given the strong effect of ART on MDR

TB treatment. Due to the significant findings of this study, it will hence be seen as both poor clinical practice, as well as non-adhering to guidelines if ART is not offered to MDR TB patients who are HIV+. The study by Loveday et al., (2015) also concluded that HIV+ patients not on ART were at an increased risk of mortality (HR 1.77).

Also of note is that participants who were HIV+ and on ART had the same treatment outcomes as those participants who were HIV-, which suggests that provision of ART renders an HIV + person with MDR TB similar to an HIV- person. A similar finding was found by Moyo et al. (2014) who did a retrospective cohort study between 2008 - 2011, in Khayelitsha, Western Cape Province, of 839 cases diagnosed with MDR TB, and found that cases who were HIV+ and receiving ART, achieved a similar treatment success rate as those who were HIV-, at 48% and 47%, respectively.

6.1.7 MDR TB and Previous TB history

Ninety-nine percent of the participants in our study had data recorded in the register on whether they had TB before or not, with 37% having no previous history of TB, but with 44% amongst clinic initiated participants and 29% amongst hospital initiated participants, hence indicating that the hospital appeared to manage more of the participants with a previous bout of TB. When further analysing this indicator, it was found that 56% of clinic initiated participants had a previous history of TB while 71% of hospital initiated participants had TB previously. This disproportionate treatment of those with previous TB at hospitals could be due to the assumption that patients with previous TB are perhaps the more complicated patients and are hence more predisposed to being managed within a hospital.

On bivariate analysis, those who previously had TB but were cured were 1.6 times more likely to be successfully treated and 0.5 times less likely to fail treatment, compared to those who previously had TB but defaulted on their treatment or whose treatment failed. However, when combining those with no previous TB and those with previous TB cured, the participants were 2 times more likely to have a successful treatment outcome and were also 0.3 times less likely to fail treatment compared to those with previous TB who had defaulted on or failed treatment.

The multivariate analysis, showed that no previous TB and previous TB cured participants were 3 times more likely to be successfully treated and were 0.1 times less likely to fail treatment than those with previous TB who had defaulted on or failed treatment. The previous treatment of TB is an immediate upstream factor and indicative of the need to strengthen the existing TB control programme, as well as the current TB prevention strategies, as this variable suggests that if previous TB is prevented or cured, there is a great chance that the pool of MDR TB can be reduced. This is thus aligned to the literature with a high percentage of patients that develop MDR TB having had a previous history of receiving TB treatment.

A retrospective case control study conducted in Estonia, between 2003-2005, by Kliiman and Altraja, (2009) reported that of the 235 patients with MDR TB, those who were not previously treated for TB compared to those previously treated for TB had higher successfully treated outcomes (71% and 47% respectively). This study concluded that previous TB is a strong risk factor for MDR TB and it significantly increases the risk of poor treatment outcomes. The study does not define ‘previous TB’ and is thus inclusive of all categories of: previously cured TB, defaulted previous TB and failed previous TB, whereas in our study the previous TB history was stratified and further analyzed. There

were however limited studies discussing these categories and its association with MDR TB treatment outcomes.

Also of significant interest in our study, 37% of the MDR TB participants had no previous TB history, this hence emphasizes that primary MDR TB (first episode of MDR TB, i.e. has not had any previous TB treatment) is particularly high and therefore community transmission of MDR TB is a real concern. A further stratification on the univariate analysis indicated that 32% of the clinic initiated participants were cured from a previous TB history as compared to the 20% hospital initiated participants, also there were only 7% of the previous TB failed participants initiated in the clinic, whereas in the hospital initiated participants there was a much greater proportion of 32%. This could be that although the participants were not seriously ill, due to them having failed a previous TB episode they were more likely to be initiated within the hospital. This particular variable was therefore a key confounder in the bivariate analysis that found an association between clinic initiated and hospital initiated participants on successful treatment and failed treatment, as it resulted in varying selection into these cohorts based on their history of previous TB.

6.1.8 MDR TB: Rural Districts vs. Urban District

Another variable which was statistically significant was the participants living in the rural districts compared to the urban district. On bivariate analysis participants living in the rural districts were 1.3 times more likely to be successfully treated and were 0.4 times less likely to have failed treatment, compared to the urban district. It thus appears that although the urban district started with decentralization quicker and the assumption is that they are also better resourced in terms of budget, facilities and staff, the rural districts appears to be having better outcomes. It should however, be noted that the burden of MDR TB is much higher within the urban district, so perhaps due to their

smaller numbers the rural districts are better able to control and manage MDR TB. This is supported by Lonnroth, Jaramilo, Williams, Dye and Raviglone (2009), who state that the tendency for the burden of TB to be higher in the urban areas, may be due to the higher population density, crowded living and working conditions, as well as the lifestyle changes associated with urban living.

In the multivariate analysis, the significant associations shown in the bivariate analysis were confounded, and thus the only significant treatment outcome in this analysis, were that the participants living in the rural districts were about 3 times more likely to die, as compared to the urban district. This could possibly be attributed to numerous logistical and systems related factors that are often unique to the rural context, such as seasonal workers, migration, accessibility to the clinics and hospitals, and the length of travel to these settings. The only study with a similar finding was a retrospective cohort study done between 2011 and 2012 in Nigeria where the authors, (Alobu, Oshi, Oshi, Ukwaja, 2014:982) found that patients residing in the rural areas had a higher risk of death (crude OR 1.5). The study then explained that the "health system in high burden countries into which TB control is fully integrated suffers from lack of human resources and limited outreach services for the rural population." This study also similarly suggested that the socio-economic circumstances of the rural population may be a hindrance to accessing health services, and then recommended that more studies be conducted to evaluate the higher risk of death amongst rural residents.

Hence more literature is required to fully support this finding; however, it does appear that the social factors unique to the rural districts contributed to this finding.

6.1.9 MDR TB and age of participants

The median age of the participants of this study was 34 years of age. This was commonly found in most literature perused, that MDR TB appears to be prevalent in the adult above 30 years of age. The median age in another study was 33 years (Brust et al., 2010). A study by Johnston et al. (2009) in their analysis of 30 studies, the mean age was 40 years. Authors (Goble et al., 1995) in their study of 171 patients in the United States of America reported a median age of 46 years. The finding of our study is thus consistent with the literature, and the assumption is that the patients develop DR TB in their thirties.

The findings from a study in the Western Cape Province, by Nyabadza & Winkler (2013), who did a simulation age specific for TB of data between 2003-2009 and reported that after the age of 14, the incidence of DS TB increases considerably as age increases, then from 35 years onwards the incidence of DS TB decreases. This is hence indicative that due a previous DS TB episode that patients developed in their early twenties perhaps predisposes these patients to develop MDR TB in their thirties.

The age of the participants in the bivariate analysis indicated that the younger participant was 0.9 times less likely to die and 1.03 times more likely to default treatment as compared to the older participants, this was further stratified into an 18-34 year category and a ≥35 year category and the only significant treatment outcome was that the younger category participants (18-35 years) were more likely to default treatment. However, to further analyze this variable, linear regression was done and there was no association with any of the treatment outcomes. On the multivariate analysis, a similar finding was found. The age of the participants was hence did not have any consistent significant effect on any of the treatment outcomes.

In other studies, however age did have significant results, according to (Moyo et al. 2015) who found that age category 15-25 years had a greater hazard to default treatment, HR 2.43 (95% CI 1.52-3.88) and older age (>35 years) was associated with a greater hazard of death; HR 3.74 (95% CI 1.13-12.37). This was also shown in the multivariate analysis by (Loveday et al. 2015) which had an increased mortality for patients > 30 years of age.

6.1.10 MDR TB and Gender of participants

On the bivariate analysis, the female participants were over 1 times more likely to have a successful treatment as compared to the males, however on the multivariate analysis; there was no significance with the main treatment outcomes. Most of the literature perused showed that being a male was a factor associated with poor treatment outcomes i.e. defaulted and failed treatment, however this was not found in this study.

Johnston et al. (2009) found that the male gender was less likely at 0.61 (0.46-0.82) to have a successful treatment outcome. Another study undertaken in Khayelitsha in the Western Cape Province by Moyo et al. (2015:13) which stated that being male was associated with a greater hazard to default treatment (HR1.93 95% CI 1.35-2.75), this is consistent with other literature. The authors explain that this finding could be due to the “high risk taking behavior in young males” as well as males’ tend to access health services less frequently than females. This study further informs that Khayelitsha is a low socio-economic township, with high unemployment rates as well as a known history of alcohol and drug abuse, which could be related to more males defaulting treatment, however, more research specific to this population group is thus required.

Goble et al. (1995) also found in their multivariate analysis that males were 2.5 times more likely to fail treatment (95% CI 1.1-6.2) and reasoned that this is possibly due to behavioural or biological factors.

6.1.11 MDR TB Standard treatment vs. Effective alternative treatment

Treatment within the intensive phase of treatment, using the standard treatment compared to treatment with an effective alternative treatment, similar findings was also founded for the intensive phase and continuation phase of treatment. The bivariate analysis indicated that participants were 2 times more likely to be successfully treatment with the standard treatment. The hospital initiated cohort, however, used more of the alternative effective treatment, this could be due to more complicated cases being seen within the hospital setting and hence the need to change the regimen, as well as the assumption that can be made that the clinical staff within the hospital setting are more willing to adapt and modify the treatment offered to the participant as compared to the clinic staff.

However there was no statistical significance shown in the multivariate analysis, this again indicating that the participants received the correct treatment and hence the DR TB guidelines have been adhered to. Anderson et al. (2013:5) in their study of all patients diagnosed with MDR TB in England, Wales and Northern Ireland in the United Kingdom between 2004 and 2007, found that,

> "treatment with a fluoroquinolone or a bacteriostatic drug were statistically significant (3.09) associated with achieving treatment success, which provides further evidence to support the WHO recommendations to include drugs belonging to Group 2, 3 and 4 in the regimen of MDR TB."

This study also reported that majority of the patients received the appropriate treatment according to the WHO guidelines. In our study, side effects were minimally recorded and hence this could not be further analyzed in this study, as

very limited information was available in the DR TB register and the electronic database. Burgos et al. (2005) reported in their study of 48 cases, in an out-patient facility in San Francisco that 48% patients reported no side effects, 17% had minor complaints, 35 % had more severe side effects and 13% had toxic side effects. Those patients that presented with side effects required discontinuation of at least 1 antituberculosis agent and for 3 of these patients, hospitalization was required.

6.1.12 MDR TB Recording and reporting

Seventy-six (11.8%) of the participants within our study, did not have treatment outcomes allocated. This is a programmatic concern as a significant amount of participants appear to be unmanaged and due to the infectious nature of this condition, and the increased chance of spreading this disease within the community. This, however, raises another great concern, and that is the follow through of data captured in the MDR TB register and subsequently into the electronic database, and the potential of incomplete or missing data if the data is not adequately captured. This is supported by, Rose et al. (2013) who found in their study, also conducted in the Western Cape Province that only 64% of the DR TB data was captured into the electronic database and emphasized that the quality of the electronic data depends on the quality of data collection, data entry and the transfer of data into the electronic system.

It is therefore essential that the completeness, accuracy and quality of the data is maintained, as this data is presented as the provincial statistics and reported at national and global levels.

6.2 Limitations

Ideally, the whole study should have been located in the year 2012, to be able to better assess and compare the clinic initiated and hospital initiated participants, within that specific timeframe. Using participants initiated on treatment in the hospitals in 2010, while it could potentially have created a selection bias, is however unlikely to have done so as there were no changes in treatment practices, including treatment regimens utilized, at the hospitals between 2010 and 2012.

Even though the study population specifically excluded complicated 'seriously ill' MDR TB patients, it seems that among those patients who met the inclusion and exclusion criteria, those being more sick than the others, although not seriously ill, were likely to have been preferentially allocated to hospital initiated treatment. This is, therefore, likely to result in higher cure rates for those treated in the clinics as they are treating less sick patients and conversely a lower cure rate for the hospitals as they are treating more sick patients.

The participants who did not culture convert (their sputum remained culture positive for TB) during the initiation phase were removed from the MDR TB register and hence were not included in the cohort and hence our treatment outcome of 'successfully treated' is likely to be inflated as these participants are much less likely to be successfully treated and conversely more likely to fail treatment or die. It is unclear whether this occurred in a differential manner between the clinic initiated and hospital initiated cohorts and hence its potential bias effect is uncertain.

The existing data variables within the MDR TB register is standardized but since it is routinely collected, it had necessarily to collect a minimum of data variables, and although those are sufficient to allow for assessment of the MDR TB

programme, it is however limited variables, which the researcher could use in the study. This study therefore was unable to measure and assess several factors that could impact on the effectiveness of treatment such as, the side effects of medication, substance abuse, psychiatric conditions, socio-economic circumstances, stigma, HIV viral load, cluster of differentiation 4 (CD4 count), TB disability grant uptake and contact tracing. Specifically the side effects of MDR TB medication is often a great concern, as the medication provided is quite toxic and hence side effects are common, however this data is not captured in the MDR TB register or the MDR TB electronic database.

Despite processes having been implemented recently to improve data collection, missing data was still found in the electronic database and the paper registers. Seventy-six (11.8%) of the participants within this study, did not have treatment outcomes allocated. This effectively decreased the sample size and increased the vagaries of chance. There is also a possible information bias in that, 33% of those with outcomes unassigned were the clinic initiated participants, with 67% being the hospital initiated participants.

The data captured from the MDR TB register and the electronic database is limited to the participants attending public health facilities, hence the findings did not extend to MDR TB participants attending private facilities.

Chapter 7: Conclusion and Recommendations

7.1 Conclusion

The key finding of this study is that clinic initiated treatment for uncomplicated MDR TB, is as effective as hospital initiated treatment, which suggests that the policy of decentralizing the treatment of MDR TB to clinics is sound and this format of management of MDR TB patients should be encouraged. Other important findings were that all participants at both clinics and hospitals were placed on the correct treatment, but that the time to treatment initiation was excessively long at both types of facilities and the incidence of participants successfully treated was quite low with a high defaulter rate. Factors associated with the treatment outcomes for MDR TB were that those treated with ART were much more likely to be successfully treated for and much less likely to die of MDR TB. Participants who had a previous TB cured and those with no history of previous TB were more likely to be successfully treated and less likely to fail treatment. There was also a higher likelihood of dying amongst participants who lived in the rural districts. Incidentally, it was noted that there were several deficiencies in the routine information system for MDR TB, with many data variables missing.

7.2 Recommendations

The Western Cape health department should definitely continue with the decentralization of MDR TB services to the clinics and could safely consider expanding the decentralization to include Pre-XDR TB and XDR TB patients.

Offering ART to HIV+ patients should be mandatory, given its clear beneficial effect on the successful treatment of MDR TB

The excessive delays in the initiation of MDR TB need to be further investigated and comprehensively addressed.

The high incidence of MDR TB patients dying in rural areas should be explored further.

The high proportion of incomplete records needs further auditing and consideration should be given to capturing of the occurrence of side effects in the MDR TB register.

References

1. Almeida, D., Rodrigues, C., Udwadia, Z.F., Lalvani, A., Gothi, G.D., Mehta, P., Mehta, A. (2003). Incidents of Multidrug- Resistant Tuberculosis in Urban and Rural India and Implications for Prevention. *Clinical Infectious Diseases*; (36): 152-159

2. Alobu, I., Oshi, N.S., Oshi, D.C., Kingsley K.N. (2014). Risk factors of treatment default and death among tuberculosis patients in a resource-limited setting. *Asian Pacific Journal of Tropical Medicine*; (14): 977-984

3. Anderson, L.F., Tamne, S., Watson, J.P., Cohen, T., Mitnick, C., Brown, T., Drobniewski, F & Abubakar, I. (2013). Treatment outcomes for multi-drug resistant tuberculosis in the United Kingdom: retrospective – prospective cohort study from 2004 to 2007. *Euro Surveillance*; 18(40): 1-9.

4. Andrew, J.R., Shah, N.S., Gandhi, N., Moll, T & Friedland, G. (2007). Multidrug- Resistant and Extensively Drug-Resistant Tuberculosis: Implications for the HIV Epidemic and Antiretroviral Therapy Rollout in South Africa. *The Journal for Infectious Diseases*; 196: 482-490

5. Andrew, J.R., Gandhi, N.R., Moodley, P., Shah, N.S., Bohlken (2008). Exogenous reinfection as a cause of multidrug-resistant and extensively drug resistant tuberculosis in rural South Africa. *Journal of Infectious Diseases*; 198: 1582–1589.

6. Bassili, A., Fitzpatrick, C., Qadeer, E., Fatima, R., Floyd, K., Jaramillo, E. (2013). Review Article: A Systematic Review of the Effectiveness of Hospital and Ambulatory-Based Management of Multidrug-Resistant Tuberculosis. *The American Society of Tropical Medicine and Hygiene;* 89(2): 271–280

7. Boehme, C. C., Nicol, M.P., Nabeta, P., Michael, J.S, Gotuzzo, E., Boehme, C.C., Nicol, M.P., Nabeta, P., Michael, J.S., Gotuzzo, E., Tahirli, R., Gler, M.T., Blakemore, R., Worodria, W., Gray, C., Huang, L., Caceres, T., Mehdiyev, R., Raymond, L., Whitelaw, A., Sagadevan, K., Alexander, H., Albert, H., Cobelens, F., Cox, H., Alland, D., Perkins, M.D. (2011). Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet;* 377: 1495–1505.

8. Brust, J., Gandhi, N., Carrara, H., Osburn, G & Padayatchi, N. (2010). High Treatment Failure and Default Rates for Patients with MDR TB in KwaZulu-Natal, South Africa, 2000–2003. *International Journal Tuberculosis Lung Disease*; 14(4): 413–419.

9. Burgos, M., Gonzalez, L.C., Paz, E.A., Gournis, E., Kawamura, L.M., Schecter, G., Hopewell, P.C., Daley, C.L. (2005). Treatment of Multidrug-Resistant Tuberculosis in San Francisco: An Outpatient-Based Approach. *Clinical Infectious Diseases*;40:968-975

10. Caminero, J.A. (2006). Treatment of multidrug-resistance:evidence and controversies. *International Journal Tuberculosis Lung Disease*; 10: 829-837.

11. Campos, P.E., Suarez, P.G., Sanchez, J., Zavala, D., Arevalo, J., Ticona, E., Nolan, C.M., Hooton, T.M., Holmes, K.K. (2003). Multidrug-resistant Mycobactrium tuberculosis in HIV infected persons, Peru. *Journal of Infectious Diseases*; 9: 1571-1578

12. Casel, M.M., Vaquero (2005). A case control study of multidrug resistant tuberculosis in a London teaching hospital. *Journal of Hospital Infection*; 39(2): 111-117

13. Chan, P., Huang, S., Yu, M., Lee, S., Huang Y., Chien, S & Lee, J. (2013). Effectiveness of a Government-Organized and Hospital- Initiated Treatment for Multidrug-Resistant Tuberculosis Patients - A Retrospective Cohort Study. *PLoS ONE*; 8 (2): 1-12.

14. Cramm, J.M., Finkenflugel, H.J.M., Moller, V., &Nieboer, A.P. (2010). TB treatment initiation and adherence in a South African community influenced more by perceptions than by knowledge of tuberculosis. *BMC Public Health*. 10:72

15. Dlamini-Mvelase, N.R., Werner, L., Phili, R., Cele, L.P., Mlisana, P. (2014). Effects of introducing Xpert MTB/RIF test on multi-drug resistant tuberculosis in KwaZulu-Natal South Africa. *BMC Infectious Diseases*; 14: 442

16. EDRWeb (2016). National Department of Health, South Africa

17. EpiInfo 7. (2007). Centre for Communicable Diseases

18. Ershova, J.V., Podewils, L.J., Bronner, L.E., Stockwell, H.G., Dlamini, S., Mametja, L.D. (2014). Evaluation of adherence to national treatment guidelines among tuberculosis in three provinces of South Africa. *South African Medicine Journal*; 104 (5): 362-368

19. Espinal, M.A., Laserson, K., Camacho, M., Fusheng, Z., Kim, S.J., Tlali, E., Smith, I., Suarez, P., Antunes, L., George, A.G., Martin- Casabona, N., Simelame, P., Weyer, K., Binkin, N., Raviglione, M.C.(2001). Determinants of drug-resistant tuberculosis: analysis of 11 countries. *International Journal of Tuberculosis Lung Disease*; 5(10): 887-893

20. Farley, J.E., Ram, M., Waldman. S., Cassell, G.H., Chaisson, R.E., Weyer. W., Lancaster, J., Van der Walt, M. (2010). Outcomes of Multi-Drug Resistant Tuberculosis (MDR TB) among a cohort of South African Patients with High HIV Prevalence. *PLoS*; 6(7): E20436

21. Friedland, G., Karim, S.A ., Karim, Q.A. (2004).Utility of tuberculosis directly observed therapy programs as sites for access to and provision of antiretroviral therapy in resources limited countries. *Clinical Infectious Diseases*; 38(5):421-428

22. Ghebrehiwet, T. (2009). *Expanding the Role of Nurses in TB prevention, Care and Treatment*. International Council of Nurses, Switzerland

23. Goble, M., Iseman, M.D., Lorie, A., Madesan, R.N., Dennis Waite, B.S.N., Ackerson, L & Horsburgh, C.R. (1995). Treatment of 171 Patients with Pulmonary Tuberculosis Resistant to Isoniazid and Rifampicin. *The New England Journal of Medicine*; 328 (8): 527-532.

24. *HAST Audit Report* (2015). Provincial Department of Health

25. Heller, T., Lessells, R.J., Wallrauch, C.G., Bärnighausen, T., Cooke, G.S., Mhlongo, L., Master, I. & Newell, M.L. (2010). Community-based treatment for multidrug-resistant tuberculosis in rural KwaZulu-Natal, South Africa. *International Journal of Tuberculosis Lung Disease;* 14 (4):420-426.

26. Holtz, T. H., Lancaster, J., Laserson, K. F., Wells, C. D, Thorpe, L., Weyer, K. (2006). Risk factors associated with default from multidrug-resistant tuberculosis treatment, South Africa, 1999-2001. *International Journal of Tuberculosis Lung Disease*; 10: 649–655.

27. Hom, J.K., Wang, B., Chetty, S., Giddy, J., Mazibuko, M., Allen, J., Walensky, R.P., Losina, E., Freedberg, K.A., Bassett, I.V. (2012). Drug-Resistant Tuberculosis among HIV-Infected Patients Starting Antiretroviral Therapy in Durban, South Africa. *PLoS ONE;* 7(8):1-5

28. Horter, S., Stringer, B., Reynolds, L., Shoaib, M., Kasozi, S., Casas, E.C., Verputten, M & Du Cros, P. (2014). "Home is where the patient is": a qualitative analysis of a patient centred model of care for multi-drug resistant tuberculosis. *BMC Health Services Research;* 14: 81-92.

29. Hughes, J., Osman, M. (2014). Diagnosis and management of drug-resistant tuberculosis in South African adults. *South African Medicine Journal*; 104(12): 894. DOI: 10.7196/ SAMJ.9097

30. Johnston, J. C., Shahidi, N. C., Sadatvi, M., Fitzgerald, J.M. (2009).Treatment Outcomes of Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis. *PLoS ONE*; 4 (9): 1-8

31. Kaplan, R., Caldwell, J., Hermans, S., Adriaanse, S., Mtwisha, L., Bekker, L.G., Jennings, K., Wood, R. (2016). An Integrated community TB-HIV adherence model provides an alternative to DOT for tuberculosis patients in Cape Town. *International Journal of Lung Disease*; 20(9):1185-1191

32. Karim, S. A., Churchyard, G. J., Karim, Q. A & Lawn, S. D. (2009). HIV infection and Tuberculosis in South Africa: urgent need to escalate the public health response. *Lancet*; 374: 921-933.

33. Khan, R.B. (2010*). The Social determinants of Multidrug resistant Tuberculosis in the United States between 2005 and 2009*. Atlanta, Georgia

34. Kirkman, M.S., Williams, S.R., Caffrey, H.H., Marrero, D.G. (2002). Impact of a Program to Improve Adherence to Diabetes Guidelines by Primary Care Physicians. *Diabetes Care*; 25:1946-1951

35. Kliiman K., Altraja, A. (2009). Predictors of poor treatment outcomes in multi- and extensively drug-resistant pulmonary TB. *European Respiratory Journal*; 33:1085-1094

36. Lessels, R.J., Swaminathan, S., Godfrey- Faussett, P. (2015). HIV treatment cascade in tuberculosis patients. *Current Opinion HIV AIDS*; 10: 439-446

37. Lonnroth, K., Jaramilo, E., Williams, B.G., Dye, C., Raviglone, M. (2009). Drivers of tuberculosis epidemics: The role of risk factors and social determinants. *Social Science and Medicine*; 68:2240-2246

38. Loveday, M., Wallengren, K., Voce A., Margot, B., Reddy T., Master I., Brust J., Chaiyachati K., & Padayatchi. N. (2012). Comparing early treatment outcomes of MDR TB in a decentralised setting with a centralised setting in KwaZulu-Natal, South Africa. *International Journal of Tuberculosis Lung Disease*; 16(2): 209-2015

39. Loveday, M., Wallengren, K., Brust, J., Roberts, J., Voce A., Margot., Ngozo, J., Master I., Cassell, G., & Padayatchi. N. (2015). Community-based care vs. centralised hospitalisation for MDR TB patients, KwaZulu-Natal, South Africa. *International Journal of Tuberculosis Lung Disease*; 19(2): 163-171

40. Mayosi, B.M., Lawn, J.E., Van Niekerk, A., Bradshaw, D., Abdool Karim, S.S., Coovadia, H.M. (2009). Health in South Africa: changes and challenges since 2009. *Lancet;* 380: 2029-2043

41. Mitnick, C., Bayona, J., Palacios, E., Shin, S., Furin, J., Alcantra, F., Sanchez, E., Sarria, M., Becerra, M., Smith Fawzi, M., Kapiga, S., Neuberg, D., Maguire, J., Yong Kim, J & Farmer, P. (2003). Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. *The New England journal of medicine*; 348:119–128.

42. Moyo, S., Cox, H.S., Hughes, J., Daniels, J., Snyman, S., De Azevedo, V., Shroufi, A., Cox, V., Van Gustem, G. (2015). Loss from Treatment for Drug Resistant Tuberculosis: Risk Factors and Patient Outcomes in a Community-Based Program in Khayelitsha, South Africa. *PLOS ONE*;10:1-13

43. Moyo, S., Hughes, J., Daniels, J., Muller, O., Shroufi, A., Van Gustem, G., Cox, V., Wilkinson, L., Cox, H. (2014). *Treatment outcomes in HIV infected and uninfected drug resistant tuberculosis patients in Khayelitsha, Cape Town*

44. Mugabo, P., Adewumi, A.O., Theron, D., Burger, T., Van Zyl, L. (2015). Do HIV infections and anitiretroviral therapy influence multidrug-resitant tuberculosis treatment outcomes. *African Journal of Pharmacy and Pharmacology*; 9(35): 875-880

45. Mulu, W., Mckonnen, D.,Yimmer, M., Admassu, A., Abera, B. (2015). Risk factors for multidrug resistant tuberculosis patients in Amhara National Regional State. *African Health Sciences*; 15(2):368-377

46. Naidoo, P., du Toit, E., Dunbar, R., Lombard, C., Caldwell, J., Detjen, A., Bertel, S., Enarson, D.A., Beyers., N.(2014). Did and Xpert MTB/RIF algorithm reduce multi-drug resistant tuberculosis treatment commencement time in a routine operational setting in Cape Town. *PLoS ONE*; 9: 1-19,

47. Narasimooloo, R., Ross, A. (2012). Delay in commencing treatment for MDR TB at a specialised TB treatment centre in KwaZulu-Natal. *South African Medicine Journal*; 102(6):360-362.

48. Nardell, E., Dharmadhikari, A. (2010). Turning off the spigot: reducing drug-resistant tuberculosis transmission in resource- limited settings. *International Journal of Lung Disease*; 14(10): 1233-1243

49. National Department of Health. (2011). *Multi Drug Resistant Tuberculosis: A policy framework on decentralized and deinstitutionalised management for South Africa*. Pretoria, South Africa: Department of Health.

50. National Department of Health. (2013). *Management of Drug Resistant TB policy guideline,* Pretoria, South Africa: Department of Health.

51. National Department of Health. (2009). EDRWeb Monitoring and Evaluation. South Africa: Department of Health.

52. National Department of Health. (2013). The South African ART Guideline. South Africa: Department of Health

53. National Health Act.(2003), South Africa

54. Nyabadza, F., Winkler, D. (2013). A simulation age-specific tuberculosis model for the Cape Town metropole. *South African Journal of Science*; 109: 1-7

55. Pooran, A., Pieterson, E., Davids, M., Theron, G., Dheda, K. (2013). What is the cost of diagnosis and management of drug resistant tuberculosis in South Africa? *PLoS One*; 8 (1):e54587. [http://dx.doi.org/10.1371/journal.pone.0054587]

56. Provincial Department of Health. (2013).Healthcare 2030. Western Cape.

57. Reid, A., Scano, F., Getahun H., Williams, B., Dye, C., Nunn, P., De Cock, K.M., Hankins, C., Miller, B., Castro, K.G., Raviglione, M.C. (2006). Towards universal access to HIV prevention, treatment, care and support: the role of TB/HIV collaboration. *Lancet Infectious Diseases*; 6:483-495

58. Rose, P.C., Schaaf, H.S., du Preez, K., Seddon, J.A., Garcia-Prats, J.A., Zimri, K., Dunbar, R., Hesseling, A.C. (2013). Completeness and accuracy of electronic recording of paediatrict drug-resistant tuberculosis in Cape Town, South Africa. *Public Health Action*; 3(3)214-219

59. Sharma, S.K & Mohan, A. (2004). Multidrug- resistant tuberculosis. *Indian journal of medicine respiratory*; 120: 354-376

60. Shina, S., Furin, J., Bayona, J., Mate, K., Yong Kim, J., Farmer, P. (2004). Community-based treatment of multidrug-resistant tuberculosis in Lima, Peru: 7 years of experience. *Social Science & Medicine;* 59: 1529–1539

61. *Statistics South Africa*: Census 2011 Report. (2012). Pietermaritzburg. South Africa. http://www.statssa.gov.za

62. Stagg, H.R., White, P.J., Riekstina, V., Cirule, A., Skenders, G., Leimane,V., Kuksa, L., Dravniece, G., Brown, J., Jackson., C.(2016). Decreased Time to Treatment Initiation for Multidrug-Resistant Tuberculosis Patients after use of Xpert MTB/RIF test, Latvia. *Emerging Infectious Diseases;* 22(3):482-490

63. Villarino, M.E., Geiter, L.J., Simone, P.M. (1992). The multidrug resistant tuberculosis challenge to public health efforts to control tuberculosis. *Public Health Reports*; 107(6): 616-625

64. Wells, C.D., Cegielski, J.P., Nelson, L.J., Laserson, K.F., Holtz, T.H., Finlay, A., Castro, K.G. & Weyer, K. (2007). HIV infection and Multidrug-Resistant Tuberculosis- The Perfect Storm. *The Journal of Infectious Diseases*; 196: 86-107

65. Weyer, K., Van der Walt, M., Brand, J., Lancaster, J., Levin, J. (2003). Survey of tuberculosis drug resistance in South Africa: Final Report. Pretoria: Medical Research Council

66. World Health Organization. (2006). *Guidelines for the programmatic management of drug-resistant tuberculosis.* WHO/HTM/TB/2006.361.Geneva: WHO.2006

67. World Health Organization. (2007). *The Global MDR TB & XDR-TB Response Plan 2006–2007*, Geneva:WHO Available: http://www.who.int/tb/publications/2007/en/index.html. Accessed: 2009 Aug 12.

68. World Health Organization. (2008). *Anti-tuberculosis drug resistance in the world. Fourth Global Report*. WHO/HTM/TB/2008.394

69. World Health Organization. (2009). Review of the South African TB Programme 6-17 July 2009 and the DR TB directorate clinical audit- June 2009

70. World Health Organization. (2011). *Guidelines for the programmatic management of drug resistant tuberculosis*- 2011 update Available: http://whqlibdoc.who.int/publications/2011/9789241501583

71. World Health Organization (2011). *Automated Real-time Nucleic Acid Amplification Technology for Rapid and Simultaneous Detection of Tuberculosis and Rifampicin Resistance: Xpert MTB/RIF System*

72. World Health Organization. (2013). *Global Tuberculosis Report 2013*

73. World Health Organization. (2015). *Multidrug Resistant Tuberculosis Update*

Appendix 1: First Line Anti-TB Drugs

GROUP	DRUG
first line oral drugs	Rifampicin (R)
	Isoniazid (H)
	Ethambutol (E)
	Pyrazanimide (Z)

Appendix 2: (National Department of Health 2013:47)

Grouping of MDR TB Drugs

GROUP	**DRUGS**
GROUP1: **first line oral drugs**	Ethambutol (E) Pyrazinamide (Z)
GROUP2: **Injectable drugs**	Kanamycin (Km) Amikacin(Am) Capreomycin (Cm) Viomycin(Vm)
GROUP3: **Fluoroquinolones**	Levofloxicin (Lvx) Moxifloxacin (Mfx) Gatifloxicin (Gfx)
GROUP4: **Oral bacteriostatics second-line drugs**	Ethionamide (Eto) Prothionamide (Pto) Cycloserine (Cs) Terizidone (Trd) Para-Aminosalicylic Acid (PAS)
GROUP 5: A**gents with unclear efficacy**	Clofazimine (Cfz) Amoxicillin/clavulanate (Amx/Clv) Clarithromycin (Clr) Azithromycin (Azr) Linezolid (Lzd) Thioacetazone (Th) Imipenem High-dose INH

Appendix 3: (National Department of Health 2013:48)

Standardized treatment regimens- Intensive Phase

Phase 1: Intensive Phase- at least 6 months guided by TB culture conversion, treatment taken at least 6 times a week, at least 5 drugs

Pyrazinamide-Kanamycin/Amikacin- Moxiflocin/Ofloxcin/Levofloxicin-Ethionamide-Terizidone-

Patient Weight	Drug	Dosage
<33 kg	Kanamycin	15-20 mg/kg
	Moxifloxicin	400mg
	Ethionamide	15-20 mg/kg
	Terizidone	15-20 mg/kg
	Pyrazinamide	30-40mg/kg
33-50 kg	Kanamycin	500-750 mg
	Moxifloxicin	400 mg
	Ethionamide	500 mg
	Terizidone	750 mg
	Pyrazinamide	1000- 1750 mg
51-70kg	Kanamycin	1000 mg
	Moxifloxicin	400 mg
	Ethionamide	750 mg
	Terizidone	750 mg
	Pyrazinamide	1750-2000 mg
>70 kg	Kanamycin	1000 mg
	Moxifloxicin	400 mg
	Ethionamide	750-1000 mg
	Terizidone	750-1000 mg
	Pyrazinamide	2000-2500 mg

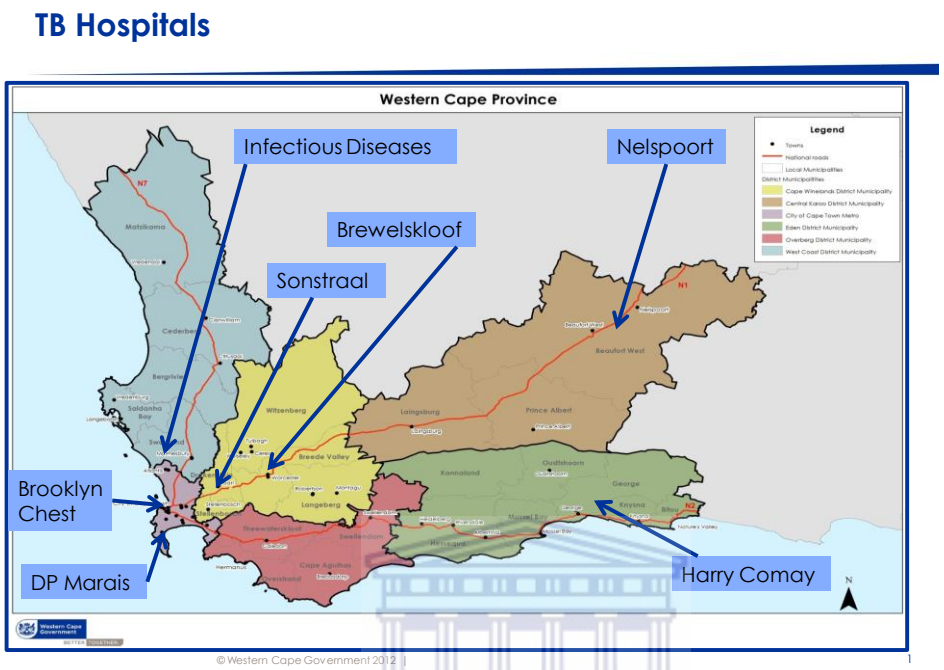
Appendix 4: (National Department of Health 2013:49)

Standardized treatment Regimen- Continuation phase

Phase 2: Continuation Phase- at least 18 months after TB culture conversion (no injectable) treatment taken at least 6 times per week.

Patient Weight	Drug	Dosage
<33 kg	Moxifloxicin	400 mg
	Ethionamide	15-20 mg/kg
	Terizidone	15-20mg/kg
	Pyrazinamide	30-40 mg/kg
33-50 kg	Moxifloxicin	400 mg
	Ethionamide	500 mg
	Terizidone	750 mg
	Pyrazinamide	1000-1750 mg
51-70kg	Moxifloxicin	400 mg
	Ethionamide	750 mg
	Terizidone	750 mg
	Pyrazinamide	1750 – 2000 mg
>70 kg	Moxifloxicin	400 mg
	Ethionamide	750 -1000 mg
	Terizidone	750 – 1000 mg
	Pyrazinamide	2000-2500 mg
*adults not able to tolerate Moxifloxicin will be given Levofloxicin Dosage: 750 mg patients below 51 kg, 1000 mg for patients => 51 kg		

Appendix 5: Specialized TB hospitals within the Western Cape Province



Appendix 6: Univariate Categorical Analysis of the MDR TB patients initiated on treatment in community and hospital settings

Variable n = 644*	**Description of variable**	**All participants n = 644**		**Clinic treatment initiated participants n =323**		**Hospital treatment initiated participants n= 321**	
		frequencies	**95% CI**	**Frequencies**	**95% CI**	**Frequencies**	**95% CI**
Outcome of previous TB history N=622	No TB history	233 (37.46%)	33.67% -41.41%	140 (45.90%)	40.23% -51.67%	93 (29.34%)	24.45% - 34.74%
	Previous TB Cured	161 (25.88%)	22.52% - 29.55%	99 (32.46%)	27.30% -38.07%	62 (19.56%)	15.42% - 24.45%
	Treatment default	104 (16.72%)	13.92% - 19.94%	44 (14.43%)	10.78% -18.99%	60 (18.93%)	14.85% - 23.77%
	Treatment failed for TB	49 (7.88%)	5.94% - 10.35%	18 (5.90%)	3.64% - 9.33%	31 (9.78%)	6.84% - 13.73%
	Treatment failed for DR TB	75 (12.06%)	9.66% - 14.94%	4 (1.31%)	0.42% - 3.55%	71 (22.40%)	18.01% - 27.47%
Further breakdown of the outcomes of previous TB n=622	Combination of no previous TB and previous TB cured	394 (63.34%)	59.40% - 67.12%	239 (78.36%)	73.23% - 82.76%	155 (48.90%)	43.28% - 54.54%
	Combination of previous TB treatment defaulted and treatment failures	228 (36.66%)	32.88% - 40.60%	66 (21.64%)	17.24% -26.77%	162 (51.10%)	45.46% -56.72%

Variable n = 644*	Description of variable	All participants n = 644		Clinic treatment initiated participants n= 323		Hospital treatment initiated participants n = 321	
		frequencies	95% CI	Frequencies	95% CI	Frequencies	95% CI
Management of HIV+ participants n= 278	Treated with both ART and Co-Trimoxazole Therapy	162 (58.27%)	52.23% - 64.13%	79 (58.52%)	49.73% -66.93%	83 (58.04%)	49.51% -66.24%
	Only treated with Anti-retroviral Therapy	85 (30.58%)	25.21% - 36.36%	41 (30.37%)	22.76% -38.87%	44 (30.77%)	23.33% - 39.03%
	Only treated with Co-Trimoxazole Therapy	9 (3.24%)	1.49% - 6.06%	5 (3.70%)	1.21% - 8.43%	4 (2.80%)	0.77% - 7.01%
	Not on any treatment	22 (7.91%)	5.03% - 11.74%	10 (7.41%)	3.61% - 13.20%	12 (8.39%)	4.41% - 14.20%
Year that participant is enrolled	2012	484 (75.16%)	71.59% - 78.41%	323 100.00%)	100.00% -100.00%	161 (50.16%)	44.56% - 55.75%
	2010	160 (24.84%)	21.59% - 28.41%			160 (49.84%)	44.25% - 55.44%
The 2012 hospital initiations vs 2010 hospital initiations =321	2012	161 (50.16%)	44.56% - 55.75%			161 (50.16%)	44.56% - 55.75%
	2010	160 (49.84%)	44.25% - 55.44%			160 (49.84%)	44.25% - 55.44%

Variable n = 644*	Description of variable	All participants n = 644		Clinic treatment initiated participants n= 323		Hospital treatment initiated participants n = 321	
		frequencies	95% CI	Frequencies	95% CI	Frequencies	95% CI
Community treatment initiated	Proportion treated at the community	323 (50.16%)	46.23% - 54.08%				
Participant lives within the city or outside the city	Within the city	334 (51.86%)	47.93% - 55.78%	174 (53.87%)	48.27% - 59.38%	160 (49.84%)	44.25% - 55.44%
	Outside the city	310 (48.14%)	44.22% - 52.07%	149 (46.13%)	40.62% - 51.73%	161 (50.16%)	44.56% - 55.75%
The broad geographical breakdown of the location of the facility that the participant is treated at	Participant from the within the city	327 (64.62%)	60.26% - 68.76%	172 (62.09%)	56.10% -67.83%	155 (67.69%)	61.21% -73.70%
	Participant from a large town	59 (11.66%)	9.06% - 14.86%	27 (9.75%)	6.52% - 13.86%	32 (13.97%)	9.76% - 19.15%
	Participant from a small town	120 (23.72%)	20.12% - 27.71%	78 (28.16%)	22.94% - 33.85%	42 (18.34%)	13.55% -23.97%
The Western Cape Provinces Districts as per municipalities breakdown	Cape Metro District	334 (52.19%)	48.24% - 56.11%	174 (53.87%)	48.27% - 59.38%	160 (50.47%)	44.84% - 56.09%
	West Coast District	74 (11.56%)	9.24% - 14.36%	64 (19.81%)	15.69% - 24.67%	10 (3.15%)	1.61% - 5.91%
	Cape Winelands District	124 (19.38%)	16.43% - 22.70%	60 (18.58%)	14.57% -23.34%	64 (20.19%)	16.00% - 25.12%
	Overberg District	17 (2.66%)	1.60% - 4.31%	8 (2.48%)	1.16% - 5.01%	9 (2.84%)	1.39% - 5.51%
	Eden District	83 (12.97%)	10.51% - 15.88%	15 (4.64%)	2.72% - 7.71%	68 (21.45%)	17.14% - 26.47%
	Central Karoo District	8 (1.25%)	0.58% - 2.55%	2 (0.62%)	0.11% - 2.46%	6 (1.89%)	0.77% - 4.28%

Variable n = 644*	**Description of variable**	**All participants n = 644**		**Clinic treatment initiated participants n= 323**		**Hospital treatment initiated participants n = 321**	
		frequencies	**95% CI**	**Frequencies**	**95% CI**	**Frequencies**	**95% CI**
TB hospital that participant is initiated on treatment at. n= 316	Brooklyn Chest Hospital (Cape Metro District)	160 (50.63%)	44.99% - 56.26%			160 (50.63%)	44.99% - 56.26%
	Infectious Diseases Hospital (West Coast District)	10 (3.16%)	1.62% - 5.93%			10 (3.16%)	1.62% - 5.93%
	Sonstraal hospital (West Coast and Cape Winelands District)	18 (5.70%)	3.51% - 9.01%			18 (5.70%)	3.51% - 9.01%
	Brewelskloof hospital (Cape Winelands District)	54 (17.09%)	13.20% - 21.80%			54 (17.09%)	13.20% - 21.80%
	Harry Comay Hospital (Eden and Central Karoo District)	74 (23.42%)	18.94%- 28.56%			74 (23.42%)	18.94% - 28.56%

*n= 644 which is the total sample, unless otherwise specified.

Appendix 7: Mutivariate Logistic Regression Modelling

Model 1:

Model 1: Variable	Successfully treated		Failed		Died		Defaulted	
	Adjusted Odds Ratio	**95% CI and P value**	**Adjusted Odds Ratio**	**95% CI and P value**	**Adjusted Odds Ratio**	**95% CI and P value**	**Adjusted Odds Ratio**	**95% CI and P value**
Community treatment initiated vs hospital initiated	1.49	1.05- 2.12 P = 0.03	0.505	0.28- 0.91 P = 0.02	0.89	0.56- 1.43 P=0.637	0.93	0.66 -1.30 P= 0.66
Treatment within the Intensive phase of treatment Participant received standard treatment or Participant received other effective treatment	2.52	1.53- 4.14 P=0.00	0.85	0.44- 1.64 P= 0.62	0.39	0.23- 0.64 P=0.00	0.89	0.58- 1.34 P=0.57

Model 2:

Model 2: Variable	Successfully treated		Failed		Died		Defaulted	
	Adjusted Odds Ratio	**95% CI and P value**	**Adjusted Odds Ratio**	**95% CI and P value**	**Adjusted Odds Ratio**	**95% CI and P value**	**Adjusted Odds Ratio**	**95% CI and P value**
Community treatment initiated vs hospital initiated	1.56	1.09 -2.22 P=0.01	0.45	0.25 - 0.84 P=0.01	0.92	0.57 -1.49 P=0.75	0.90	0.64 -1.27 P=0.56
Treatment within the Intensive phase of treatment Participant received standard treatment or Participant received other effective treatment	2.56	1.56 - 4.22 P=0.00	0.81	0.45 -1.60 P=0.54	0.39	0.23 - 0.64 P=0.00	0.88	0.58 -1.34 P=0.55
Participant lives within the city vs outside the city	01.67	01.69 - 0.86 P=0.00	0.35	0.19 - 0.67 P=0.0014	1.47	0.91 -2.36 P=0.10	0.72	0.51 -1.01 P=0.06

Model 3:

Model 3: Variable	Successfully treated		Failed		Died		Defaulted	
	Adjusted Odds Ratio	95% CI and P value	Adjusted Odds Ratio	95% CI and P value	Adjusted Odds Ratio	95% CI and P value	Adjusted Odds Ratio	95% CI and P value
Community treatment initiated vs hospital initiated	1.42	0.97 - 2.07 P=0.07	0.49	0.26-0.90 P=0.22	1.00	0.59 - 1.69 P=0.99	0.85	0.59 -1.22 P=0.38
Treatment within the Intensive phase of treatment Participant received standard treatment or Participant received other effective treatment	2.57	1.54 - 4.29 P=0.00	0.80	0.41- 1.57 P=0.51	0.38	0.23 - 0.65 P=0.00	0.88	0.57 - 1.34 P=0.54
Participant lives within the city vs outside the city	1.52	1.05 – 2.20 P=0.03	0.38	0.20- 0.72 P=0.00	1.47	0.90-2.40 P=0.13	0.72	0.50 - 1.97 P=0.07
No Tb and previous TB cured participants	1.60	1.06 - 2.39 P=0.02	0.52	0.24 – 1.15 P=0.10	0.69	0.41-1.17 P=0.17	1.19	0.81 -1.75 P=0.36

Model 4:

Model 4: Variable	Successfully treated		Failed		Died		Defaulted	
	Adjusted Odds Ratio	**95% CI and P value**	**Adjusted Odds Ratio**	**95% CI and P value**	**Adjusted Odds Ratio**	**95% CI and P value**	**Adjusted Odds Ratio**	**95% CI and P value**
Community treatment initiated vs hospital initiated	1.46	1.00 -2.13 P=0.05	0.66	0.34 -1.27 P=0.21	0.99	0.59 - 1.68 P=0.98	0.83	0.58 - 1.21 P=0.34
Treatment within the Intensive phase of treatment Participant received standard treatment or Participant received other effective treatment	2.62	1.57 - 4.39 P=0.00	0.87	0.44 -1.72 P=0.68	0.38	0.23 - 0.64 P=0.00	0.87	0.57 - 1.34 P=0.53
Participant lives within the city vs outside the city	1.55	1.07- 2.24 P=0.02	0.46	0.24 – 0.88 P=0.02	1.47	0.90 – 2.41 P=0.13	0.72	0.50 -1.02 P=0.07
No Tb and previous TB cured participants	1.58	1.05 -2.37 P=0.03	0.37	0.19 - 0.70 P=0.00	0.70	0.41 - 1.18 P=0.18	1.21	0.82 - 1.77 P=0.33
Female participants	1.52	1.05-2.18 P=0.03	0.90	0.50 - 1.63 P=0.74	0.84	0.51 - 1.38 P=0.49	0.77	0.54 - 1.09 P=0.14

Model 5:

Model 5: Variable	Successfully treated		Failed		Died		Defaulted	
	Adjusted Odds Ratio	**95% CI and P value**	**Adjusted Odds Ratio**	**95% CI and P value**	**Adjusted Odds Ratio**	**95% CI and P value**	**Adjusted Odds Ratio**	**95% CI and P value**
Community treatment initiated vs hospital initiated	1.06	0.57-195 P=0.86	1.39	0.49 -3.90 P=0.53	0.69	0.30-1.60 P=0.39	1.06	0.59-1.90 P=0.84
Treatment within the Intensive phase of treatment Participant received standard treatment or Participant received other effective treatment	0.52	0.20-1.39 P=0.19	0.87	0.44 -1.72 P=0.68	0.76	0.33 – 1.73 P=0.50	0.87	0.46 - 1.89 P=0.65
Participant lives within the city vs outside the city	0.54	0.19-1.51 P=0.24	0.46	0.24 – 0.88 P=0.02	2.70	1.27 – 2.80 P=0.01	0.72	0.41 -1.02 P=0.07
No Tb and previous TB cured participants	2.86	1.48-5.53 P=0.00	0.12	0.04 - 0.36 P=0.00	0.65	0.29-1.45 P=0.29	1.13	0.63- 2.03 P=0.69
Female participants	1.69	0.95-3.00 P=0.07	0.84	0.34 – 2.08 P=0.71	1.06	0.50- 2.22 P=0.88	0.67	0.40 - 1.14 P=0.14
HIV+ on ART vs HIV+ not on ART	6.67	1.48-29.84 P=0.01	1.28	0.27-6.34 P=0.77	0.22	0.09-0.57 P=0.00	0.89	0.37-2.13 P=0.79

UNIVERSITY of the
WESTERN CAPE

OFFICE OF THE DEAN
DEPARTMENT OF RESEARCH DEVELOPMENT

18 December 2014

To Whom It May Concern

I hereby certify that the Senate Research Committee of the University of the Western Cape approved the methodology and ethics of the following research project by:
Ms R Vallie (School of Public Health)

Research Project:	Assessing and comparing the effectiveness of treatment for multi-drug resistant tuberculosis between specialized Tb hospital in-patient and general out-patient clinic settings within the Western Cape Provinces, South Africa.
Registration no:	14/10/36

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

Private Bag X17, Bellville 7535, South Africa
T: +27 21 959 2988/2948 . F: +27 21 959 3170
E: pjosias@uwc.ac.za

CITY OF CAPE TOWN
ISIXEKO SASEKAPA
STAD KAAPSTAD

CITY HEALTH

Dr Hélène Visser
Manager: Specialised Health

T: 021 400 3981 **F:** 021 421 4894 **M:** 083 298 8718
E: Helene.Visser@capetown.gov.za

2015-06-08

Re: Research Request: Assessing and comparing the effectiveness of treatment for multi-drug resistant tuberculosis between specialized TB hospital in-patient and general outpatient clinic settings within the Western Cape Province, South Africa (ID No: 10493)

Dear Ms Vallie,

Your research has been approved as per your request to have access to City Health Clinics for paper based registers in all 8 Sub Districts.

Eastern Sub District:
Contact People
Dr P Nkurunziza (Sub District Manager)
Tel: (021) 850-4315 / 084 800 0644
Mrs T de Villiers (Head: PHC & Programmes)
Tel: (021) 850-4312

Northern Sub District:
Contact people
Dr A Zimba (Sub District Manager)
Tel/Cell: (021) 980-1230 / 084 627 2425
Mrs J Coetzee (Head: PHC & Programmes)
Tel/Cell: (021) 980-1211

Mitchells Plain Sub District:
Contact People
Mrs S Elloker (Sub District Manager)
Tel: (021) 391-5012/ 084 222 1478
Mrs N Nqana (Head: PHC & Programmes)
Tel: (021) 391-0175/ 084 2221489

Southern Sub District:
Contact People
Mr M Cupido (Acting - Sub District Manager)
Tel: (021) 710-8295/ 084 2200 145
Mrs K Shuping (Acting Head: PHC & Programmes)
Tel: (021) 710-9383

Klipfontein Sub District:
Contact People
Mr K Nkoko (Sub District Manager)
Tel: (021) 630-1667/ 082 433 1332
Mrs T Nojaholo (Head: PHC & Programmes)
Tel: (021) 630-1626/ 084 220 0133

Khayelitsha Sub District:
Contact People
Dr V de Azevedo (Sub District Manager)
Tel: (021) 360-1258/ 083 629 3344
Mrs S Patel Abrahams (Head: PHC & Programmes)
Tel: (021) 360-1153/ 084 405 6065

Tygerberg Sub District:
Contact People:

Mrs M Alexander (Sub District Manager)
Tel: (021) 938-8279 / 084 222 1471
Mrs D Titus (Head: PHC & Programmes)
Tel: (021) 938-8281 / 084 308 0596

Western Sub District:
Contact People:

Mrs G Sifanelo (Sub District Manager)
Tel/Cell: (021) 514-4122 / 084 630 2903
Mrs M Stanley (Head: PHC & Programmes)
Tel/Cell: (021) 514-4124 / 072 329 6361

Please note the following:

1. All individual patient information obtained must be kept confidential.
2. A copy of the final report must be sent to the City Health Head Office, P O Box 2815 Cape Town 8001, within 6 months of its completion and feedback must also be given to the clinics involved.
3. Your project has been given an ID Number (10493). Please use this in any future correspondence with us.

Thank you for your co-operation and please contact me if you require any further information or assistance.

Yours sincerely

DR G H VISSER
MANAGER: SPECIALISED HEALTH

cc. Dr Nkurunziza & Ms de Villiers
Mrs Elloker & Ms Nqana
Mrs Alexander & Mrs Titus
Mr Cupido & Mrs K Shuping
Mrs Sifanelo & Mrs Stanley
Dr Zimba & Ms Coetzee
Mr Nkoko & Mrs Nojaholo
Dr de Azevedo & Mrs Patel Abrahams
Dr Jennings
Ms Caldwell

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 6857: fax: +27 21 483 9895
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za

REFERENCE: 2014RP135
ENQUIRIES: Ms Charlene Roderick

20 Rajah Road
Cravenby Estate
7490

For attention: **Razia Vallie**

Re: ASSESSING AND COMPARING THE EFFECTIVENESS OF TREATMENT FOR MULTI DRUG RESISTANT TUBERCULOSIS BETWEEN SPECIALIZED TB HOSPITAL IN-PATIENT AND GENERAL OUTPATIENT CLINIC SETTINGS WITHIN THE WESTERN CAPE PROVINCE, SOUTH AFRICA

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.
Please contact the following people to assist you with any further enquiries in accessing the following sites:

Khayelitsha / Eastern Sub District DR TB Registers:

Macassar	**C Alexander**	**Contact No. 021 357 2330**
Site B	**D Binza**	**Contact No. 021 360 5208**
Michael Mapongwana	**K Jacobs**	**Contact No. 021 361 3353**
Strand	**D van Nelson**	**Contact No. 021 853 8210**
Gastrouw	**D van Nelson**	**Contact No. 021 845 5180**

[redacted]

2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final report within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

3. The reference number above should be quoted in all future correspondence.

Yours sincerely

DR J EVANS
ACTING DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 14/01/15
CC **A HAWKRIDGE** **DIRECTOR: KHAYELITSHA / EASTERN**

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 6857; fax: +27 21 483 9895
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: 2014RP135
ENQUIRIES: Ms Charlene Roderick

20 Rajah
Cravenby Estate
7490

For attention: **Razia Vallie**

Re: Assessing and comparing the effectiveness of treatment for multi-drug resistant tuberculosis between specialized TB hospital in-patient and general outpatient clinic settings within the Western Cape Province, South Africa.

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.
Please contact the following people to assist you with any further enquiries in accessing the following sites:

West Coast	**D Schoeman**	**Contact No: 022 487 9207**
Eastern / Khayelitsha	**D Heyns**	**Contact No: 021 3604 622**
Northern / Tygerberg	**A Patentia**	**Contact No: 021 713 7650**
Southern / Western	**K Grammer**	**Contact No: 021 202 0906**
Mitchells Plain / Klipfontein	**J Samuels**	**Contact No: 021 370 5007**
Cape Winelands	**S Neethling**	**Contact No: 023 348 8120**
Eden /Central Karoo	**T Marshall**	**Contact No: 044 803 2752**
Overberg	**R Zondo**	**Contact No: 028 214 5800**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final report within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

3. The reference number above should be quoted in all future correspondence.

Yours sincerely

A T HAWKRIDGE.

DR A HAWKRIDGE
DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 5/2/2015.

CC **D HEYNS**
K GRAMMER
L PHILLIPS
P OLCKERS
H SCHUMANN

ACTING DIRECTOR: KHAYELITSHA/ EASTERN
DIRECTOR: NORTHERN/ TYGERBERG
DIRECTOR: CAPE WINELANDS
DIRECTOR: KLIPFONTEIN/ MITCHELLS PLAIN
DIRECTOR: EDEN/ CENTRAL KAROO