DEDICATION

In memory of my late father, Yutuko Manuel Haumba Malwa, wishing he could have been here. I owe my beginnings, foundation and achievements to him, for what he stood for, and what he wanted me to achieve. He always inspired me in all aspects of my life.

To my dear mother, Edith Mary Malwa, to Timothy Emmanuel Haumba Malwa, my son and his siblings Samantha Haumba, Tracey Haumba, Ruth Haumba and to my beloved wife, Eunice Marion Twongyeirwe Haumba for their love, encouragement and relentless support in making the research project achieve its intended objectives.

To the Almighty, my God, who has carried me through all the challenges, sometimes bringing a smile to my face, even in the very difficult and trying moments of this study. To know Him and to know that He is able, He is good all the time, and that the glory is His, has been an inspiration throughout my life’s journey.
DECLARATION

STUDENT NUMBER: 356-0280-3

I declare that BEST PRACTICE GUIDELINES TO MONITOR AND PREVENT HEARING LOSS RELATED TO DRUG RESISTANT TUBERCULOSIS TREATMENT is my own work and that all sources that I have used or quoted have been indicated and acknowledged by means of complete references.

Signature:  
14 June 2015
(Mr Samson M. Haumba)  
Date
ACKNOWLEDGEMENTS

This thesis would not have been possible without the guidance and support from many people and institutions. I want to thank the following persons for their respective contributions to this thesis:

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Finally, I acknowledge the Africa Doctoral Dissertation Fellowship managed by APHRC and IDRC for the partial funding of the research work.
ABSTRACT

The purpose of the study was to develop best practice guidelines to prevent permanent hearing loss associated with the management of multi-drug resistant tuberculosis (MDR-TB) through raised awareness and monitoring. The Human Immunodeficiency Virus (HIV) and MDR-TB are global public health problems requiring urgent scale-up of treatment services. Irreversible sensorineural hearing loss (SNHL) is one of the adverse drug reactions of the current World Health Organization (WHO) recommended MDR-TB chemotherapy fuelling another public health problem, that disabling hearing loss, which is the second highest contributor of Years Lived with Disability (YLD) according to the World Health Report (2003). Expansion of MDR-TB treatment threatens to increase incidence of SNHL unless there is urgent implementation of intervention towards preservation of hearing for patients on treatment. This empirical study determined and documented the incidence of SNHL in HIV positive and HIV negative patients on MDR-TB treatment, the risk factors for SNHL, from the time treatment initiation to SNHL. Based on the findings, developed and improved the understanding of best practice guidelines for monitoring and prevention of MDR-TB treatment-related SNHL.

The empirical study recruited a cohort of 173 patients with normal hearing status, after diagnosis with MDR-TB and enrolled on MDR-TB therapy over thirteen month period. Patients in the cohort received monthly hearing sensitivity testing during the intensive MDR-TB therapy when injectable aminoglycoside antibiotics are part of the treatment regimen. The three study endpoints included completion of the eight-month intensive treatment phase without developing hearing loss, development incident hearing loss or loss to follow up. Data was analysed using STATA statistical software and summarised using frequencies, means, proportions, and rates. The study documented incidence of SNHL, time to hearing loss and risk factors for
hearing loss. Recommendations to prevent and monitor hearing loss are made based on the study findings.

**Key concepts**

Sensorineural hearing loss, cochleotoxicity, multi drug resistant tuberculosis, aminoglycoside antibiotics, Audiometry, incidence, time-to-event, best practice guidelines, prevention, monitoring.
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<td>Lamivudine</td>
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<td>AAA</td>
<td>American Academy of Audiology</td>
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<td>ABC</td>
<td>Abacavir</td>
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<td>AC</td>
<td>Air Conduction</td>
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<td>Advocacy, Communication and Social Mobilisation</td>
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<td>AD</td>
<td>Right</td>
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<td>AIDS</td>
<td>Acquired Human Immunodeficiency Syndrome</td>
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<td>ANSI</td>
<td>American National Standards Institute</td>
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<td>Better ear hearing loss</td>
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<td>Drug Susceptibility Testing</td>
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<tr>
<td>EC</td>
<td>European Commission</td>
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<tr>
<td>EFV</td>
<td>Efavirenz</td>
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<tr>
<td>EHDI</td>
<td>Early Hearing Detection and Intervention</td>
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<tr>
<td>EMF</td>
<td>Enhanced Monitoring Framework</td>
</tr>
<tr>
<td>ENT</td>
<td>Ear, Nose and Throat</td>
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<tr>
<td>EU</td>
<td>European Commission</td>
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<tr>
<td>HA</td>
<td>Hearing Aid</td>
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<tr>
<td>HAE</td>
<td>Hearing Aid Evaluation</td>
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<tr>
<td>HB</td>
<td>Haemoglobin level</td>
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<tr>
<td>HFA</td>
<td>High Frequency Average</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HL</td>
<td>Hearing Level</td>
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<tr>
<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
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<tr>
<td>IEC</td>
<td>Information, Education and Communication</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile Range</td>
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<tr>
<td>IL</td>
<td>Intensity level</td>
</tr>
<tr>
<td>INH</td>
<td>Isoniazid</td>
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<tr>
<td>K</td>
<td>Kanamycin</td>
</tr>
<tr>
<td>KHz</td>
<td>Kilo hertz</td>
</tr>
<tr>
<td>MCL</td>
<td>Most Comfortable Loudness level</td>
</tr>
<tr>
<td>MDG</td>
<td>Millennium Development Goals</td>
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<tr>
<td>MDR</td>
<td>Multi drug resistant</td>
</tr>
<tr>
<td>MHL</td>
<td>Mild bilateral Hearing Loss</td>
</tr>
<tr>
<td>MM</td>
<td>Multiple morbidities</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>MSNHL</td>
<td>Minimal Sensorineural Hearing Loss</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
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<tr>
<td>NIDCD</td>
<td>National Institute on Deafness and Other Communication Disorders</td>
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<tr>
<td>NIHL</td>
<td>Noise Induced Hearing Loss</td>
</tr>
<tr>
<td>NIOSH</td>
<td>National Institute for Occupational Safety and Health, USA</td>
</tr>
<tr>
<td>NITS</td>
<td>Noise-Induced Threshold Shift</td>
</tr>
<tr>
<td>NOHSC</td>
<td>National Occupational Health and Safety Commission</td>
</tr>
<tr>
<td>NR</td>
<td>No Response</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non-Nucleoside Reverse Transcriptase Inhibitor</td>
</tr>
<tr>
<td>NRTI</td>
<td>Nucleoside Reverse Transcriptase Inhibitor</td>
</tr>
<tr>
<td>NSM</td>
<td>Neuman's Systems Model</td>
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<tr>
<td>OAE</td>
<td>Otoacoustic Emissions</td>
</tr>
<tr>
<td>OHS</td>
<td>Occupational Health and Safety</td>
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<tr>
<td>ONIHL</td>
<td>Occupational Noise-Induced Hearing Loss</td>
</tr>
<tr>
<td>PHPs</td>
<td>Personal Hearing Protectors</td>
</tr>
<tr>
<td>PLHIV</td>
<td>People Living with HIV</td>
</tr>
<tr>
<td>PRN</td>
<td>Pro re nata (from Latin) As needed. Decision on when to administer drug is left to nurse, care giver of patients prerogative</td>
</tr>
<tr>
<td>PTA</td>
<td>Pure Tone Average</td>
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<tr>
<td>PTB</td>
<td>Pulmonary Tuberculosis</td>
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<tr>
<td>PZA</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td>RTC</td>
<td>Return To Clinic</td>
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<tr>
<td>RNID</td>
<td>Royal National Institute for Deaf and Hard of Hearing People</td>
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<tr>
<td>SAT</td>
<td>Speech Awareness Threshold</td>
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<tr>
<td>SIDS</td>
<td>Swaziland Demographic and Health Survey</td>
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<tr>
<td>SLD</td>
<td>Second Line Drugs [TB]</td>
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<tr>
<td>S/N-SIFTER</td>
<td>Signal-to-Noise (ratio) SIFTER</td>
</tr>
<tr>
<td>SNHL</td>
<td>Sensorineural Hearing Loss</td>
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<tr>
<td>SPL</td>
<td>Sound Pressure Level</td>
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<tr>
<td>SRT</td>
<td>Speech Reception Threshold</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TDF</td>
<td>Tenofovir</td>
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</tbody>
</table>
Trizivir Abacavir/Lamivudine/Zidovudine
UCL Uncomfortable Loudness Level
UHL Unilateral Hearing Loss
VT Vibrotactile Response
WHO World Health Organization
WNL Within Normal Limits
WRD WHO Recommended rapid Diagnostics [TB]
XDR Extensively drug resistant
LIST OF DEFINITIONS AND DISTINCTIONS OF TERMS USED IN THE STUDY

**Age-related hearing loss:** Loss of hearing that progresses with age. Also known as presbycusis.

**Assistive Device:** An Assistive Device is any device that helps someone do something that they might not otherwise be able to do well or at all. Generally, the term is used for devices that help people overcome a handicap such as a mobility, vision, mental handicap, and dexterity or hearing loss.

**Audiogram:** An Audiogram is a means of recording the results of a hearing test. It will include a table and a graph for each ear showing how well someone could hear sounds at various frequencies. This graph dominates the Audiogram and measures the lowest volume that someone can hear pure tone signals at different frequencies for each ear.

**Audiometry:** A test to measure an individual’s hearing threshold level.

**Auditory Brainstem Response (ABR):** A test that is used to screen or to diagnose hearing loss. The ABR evaluates the nervous system response to sound.

**CD4:** A glycoprotein that serves as a differentiation antigen found on the surface of T lymphocytes and macrophages. The CD in CD4 stands for cluster of differentiation. The presence of CD4 characterises the helper/inducer cell. It also serves as HIV receptors where the virus binds directly with its envelope protein, gp120.

**Cochlea:** The cochlea is the sense organ that translates sound into nerve impulses to be sent to the brain. Each person has two cochlea, one for each ear. The cochlea is a fluid-filled, snail-shaped cavern in the mastoid bone of your skull behind each ear. Tiny bones in the middle ear transmit sound from the eardrum across the middle ear and vibrate against the cochlea. Vibrations in the fluid cause tiny hair cells in the fluid inside the cochlea to vibrate and generate nerve impulses that then travel to the brain.


**Decibel**: The unit used to indicate the relative magnitude of sound pressure level and other acoustical quantities, abbreviated as ‘dB’. A decibel, or dB, is an appraised signal strength in terms of relative loudness heard by the ear. The decibel is 1/10 of a bel, a unit of sound named after Alexander Graham Bell. A change of 1 dB is just detectable as a change in loudness under ideal conditions. The decibel is a relative unit.

**deaf (lower case “d”)**: In this uncapsulated form, the word “deaf” simply means unable to hear. It says nothing about the individual, the individual’s language or culture. Some deaf people also consider themselves "Deaf" with a capital "D", which does imply a lot about their language and culture. Technically, Deaf people, some hard of hearing people, and all late deafened people, are deaf.

**Deaf (Upper Case "D")**: In this capitalised form, the word “Deaf” generally implies that the person does not hear well enough to understand speech from their hearing alone, but it also means that they consider themselves part of the "Deaf Community". People in the "Deaf Community" typically use sign language.

**Frequency**: The number of cycles per second (Hertz) (abbreviated as, Hz) of anything that oscillates is called the "frequency". The electricity of an AC wall outlet is said to have a frequency of 60 Hertz as it cycles negative and then positive, 60 times each second.

**Full Diagnostic Audiologic Testing**: An in-depth evaluation of hearing using different tests to determine if a hearing loss exists. If a hearing loss is identified, the evaluation determines the type, degree, and configuration of the hearing loss.

**Hair cells**: Hair cells in the cochlea are moved by the vibrations of the cochlea and of the fluid in the cochlea caused by sound waves. The cells at the base of the hair cells convert their motion into electrical signals to be sent up the acoustic nerve to be interpreted by the brain as sound. Actually, the hair cells are not really hair; but they behave somewhat like hair might. Damage to hair cells (or the lack of them) is one of the major causes of hearing loss.
**Hearing aid:** A hearing aid is anything that helps you to hear better than before. Early hearing aids were mechanical, and typically involved horns or funnels and tubes to direct sound into a person's ears.

**Hearing impairment:** Hearing loss that causes some degree of disability.

**Hearing loss:** Reduced ability in a person to detect sound.

**Hearing screening:** An objective screening method performed to identify who may have hearing loss and who need follow up or more in-depth diagnostic hearing loss assessment.

**Hearing threshold level:** The quietest sound a person can detect at a particular frequency relative to young people with normal hearing.

**Incidence:** Number of new cases of disease or condition of interest of during a defined period.

**Intervention:** A programme, strategy, or specific measure aimed at eliminating or minimising a risk.

**Noise:** Any unwanted or damaging sound.

**Occupational noise:** Noise experienced in the workplace.

**Organ of Corti:** The spiral structure within the cochlea which contains the hair cells which convert the vibrations representing sound into nerve impulses.

**Otoacoustic emissions (OAEs):** A screening method that measures sounds made by the sensory cells in a healthy ear that can be recorded from the ear canal. For screening purposes, the test is fully automated.

**Ototoxic drugs:** Ototoxic drugs are drugs that can cause temporary or permanent hearing loss. They can also make an existing hearing loss worse. They may also cause other related problems including such things as: tinnitus, hyperacusis,
pressure in the ear, ceruminosis, dizziness, vertigo, ataxia, nystagmus, oscillopsia, ear pain, auditory hallucinations, various eye problems, or muscle pain in the neck.

**Presbycusis**: refers to hearing loss related to age. It is also referred to as age-induced hearing loss. Age, itself, does not cause hearing loss, but the prevalence of hearing loss does increase with age.

**Sound**: Energy in the form of pressure waves that move through air and other media and are capable of exciting the sensation of hearing in a listener. It is an oscillating wave, but it has a broad range of frequencies. A low frequency sound (say, 50 Hz) might sound like a low rumble, while a high frequency sound (say 12,000 Hz), might sound more like a "sizzle". A person with normal hearing can hear all the way up to about 20Hz to 20,000 Hz.

**Sound pressure level**: The relative magnitude of sound pressure expressed in decibels referenced to 20 micropascals.

**Temporary threshold shift**: Temporary hearing loss, usually as a result of short-term exposure to loud noise.
CHAPTER 1

ORIENTATION TO THE STUDY

1.1. INTRODUCTION

This chapter focuses on the exposition of the problem, the research objectives, research questions and the salient methodological and ethical considerations. It provides the basis for the research problem and the scope of the research, given that the reasons for undertaking the study link closely to the principles of the research problem. The chapter reflects these in the description of the problem and its background including the socio-economic and the policy importance of this investigation.

Tuberculosis, or TB, is an infectious bacterial disease caused by *Mycobacterium tuberculosis*. According to World Health Organization, in 2012, worldwide, 450,000 and 170,000 people developed and died multi drug resistant TB (MDR-TB), one of most serious and urgent public health challenges of the 20th century (Upshur, Singh & Ford 2009:481; WHO 2013). Multidrug-resistant tuberculosis (MDR-TB) is TB that does not respond to at least isoniazid and rifampicin, the two most powerful anti-TB drugs (Chiang, Centis & Migliori 2010:413). Marginal evidence shows an increase in the risk of MDR-TB among people with HIV infection (Mesfin, Hailemariam, Biadgilign & Kibret 2014). Treatment outcomes for MDR-TB are poorer than for drug susceptible TB and adversely affected by the longer duration of treatment, serious side effects and high costs (Araújo-Filho, Vasconcelos-Jr, Sousa, Silveira, Sousa, Severo, Vieira, Kipnis & Junqueira-Kipnis 2008:94). Wu, Zhang, Sun, Chen, Zhou, Wang and Zhan (2013) report that pooled estimate of 70.4% of patients on MDR-TB treatment required a change in their treatment because of adverse drug reactions. Disabling hearing loss is one such severe drug adverse reactions affecting outcomes (Javadi, Abtahi, Gholami, Safari Moghadam, Tabarsi & Salamzadeh 2011:905-11; Modongo, Sobota, Kesenogile, Ncube, Sirugo, Williams & Zetola 2014). There is no other period in recent history when there was such an urgent search for new and

The Agency for Healthcare Research and Quality identifies the minimisation of treatment-related adverse events (AEs) or harms, as patient safety practice and defines patient safety as:

“A type of process or structure whose application reduces the probability of adverse events resulting from exposure to the health care system across a range of diseases and procedures”


To this end, a proportion of patients treated for MDR-TB have to contend with the consequences of an irreversible toxicity, literally “separating them from their loved ones and from their communities” because of a new identify as hearing-impaired.

“Blindness separates people from things; deafness separates people from people.”

— Helen Keller (Keller, [Sa])

The status quo prevails because:

- Injectable aminoglycoside antibiotics are a backbone in the MDR-TB treatment regimen and increased duration of the injectable aminoglycoside is associated with improved treatment outcomes (Caminero, Sotgiu, Zumla & Migliori, 2010:621-9; Modongo et al 2014; World Health Organization, 2011b:6, 16-22).
- The second line anti-tuberculosis treatment (ATT) available for treatment of MDR-TB are limited in number (Caminero et al 2010:621).
- The serious adverse reactions of MDR-TB treatment like ototoxicity (comprised of vestibulotoxicity and cochleotoxicity) and specifically the irreversible sensorineural hearing loss (cochleotoxicity) have not been investigated adequately, there is lack of high quality clinical data to inform
guidelines and modifiable risk factors are largely unknown, or seldom reported in studies (Bloss, Kuksa, Holtz, Riekstina, Skripconoka, Kammerer & Leimane 2010:275-81; Javadi et al 2011:906-10; Sturdy, Goodman, Jose, Loyse, O'Donoghue, Kon, Dedicoat, Harrison, John, Lipman & Cooke 2011:1815).

- Cutting prevalence and death rates due to MDR-TB through expansion of treatment is arguably a more important goal in the short-term (World Health Organization 2011b:5).

Given that universal treatment of MDR-TB patients is critical and, will most likely, escalate the burden of SNHL in the country in the absence of better drugs, interventions aiming at prevention and hearing conservation are critical contributions in improving quality of life of MDR-TB patients and their families. The WHO has heightened awareness about disabling hearing impairment in the past, as is still doing so today. In 1995 through a World Health Assembly resolution, WHA48.9, disabling hearing loss was tagged as a new public health problem (Resolution 1995). According to the WHO, the number of people with such impairment increased from 42 million in 1985, to about 420 million in 2011 (Olusanya, Neumann & Saunders 2014b). The cost of rehabilitative services is so high and primary prevention is emphasised. Deliberate effort is required to stop the silent progress of hearing loss associated with MDR-TB treatment through monitoring any deterioration in hearing sensitivity and implementation of interventions that preserve hearing and communication functionality. Public health actions are early detection and prompt action (Ahmad & Mokaddas 2009:1777; Guthrie 2008:91; Wu et al 2013; Yew 2011:9).

The sense of hearing is essential for enabling us to live and participate in life more fully, first and far most. Good hearing also helps to keep us safe, by warning us of potential danger. Therefore, post lingual and adult onset loss of hearing can be a very devastating and life-changing experience for patients, affecting the way they communicate, relate, perceive self, earn a living and/or are perceived (Ask, Krog & Tambs 2010:271-275; Morris, Quezada, Bhat, Moser, Smith, Perez, Laniado-Laborin, Estrada-Guzman & Rodwell 2013:954; Wallhagen 2004:S190-119; Wallhagen 2010:66-75). The impact of adult onset hearing loss can also have
profound effects on the victim and the family members. Shannon describes her personal experience with hearing loss:

“Deafness, however, left me and those around me at a loss. I had always taken hearing for granted. I was a musician and my training, my dreams and my life, revolved around music. Now all I had left was a distorted form of inner noise...”

- Shannon (2006:6)

In Swaziland, Groce, Yousafzai, Dlamini, Zalud and Wirz (2006) and Groce (2003) found that the majority, (99%) of deaf people, report difficulties in communicating with healthcare facility staff affecting their utilisation of health preventive and curative services. In another study, the deaf population in Swaziland was more likely to believe in incorrect modes of HIV transmission than the normal hearing population (Groce, Yousafzai, Dlamini, Zalud & Wirz 2006:319-324; Groce 2003:1401-1402). Yet hearing preservation, and if possible restoration of hearing in affected MDR-TB patients, can mean a big change in the quality of life of the individual and their families (Ask et al 2010:271-5; Lotfi, Mehrkian, Moossavi & Faghih-Zadeh 2009:265-70; Newberry 2011:S24-6).

1.2 BACKGROUND INFORMATION ABOUT THE RESEARCH PROBLEM

1.2.1 Source of the Problem

Swaziland has a population of about 1.2 million inhabitants and a very high per capita burden of HIV and TB. Recent statistics show that about 31% of the adults aged 18-49 years are living with HIV infection. Coupled with the high HIV rate is the high HIV related TB incidence. About 13 people in 1000 develop tuberculosis disease every year, and 80% of those developing TB are HIV infected (Bicego, Nkambule, Peterson, Reed, Donnell, Ginindza, Duong, Patel, Bock, Philip, Mao & Justman 2013; Central Statistics Office (CSO) [Swaziland] and Macro Inc, 2008:221-222; World Health Organization 2012). Closely linked with the high HIV and TB per capita burden is the country’s MDR-TB rate which is 7.7% in new TB patients (higher than the global average of 3.5% among new TB patients) and 33.9% among
previously treated TB patients (Sanchez-Padilla, Dlamini, Ascorra, Rusch-Gerdes, Tefera, Calain, de la Tour, Jochims, Richter & Bonnet 2012:29-37; World Health Organization 2014b). Hedt, van Leth, Zignol, Cobelens, van Gemert, Nhung, Lyepshina, Egwaga & Cohen (2012:293-300) define thresholds for low and high prevalence of MDR TB as 2% or less and 10% or higher among new cases, respectively. According to the Swaziland Ministry of Health annual report of 2013, the annual number of cases initiated on MDR-TB treatment increased from 54 cases in 2007 to 562 in 2012. The incidence of MDR-TB is likely to continue increasing, an indication that more and more patients will be exposed to potentially cochleotoxic medications resulting in more cases of MDR-TB related sensorineural hearing loss (NTCP 2013).

Cure, prompt initiation of treatment, avoiding acquisition of resistance and survival are the top four priorities for MDR-TB control (World Health Organization, 2011b:5). However, the long-term aim of MDR-TB control is to eliminate new cases (Gandhi, Nunn, Dheda, Schaaf, Zignol, van Soolingen, Jensen & Bayona 2010:1830-43). To that end, the WHO guideline development group ranks avoiding toxicity and adverse drug reactions associated with MDR-TB as a number 14 priority in the recommendations for a treatment regimen (World Health Organization 2011b:5). While WHO also recommends pharmacovigilance, monitoring adverse events among MDR-TB patients as a safety prerequisite, most MDR-TB treatment programmes lack hearing status monitoring equipment and personnel and there is no high quality data to inform guidelines (Sturdy et al 2011:1815).

1.2.2 Background to the research problem

Research and anecdotal evidence suggest that treatment of MDR-TB is be associated with significant adverse drug reactions (ADRs) as elaborated in section 1.1. Yet ADRs to treatment are inadequately reported by patients and health care workers (Lopez-Gonzalez, Herdeiro & Figueiras 2009b:19-31). The main barriers for reporting ADRs are ignorance about ADRs, indifference about reporting ADRs, complacency, and lack of guidelines and structures (Lopez-Gonzalez et al 2009b:19-31; Sturdy et al 2011:1815). Lack of recognition of sensorineural hearing loss during MDR-TB treatment due to the high cost of audiometry equipment and lack of skilled
personnel to conduct audiometry is a major contributor for underreporting SNHL (Fausti, Wilmington, Helt, Helt & Konrad-Martin 2005; Jacob, Aguiar, Tomiasi, Tschoeke & Bitencourt 2006:836-44; Javadi et al 2011:906; Merriam-Webster Medical dictionary [Sa], Sturdy et al 2011:1815-1820). Coleman, Ferner and Evans (2006:371-372) underscore the importance of a systematic monitoring health status and reporting any ADRs during treatment as the process of proactive targeted observation, analysis and action in order to avoid or mitigate harm from adverse drug reactions.

1.3 THE RESEARCH PROBLEM

The analysis of the research problem deals with becoming aware of the problem, a preliminary literature study to investigate the problem and finally, formulation of the research problem statement.

1.3.1 Awareness of the Problem

The researcher become aware of the problem because of his involvement in the management of MDR-TB patients since 2006. As a public health physician involved in the management of patients with multi drug resistant tuberculosis, the researcher interacted with many patients who developed hearing loss while on MDR-TB treatment. Each patient, with a heart-breaking story. Relatives expressed concerns about the changed identity of their loved ones. Linda is one of the MDR-TB patients. She notes...:

“Losing my hearing was very difficult for me…but I tried to be positive about it, telling myself that the doctors knew what they were doing. Eventually I accepted that this was the price I had to pay for my health”

-Linda (MSF, August, 2013).
1.3.2 Preliminary questions

The awareness increased the sentience of the following questions about hearing loss related to MDR-TB treatment:

- What is the incidence of sensorineural hearing loss among MDR-TB patients receiving MDR-TB treatment in Swaziland and who is affected, when are they affected, what factors are associated with development of SNHL?
- What are best practices for monitoring and prevention of MDR-TB treatment related hearing loss?

1.3.3 Policy Relevance of the Research

The detection of preventable adverse events is a primary step in achieving a safe healthcare system (Forster, Worthington, Hawken, Bourke, Rubens, Shojania & van Walraven 2011:756; Steinman, Handler, Gurwitz, Schiff & Covinsky 2011:1513-20; World Health Organization 2005, 2010b). Many settings including Swaziland lack local evidence to address the questions in section 1.3.2. The research findings can play a catalytic role in increasing awareness of MDR-TB treatment related hearing loss among the key decision and policy makers. Among others, key policy makers include the directors and managers in the Ministry of Health, in the Ministry of Education, in the department of Social welfare in the Prime Minister’s office, in the relevant health care service organisations as well as members of the legislature and sectoral committee on health. Other stakeholders involved in guideline development and policy formulation are the clinicians and health management committees. The aforementioned policy makers are responsible for making, laws, creating a conducive environment for policy dialogue and legislation as recommended by the World Health Assembly resolution WHA.48.9 of 1995.

Policy makers engage in a wide range of health care concerns such as health care costs, disease burden and treatment effectiveness. They can effectively address the concerns aforesaid concerns if there is contemporary data to drive the public health urgency to do something. (Armstrong, Waters, Dobbins, Anderson, Moore,

The absence of programmatic and research data on the social, economic, morbidity and disabling disability burden as evidence for planning decisions may hamper the desired and appropriate response by policy makers to do something about MDR-TB treatment related hearing loss. From the social perspective hearing impaired persons require specialised educational, social services and other resources in order to function in society (Mohr, Feldman, Dunbar, McConkey-Robbins, Niparko, Rittenhouse & Skinner 2000). From the economic perspective the costs for hearing aids can put a strain on the Ministry of Health budget given the costs about $1800-$6800 per hearing aid which lasts for only 4-6 years and maximum benefit occurs if the hearing aids are introduced when the hearing impairment is mild to moderate (Donahue, Dubno & Beck 2010:3-4). While from a health care access perspective, a number of studies suggest that barriers for prevention of MDR-TB related hearing loss result from of lack of conducive policy environment, guidelines, equipment and skilled personnel (Javadi et al 2011:906; Seddon, Godfrey-Faussett, Jacobs, Ebrahim, Hesseling & Schaa, 2012).

While hearing health care access is not universal even in the most developed countries, anecdotal evidence suggests that in Swaziland, the burden of MDR-TB treatment related hearing loss is unknown to the policy makers and neither are the resources needed to increase accessibility and affordability of hearing preservation (Donahue et al 2010:2-6; Sturdy et al 2011:1815). Research evidence is a powerful tool for advocacy with policy makers because it enables them to make the right policy decisions and the desired resource allocations to address the existing health systems challenges. Best practice research evidence also occupies the moral high ground because its practitioners do “what works” and generates contemporary data to drive clinical practice (Murthy, Sheperd, Clarke, Garner, Lavis, Perrier, Roberts & Straus 2012).

This study developed a technical briefing report and best practice guidelines. Among the most frequent sources was advice from an expert and consulting technical reports. Summaries from systematic reviews and technical documents also enable
ease with which the policy makers access evidence (Dobbins, Jack, Thomas & Kothari 2007; Zardo & Collie 2014). The presentation of a technical report and guidelines is one way to encourage policy makers’ access research evidence about hearing loss and encouraging greater use of this evidence to do something about hearing preservation in MDR-TB patients.

1.3.4 Statement of the Problem

Every year, MDR-TB and HIV contribute significantly to mortality and morbidity in Swaziland. Anecdotal evidence suggests that the role out of MDR-TB treatment as a response to the threat MDR-TB poses of public health is also associated with a rising incidence of MDR-TB treatment related hearing loss. Numerous studies conducted in other parts of the world confirm the association of hearing loss and the aminoglycoside antibiotics used in the intensive phase of MDR-TB treatment. A closer examination of the situation reveals that while the current MDR-TB guidelines mention performance of audiometry of patients presenting with hearing loss, they provide little guidance on how to detect ototoxicity before overt hearing loss and how to prevent or minimise development of hearing loss associated MDR-TB treatment in the first place.

There is a clear gap in the knowledge of the burden of MDR-TB treatment related hearing loss and the associated factors. The lack of local studies on hearing loss in the context of the dual epidemic of MDR-TB and HIV further exacerbates the knowledge gap. For instance, the unknown impact of HIV infection on the incidence of hearing loss related to MDR-TB treatment exposes a major gap in the evidence base for guidelines development (Seddon et al 2012; Sturdy et al 2011:1815; World Health Organization 2011c). The generation and use of high quality data to recommend guidelines and for advocacy with policy makers and donors has the potential for catalyst action for additional investments in hearing health and quality of life for MDR-TB patients.

The design of the study contributes to a deeper and clearer understanding of the situation regarding MDR-TB treatment related hearing loss and the risk factors, so that health care workers and stakeholders are in a better position to initiate remedial
measures. This research addresses both the gap in clinical data and evidence for the urgent call to action on monitoring hearing loss and provides best practice guidelines to guide establishing an ototoxicity program. It also provides an empirical framework for integrating hearing loss monitoring and hearing preservation actions within the health system in Swaziland (Atun et al 2010:104; Geib 2002:235; Sturdy et al 2011:1815).

1.4 AIM OF THE STUDY

1.4.1 Research Purpose

The purpose of the research was determine the incidence of sensorineural hearing loss associated with MDR-TB treatment, the risk factors for hearing, time from treatment initiation to development of hearing loss and to develop best practice guidelines for prevention and monitoring hearing loss associated with MDR-TB treatment in Swaziland. The aim of the best practice guidelines is to contribute to strengthening institutional capacity for prevention of hearing loss, ototoxicity monitoring and early identification of SNHL to facilitate of timely remedial actions aimed at preservation of communication.

1.4.2 Study Objectives

The specific objectives of the study were to:

- Establish the incidence of sensorineural hearing loss among MDR-TB patients during the intensive phase of MDR-TB treatment in Swaziland.
- Identify risk factors for sensorineural hearing loss during the intensive phase of MDR-TB treatment in Swaziland.
- Determine the impact of HIV/AIDS influences the incidence of sensorineural hearing loss in MDR-TB patients in Swaziland.
- Assess the time it takes from start of intensive MDR-TB treatment to the development of hearing loss and recommend the optimal frequency for audiometric monitoring of patients on MDR-TB treatment in Swaziland.
• Develop best practice guidelines for prevention and monitoring MDR-TB related hearing loss in Swaziland.

1.4.3 Study Hypotheses

In the study, it is hypothesised that:

*Study hypothesis 1:*

The incidence ratio of sensorineural hearing loss during the intensive phase of MDR-TB treatment increases proportionally with the duration of treatment.

*Study hypothesis 2*

MDR-TB patients living with HIV infection have a higher incidence ratio of sensorineural hearing loss than HIV negative MDR-TB patients during the intensive phase of MDR-TB treatment.

1.5 SIGNIFICANCE OF THE STUDY

The rapid scale up of current treatments for DR-TB, accompanied by an increasing challenge of post lingual SNHL associated with MDR-TB treatment poses a new dilemma for health professionals, patients, and families, most importantly, the psycho-socio-economic impact. The knowledge generated has many potential applications for advocacy, community sensitisation, and clinical practice to mitigate the many psychological, physical, social, and economic consequences of a silent, but destructive, condition and contribute to the alleviation of human suffering related to this condition. Thus, the expected benefits of the study are the contributions to clinical practice, contributions to public health and policy dialogue and contributions to knowledge.
The main contribution of this study is the advancement of science. As this is a case study of the local value, the study will increase awareness about hearing health and actions for hearing preservation, and could bring about change and improvement in the way health care workers manage their patients because of the guidelines developed as part of this study. The study responds to the World Health Assembly resolution WHA48.9 of May 1995, that requested the Director General “to promote and support, to the extent feasible applied and operations research for the optimal prevention and treatment of the major causes of hearing impairment” (World Health Assembly 1995).

In so doing, the study directly contributes to the needs of the secondary beneficiaries who are the clinicians, the policy makers, as well as the community and families as follows:

1. **Improving clinical practice and patient care through systematic practice improves quality of life.**

The study responds to a call from other researchers for better clinical data to inform guidelines for monitoring hearing loss related to MDR-TB treatment by providing robust data and best practice guidelines (Sturdy et al 2011:1815). Davies et al (2008:29), Dulko (2007:29), Herdeiro, Polonia et al (2004:483-9), Ploeg, Davies et al (2007:201-9) and Tanenbaum (2005:163-73) contend that the goal of research evidence is to change practitioners’ behaviour by bridging the distance from research to practice and securing a central place for research in the consulting room. Synthesis of the results of the study and the development of guidelines is a positive step in the implementation of interventions to mitigate the impact of hearing loss among MDR-TB patients. The study provides a basis for implementation of standardised monitoring practices to improve quality of patient care and minimise variations in service delivery and plays a catalytic role in the renewal of interest in pharmacovigilance (Eccles & Mason 2001).
2. **Increasing services to support patients and families.**

The best practice guidelines, a product of this study provides standardised recommendations for hearing preservation and engagement of patients and their families. The principles and tools suggested for monitoring ototoxicity are a potential catalyst for establishment of systems for monitoring all the ADRs associated with MDR-TB treatment. For the patients who develop hearing loss and their families and communities, the guidelines provide minimum standards for counselling services, establishment of communication skills for patients, provision of hearing aids and training in sign language. Collaboration with sign language organisations, the guidelines call for the training of staff at the MDR-TB treatment sites on an essential package of hearing health care and its integration the community linkages component of MDR-TB care to assist patients with hearing loss to preserve communication with family and community.

3. **Advocacy and guidance to policy makers and health planners to investment opportunities in public health and hearing health care.**

This research documents the quantifiable outcomes of a standardised intervention and enables evidence based planning and a basis for construction of a hearing health policy for MDR-TB patients. Policy makers and health planners can use the evidence to create an enabling environment for early preventive interventions and use the data for planning procurement of hearing aid services/ assisted listening devices, rehabilitation, and reintegration for patients who do not benefit from prevention and develop hearing impairment. Policy makers can also promote family counselling and education, and legislation concerning use of ototoxic medicines or introduction of safer medicines in the health systems such as the new and old repurposed drugs for MDR-TB through the use of informed data for informed decisions (Atun et al 2010:104; Chasin & Russo 2004:35-47; Rogers 2003).
1.6 DEFINITION OF TERMS

1.6.1 Adverse drug reactions

An adverse drug reaction as “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product” (Davies, Green, Taylor, Williamson, Mottram & al., 2009; Edwards & Aronson 2000:1255-59). The WHO defines an adverse drug reaction as a “response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function (World Health Organization, 1969).” The definition excludes therapeutic failures, intentional or accidental poisoning, and drug abuse (Naranjo, Busto, Sellers, Sandor, Ruiz, Roberts, Janecek, Domecq & Greenblatt 1981:240; World Health Organization 1969). Of note is that adverse drug reaction is harm caused directly by the drug at normal doses, during normal use. There are six types of ADRs: dose-related (Augmented), non-dose-related (idiosyncratic, bizarre), dose-related and time-related (Chronic), time-related (Delayed), withdrawal (End of use), and failure of therapy (Failure). Suspected ADRs can also be classified in terms of causality and avoidability according to validated algorithms (Davies et al 2009). Included in this definition, is the term ADE, which refers to harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug (including dose reductions and discontinuations of drug therapy) (Nebeker, Barach & Samore 2004b:795-801).

1.6.2 Audiogram

An audiogram is a graph that shows the softest sounds a person can hear at different pitches or frequencies. An “O” represents responses for the right ear and an “X” for responses of the left ear. An audiogram shows the audible threshold for standardised frequencies as measured by an audiometer, which
is an instrument used to obtain air conduction thresholds on all examinees. The Y-axis represents intensity measured in decibels and the X-axis represents frequency measured in Hertz. The threshold of hearing plotted is relative to a standardised curve that represents 'normal' hearing, in dB (HL). Audiograms are set out with frequency in hertz (Hz) on the horizontal axis, most commonly on a logarithmic scale, and a linear dBHL scale on the vertical axis. Frequency is cycles per second and pitch is the perceptual correlate of frequency and measured in hertz. The intensity is the level of sound power measured in decibels and loudness is the perceptual correlate of intensity (Gelfand 2009:144; Wikidepia, ibid-a).

1.6.3 Best Practice guidelines

A best practice is a method or technique that has consistently shown results superior to those achieved with other means, and used as a benchmark. In addition, a "best" practice can evolve to become better as improvements are discovered. Best practices are used to maintain quality as an alternative to mandatory legislated standards and can be based on self-assessment or benchmarking (Bogan & English 1994). However, in clinical practice, this refers to clinical practice guidelines, which is a document with the aim of guiding decisions and criteria regarding diagnosis, management, and treatment in specific areas of healthcare. It contains professional procedures and systematically developed statements that are accepted or prescribed as being correct or most effective, and assists both practitioner and patient decisions in specific circumstances. Best practice guidelines are based on an examination of current evidence within the paradigm of evidence-based medicine (Medicine 2011; The Agree Collaboration 2003, Wikidepia.). Guidelines are viewed as useful tools for making care more consistent and efficient and for closing the gap between what clinicians do and what scientific evidence supports (Burgers, Grol, Klazinga, Mäkelä & Collaboration 2003).
1.6.4 Hearing loss/Hearing impairment/Deafness

Hearing loss refers to any reduction of, or difficulties with, hearing and there are three aspects for describing hearing loss: type of hearing loss, degree of hearing loss, and configuration of hearing loss. The basic types of hearing loss are the conductive, SNHL, and mixed hearing loss. The degree of hearing loss refers to the severity of the loss, and WHO (WHO 2013) defines a person who is not able to hear the hearing thresholds of 25dB or better in both ears as having hearing loss, which may be mild, moderate, severe, or profound. While configuration, or shape, of the hearing loss refers to the degree and pattern of hearing loss across frequencies (tones) as illustrated in a graph called an audiogram as described above in section 1.6.2 (ASHA 2011). On the other hand, ‘Hard of hearing’ refers to people with hearing loss ranging from mild to severe. They usually communicate through spoken language and can benefit from hearing aids, captioning, and assistive listening devices. People with more significant hearing losses may benefit from cochlear implants. ‘Deaf’ people mostly have profound hearing loss, which implies very little or no hearing. They often use sign language for communication.

1.6.5 Multi-Drug Resistant Tuberculosis

Multi-drug resistant TB is defined as tuberculosis strains with resistance to at least two anti-tubercular drugs, Isoniazid and Rifampicin (Gandhi et al., 2010). A subcategory of extensively drug-resistant TB (XDR TB), has additional resistance to Fluoroquinolone and to at least one of three injectable anti-TB drugs; namely, Kanamycin, Capreomycin, or Amikacin (Chiang et al., 2010). It excludes mono resistant and poly resistant tuberculosis(WHO 2011b) (World Health Organization 2011b).

1.6.6 Pure Tone Audiometry

Pure tone audiometry is an air conduction behavioural test that tests the hearing sensitivity of the entire auditory system by presenting pure tone
signals to the ear through earphones, and varying the intensity of the signals until the level is identified at which the person is just able to hear the sound. This level is known as the person’s threshold; clinically, threshold is usually defined as the level at which the subject will be able to detect the signal 50% of the times that it is presented. Pure tones are presented at different frequencies across the range of human hearing and this type of testing evaluates the auditory system as a whole, and is capable of identifying hearing problems at almost any level within the auditory system (Gelfand 2009:139; National Center for Health Statistics & Centers for Disease Control and Prevention 2005).

1.6.7 Ototoxicity Monitoring

Ototoxicity is the property of being toxic to the ear, specifically the cochlea or auditory nerve, and sometimes the vestibular system (Medical dictionary, Sa). Ototoxicity causes hearing loss. The term “ototoxicity monitoring” therefore refers to the steps taken for early identification changes to hearing status, presumably attributed to a drug/treatment as well as early intervention audiologic intervention when handicapping hearing impairment has occurred (American Academy of Audiology 2009:3).

1.6.8 Threshold shift

The smallest intensity of sound that a person requires to detect its presence is a threshold. Therefore, the threshold shift refers to the degree of hearing loss or impairment in terms of a decibel shift from a patient's previous audiogram. Audiometric monitoring programmes will encounter two types of changes in hearing sensitivity, that is, threshold shifts: permanent threshold shift (PTS) and temporary threshold shift (TTS). As the names imply, any change in hearing sensitivity, which is persistent, is a PTS. Persistence is assumed if the change is observed on a 30-day follow-up exam (Gelfand 2009:139).
1.7 THEORETICAL FOUNDATIONS OF THE STUDY

1.7.1 Research paradigm

Ideological positions called paradigms or “worldviews”, guide research activity. Each of the paradigms is organised around concepts, theories, assumptions, beliefs, and principles that form a way that a discipline interprets the subject matter. All researchers work from these frameworks, “worldviews” underpinning philosophical assumptions. The paradigms or worldviews refer to a basic set of beliefs (assumptions) that guide action and have been described as ontological (beliefs about the nature of reality and humanity), epistemological (the nature of knowledge that informs the research), and methodological (how that knowledge may be gained) premises (Creswell 2014a:6; Curtis & Drennan 2013b:20). In the execution of the current study, the post-positivist/quantitative paradigm was utilised. The quantitative approach is associated with an objectivist ontology, a positivist epistemology, and uses quantitative methods that aim to produce findings that are objective, reliable, valid and reproducible (Curtis & Drennan 2013a:133). The implications these assumptions have on the study to hold true to the paradigm are:

- Data collection instruments completed by the respondents and/or observations recorded by the researcher;
- Standards of validity and reliability examine the methods and conclusions for bias;
- Statements that explain causal relationships of SNHL related to MDR-TB treatment use quantitative terms such: the number (and proportion) of respondents developing SNHL, time to hearing loss, incidence ratios, hazard ratios and cumulative incidence; and
- Inferential statistics generalise the results from the sample to match those of the population under study, knowing that the absolute truth can never be found and that evidence established by research is imperfect and fallible.
1.7.2 Meta-theoretical assumptions of the study

This study is based on the general philosophical orientation about the world and the nature of the quantitative research and numeric measures of observations, and is linked to study outcomes (Creswell 2014a:6). Mouton ad Marais (1994:192) contend that no scientific findings can be conclusively proved based on empirical research data and the researchers are compelled to make assumptions justifying specific theories and methodological strategies. A brief discussion of this perspective in the subsections below reveals that the epistemology, ontological and methodological assumptions guided this study and are summarised in Table 1-1.

1.7.2.1 Epistemological assumptions

Epistemology is an underpinning philosophical assumption about the nature of knowledge or how we come to know (Curtis & Drennan 2013b:19-21). Epistemology poses the question on the relationship between the knower/inquirer and those being studied, what is known, and how do we know what we know (Krauss 2005:759; Polit & Beck 2008:11). The epistemological assumptions in this study contend that the MDR-TB treatment related hearing loss is a phenomenon that occurs in individuals receiving a certain regimen of MDR-TB treatment. Direct observations of measurements of the phenomena are the basis for the discovery and verification of the knowledge of MDR-TB treatment related hearing loss. Central to this positivist epistemology is the assumption that observation and measurement are at the core of scientific endeavour; and perspective seeks to explain and predict what happens in the social world by searching for regularities and casual relationships between MDR-TB related hearing loss constituent elements related to its occurrence (Krauss 2005:759). The axiological assumptions that flow from this perspective is that the research is value neutral and the researcher’s values do not bias the research.

1.7.2.2 Ontological assumptions

This research assumes that there is a single unitary reality apart from our perceptions about hearing loss associated with MDR-TB treatment. The ontological assumption is that each researcher’s individual cannot bias research, being objective
is an essential aspect of competent inquiry, and hence the researchers must examine the methods and conclusions for bias. It is therefore very important that we “establish validity” in an external and objective sense (Creswell 2014a:7; Krauss 2005:759). See Table 1.1

1.7.2.3 Methodological assumptions

Methodology identifies the particular practices used to attain knowledge by the inquirer (Krauss 2005:759). This study uses quantitative methods associated with positivism to obtain knowledge on the incidence, risk factors and hazard rate ratios of MDR-TB treatment related hearing impairment. Numeric information is collected and analysed within the traditional scientific method based on what was observed and what was measured (Polit & Beck 2008). Another methodological assumption of quantitative studies is that the empirical findings are generalisable beyond the single setting. Postulation of theories that are to be tested use deductive reasoning and, based on the results of studies, we may learn that a theory does not fit the facts well and so the theory must be revised to better predict reality (Creswell 2014a:5-8; Krauss 2005:760; Phillips & Burbules 2000:8-26).
Table 1.1: Ontological, Epistemological and Methodological assumptions under the research paradigm

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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| Purpose of research      | - The empirical study determines incidence, risk factors, and hazard rate ratios of hearing loss in HIV positive and HIV negative patients on MDR-TB treatment in Swaziland  
| Ontology (Objectivist)   | - There are laws or theories that govern the world.  
                          - Laws and theories need to be tested or verified and refined so that we can understand the world.  
                          - Researchers advance the relationship among variables and pose this in terms of questions or hypotheses.  
                          - Researcher begins with a theory or hypothesis, collects data that either supports or refutes the theory, and then makes necessary revisions and conducts additional tests.  
                          - Researchers do not prove a hypothesis; instead, they indicate a failure to reject the hypothesis because evidence established in research is always imperfect and fallible. |
| Epistemology (Positivist)| - Knowledge is based on careful observation and measurement of the objective reality that exists “out there” in the world.  
                          - Data, evidence, and rational considerations shape knowledge.  
                          - Research seeks to develop relevant, true statements; ones that can serve to explain the situation of concern or that describe the causal relationships of interest. |
| Methodology              | - The researcher collects information on instruments based on measures completed by the respondents or by observations recorded by the researcher.  
                          - Being objective is an essential aspect of competent inquiry; researchers must examine methods and conclusions for bias.  
                          - For example, standard of validity and reliability are important in quantitative research. |
1.7.3 Theoretical framework

1.7.3.1 Neuman Systems Model Nursing Theory

In the formulation of a theoretical perspective for studying hearing loss related to MDR-TB treatment, Neuman Systems Model (NSM) provided a useful theoretical prototype. Neuman Systems Model focus is on the client as a system (which maybe an individual, family group or community) and on the client’s response to stressors (Freese & Lawson 2010:311-15). The medicines used in the treatment of MDR-TB affect the internal environment of the patient (physiological and pathophysiological) and treatment affects the external environment of the client (patient) system (perceptual, operational, and conceptual). The conceptual environment can be viewed as hearing, language and expression of emotion (Levine 1990:189; Schaefer 2010:227-229).

The client system includes physiological, psychological, sociocultural, developmental, and spiritual aspects. The client system is conceptualised as having an inner core or basic structure (basic energy resources) that is protected by concentric circles representing a normal line of defence and flexible line of defence. The normal line of defence represents the usual level of health that also, in turn, is protected by a flexible line of defence. Tension-producing intrapersonal, interpersonal and extra-personal stressors, which arise from the internal, external, and created environment, affected these lines of defence (Freese & Lawson 2010:309-334). When stressors break through the flexible line of defence, the client system is invaded and the lines of resistance are activated with the client system moving into illness on a wellness-illness continuum. If adequate energy is available, the system will be reconstituted with the normal line of defence restored at below, or above its previous level (Freese & Lawson 2010:315-323).

According to NSM, nurses and doctors treating patients with MDR-TB facilitate conservation of hearing as part of preservation of the wholeness of the individual so that his or her participation and place in the family, community, and society can be preserved using prevention as an intervention (three levels). Primary prevention of SNHL starts at the client’s baseline assessment to identify risks and address
preventable ones prior to the administration of injectable anti-TB medicines. Secondary prevention starts once there is detection of signs of hearing impairment. In order to implement secondary prevention, regular monitoring of hearing status is critical to identify those at risk for secondary prevention. The purpose of secondary prevention is to slow worsening of the impairment to preserve hearing. Tertiary prevention is part of restoration of hearing and/or to prevent consequences of hearing loss through maintenance of communication. The three levels are used for retention, attainment, and maintenance of optimal client system wellness (Freese & Lawson 2010:311-314; Neuman 2001:321-9).

1.7.3.2 Conceptual framework for the best practice guidelines

Based on Neuman Systems Model, the stages of the medical process form a continuum:

- At diagnosis, the identification and diagnosis of stressors is done, as well as the cognisance of the dynamic interaction with the five variables;
- At enrolment, treatment goals negotiated with the patient, taking into account the patient’s and nurse’s perceptions of variance from wellness.

The conceptual framework is presented in Chapter 2 of this thesis.

1.8 RESEARCH DESIGN AND METHODS

1.8.1 Research Design

Research design refers to the broader plan for management of the study, encompassing the plan for data collection, utilisation, measurement and analysis. The research methods refer to data collection using the specific instruments and techniques to achieve the outcomes of the study (Curtis & Drennan 2013a:131; Mouton 2001:55-56). This study was an observational prospective cohort with a nested case-cohort approach. The cohort involved normal hearing HIV negative and HIV positive patients initiating MDR-TB treatment, followed up until hearing loss
developed, completed 8 months of the injectable intensive phase of DR-TB treatment, or were lost to follow up. Analysis of incident hearing loss involved calculation of incidence, association exposure to various risk factors and time to development of hearing loss (Creswell 2014a:11-17; Duggal & Sarkar 2007; Krauss 2005:759-60). The Cohort design allowed for the determination of population-based incidence; accurate relative risk (risk ratio) estimation; inference to the temporal relationship; time-to-hearing loss analysis (Pfeiffer, Ryan, Litonjua & Pee 2005:982-91).

1.8.2 Research Methods

Research methods involve the forms of data collection, analysis and interpretation that the research utilises for the studies (Creswell 2014a:16-17). Longitudinal data collection methods were utilised for the study.

1.8.2.1 Population, Sampling and Research sites

A two-stage multi stage sampling was done in order to study the target population, which comprised of patients diagnosed (confirmed and suspected) with DR-TB patients enrolled into an MDR-TB treatment regimen. The first stage was identification of study sites from a list of six MDR-TB treatment sites in the country. The second stage of sampling was selection of patients who eventually enrolled into the study. The study setting was in a high per capita burden of DR TB and HIV co-infection setting. Patients attending DR-TB treatment sites were the accessible population and the study sample comprised MDR-TB patients enrolled onto MDR-TB treatment at two centres in Swaziland, namely National TB Hospital, and Pigg’s Peak Hospital. Referrals from other treatment sites, such as Manzini Comprehensive Clinic and Good Shepherd hospital were also attended to as long as they fulfilled the including criteria.

Before establishment of their own audiometry services, patients from Pigg’s Peak Hospital were referred to the National TB Hospital for audiometry testing. The criteria for inclusion in the study were: i) have a diagnosis of DR-TB; ii) normal pre-treatment hearing level, (iii) normal hearing level for those on treatment for no more than 72
hours; (iv) aged 15-65 years; (v) clinically stable; and (vi) provide informed consent to participate in the study. Excluded from the study were the following: (i) patients with extensive resistant tuberculosis strains, (ii) patients with exhibited psychiatric conditions, (iii) pre-treatment clinical assessment of infective pathology in the ear, and (iv) pre-existing hearing loss. All consecutive patients who fulfilled the inclusion criteria and consented to participate were enrolled into the study.

1.8.2.2 Ethical Considerations

The Research Ethics Committee of the Department of Health Studies Higher Degrees Committee (DHS HDC) of University of South Africa and the Scientific and Ethics Committee of the Ministry of Health in Swaziland granted ethical clearance and approval for the study. Institutional approvals was also provided by the National tuberculosis programme and National TB Hospital and participating MDR-TB treatment centre. Ethical considerations during sampling and during data collection are of this study are presented in sections see section 3.3.1.4 and 3.3.2.5. As part of the design of the study, the principles of “do good” (beneficence) and “do no harm” (non-maleficence) were some ethical considerations made in the design and plan for data collection in the study. Information was the purpose of the study, study procedures rights, risks, discomforts, as well as the constraints of participation. Patients’ autonomy, informed consent, right to withdraw from the study at any time, assurance of confidentiality, anonymity, and privacy were the other of the ethical considerations under the respect for the human subjects involved in research.

1.8.2.3 Data collection

An interviewer-administered questionnaire was used to capture: socio-demographic data, medical history, lifestyle characteristics, biometric and physical measurements; medical and laboratory results abstracted from laboratory and medical records; medical and family history of hearing; results of screening examinations that included otoscopy and tympanometry for identification of ear canal abnormality or cerumen impaction conducted; and the baseline and continuing audiology results. Referral for immediate medical cerumen management was done, as appropriate (ASHA 1997)
1.8.2.4 Instrumentation

Data collection instruments were the face-to-face interviewer-administered questionnaire and an audiometry protocol and equipment used to collect and test the respondents’ hearing threshold (in decibels, dB) at six frequencies, collected in a soundproof room. For each ear tested, results of the hearing threshold (in decibels) at frequencies of: 250 hertz; 500 hertz; 1 000 hertz; 2 000 hertz; 4 000 hertz; 8 000 hertz were recorded using standard symbols in an audiogram (ASHA 1990:32-35).

1.8.2.5 Case definition

Hearing loss was graded according to the WHO criteria using audiometric ISO values that are averages of pure tone values at 250, 500, 1 000, 2 000 and 4 000 hertz as: 0-25 dB Normal hearing; 26-40 dB Mild hearing loss; 41-60 dB Moderate hearing loss; 61-80 dB severe hearing loss; 81+ dB Profound hearing loss. It should be noted, however, that given that different frequencies may be affected in a given person, averaging across all frequencies tested may wash out ototoxic change (Dobie, 2005b:62-63, Gordon, Konrad-Martin, Reavis, Wilmington, Bratt & Fausti).

Some studies however, have validated that use of pure tone average (PTA) or any frequency (AF) criteria depends on the choice and whether the genuine threshold shift has occurred at a single frequency or across a range of frequencies (Dobie, 2005b:62-67). For that reason, additional criteria for defining hearing loss included consideration of significant threshold shift compared to baseline measurements if: 1) a 20 dB decrease at any one frequency or 2) a 10 dB decrease at any two adjacent frequencies (American Speech-Language-Hearing Association 1994).

1.8.2.6 Data Analysis

Before detailed statistical analysis, the nature of the data available and questions of interest were reviewed using exploratory analysis and preliminary tabulations to clean up the data and resolve any inconsistencies in the data. This study design
allows for three major analytic approaches, namely, analysis as a cohort study, a case-cohort study and a nested case control. Analysis as a cohort study is the main approach that is utilised given that baseline data was retrieved on all respondents. Given that the time-to-event outcome is binary in nature, non-standard statistical analyses were not required for the case cohort (Barlow, Ichikawa, Rosner & Izumi 1999:1165-70; Pasupathy, Dacey, Cook, Charnock-Jones, White & Smith 2008:1165).

**a. Descriptive analysis**

Objective 1 and 4: descriptive data analysis was done to address each sub problem statistically, using measures of central tendency (mean, standard deviation and median) calculated from the continuous data, analysis of time-to-event data and using epidemiological estimates (rates, proportions, and ratios).

**b. Explanatory analysis**

Objectives 2 and 3: analysis tests the study hypotheses and establishes the risk factors and determinants that are responsible for producing the state of hearing impairment details, and this is provided in Chapter 3 of this thesis. Logistic regression and the proportional hazards regression are used to study the effect of HIV status.

**c. Predictive analysis**

Objective 4, to assess the time-to-hearing loss and hence the optimal frequency for audiologic testing for monitoring of patients on MDR-TB treatment, utilised the proportional hazards regression and hazard function to predict the probability that if a person survives to t, they will experience the event in the next instant.
d. Literature review of existing guidelines and synthesis of results of the empirical study

To achieve Objective 5 that aims to develop best practice guidelines, data from the empirical research and relevant literature were used to make recommendations and guidelines for monitoring and prevention of hearing loss associated with MDR-TB treatment in Swaziland based on internationally recommended hierarchy and methods for grading the evidence (Ansari & Rashidian 2012; Curtis & Drennan 2013b:18).

1.8.2.7 Internal and external validity of the study

To ensure the internal and external validity, and reliability of the study, methods and techniques used included the following:

i) Standardisation of conditions, controlling for quality of procedures and techniques and execution of pilot test of procedures, equipment, and questionnaires. The procedure manuals provided details of each step, including regular calibration of audiometry equipment according to international standards, staff training on details of study procedures, data collection techniques and data entry, standardised tools for data collection. These methods ensured reliability of the audiology test results as well as accurate and complete entry of questionnaires. The researchers also had a written schedule for progress meetings and review reports, and timely trouble shooting was implemented to ensure that the findings match reality and what is captured or measured is what is supposed to be measured or captured;

ii) Making adjustments for confounders through identification of a priori potential confounders, dealing with those discovered later during the data collection; restriction to participation in the study; stratified analysis within strata of the confounding variable (for example, age, gender) and; intent-to treat analysis addresses drop out and non-compliance ensures translation of the measured constructs into functioning reality;

iii) Selection bias and error were addressed in accordance with the recommendations in (Enarson, Kennedy, Miller & Bakke 2001:97-104). where the researchers employed rigor in defining the target population, collecting
and reporting demographic characteristics of respondents, inclusion of all cases meeting the eligibility criteria and not omitting “hard to find” persons. Skills to ensure high acceptance rate and lower dropout rate were imparted;

iv) Information Bias (Error or bias in measurements) was minimised by strict observance of diagnostic criteria; testing for inter- and intra-observer variability; and implementing regular quality assurance procedures to ensure that there is no “drift” in the precision of the results;

v) Blinding: The respondents and the research assistants are “blinded” on the hypothesis being tested in order to avoid the risk that personal expectations might influence, bias the result, and reduce reliability and validity; and

vi) Oversampling of HIV negative patients to increase proportion of HIV negative respondents in the cohort to at least one third, given the very high HIV prevalence (75%) among the MDR-TB patients.

1.9 THE SCOPE OF THE STUDY

The study falls within the field of health studies encompassing fields of health systems research, quality of patient care and translation of evidence into practice through the development of guidelines for monitoring and prevention of adverse drug events. The study evaluated the incidence, risk factors and time-to-hearing loss in a setting with a very high per capita burden of high HIV and MDR-TB. The population accessed for the study was a cohort of 173 MDR-TB patients enrolled from November 2012 and December 2013 at three health facilities managing MDR-TB in Swaziland. During the same period, 353 MDR-TB patients were enrolled into treatment nationally. Data collected during the study indicates the need for guidelines for monitoring and prevention of SNHL for MDR-TB patients of injectable second-line anti-tuberculosis treatment.

The study might have the following limitations:

i) This study was an observational study with a main weakness of confounding, given that the researcher did not allocate which study respondent was exposed or not exposed to HIV (exposure) (Harris, Bardien, Schaaf, Petersen,
Specific measures to minimise confounding included *a priori* identification of potential confounders and dealing with those discovered later during the data collection. Restriction to participation in the study, stratified analysis within strata of the cofounding variable (for example, age) and intent-to-treat analysis were used to address drop out and non-compliance at analysis stage;

ii) The study reports incidence at 8 months, although some studies show that progressive ototoxic effects on hearing by MDR-TB treatment may continue even after the stoppage of the offending drug;

iii) The frequency of audiometry was limited to intervals of two-weekly, four-weekly and eight-weekly because the patients and doctors, and not the researcher, decided the follow-up appointment dates;

iv) Repeated testing of respondents over time can also lead to confounding due to learning effects. Where indicated, ABR studies were conducted to negate this effect; and

v) Increased possibility of missing data common for longitudinal research could affect results. Some patients could fail to honour their appointments for audiometry. Patient phone reminders were used to minimise loss to follow up as well as using thorough training of study assistants with the skills to ensure high acceptance rate and lower dropout rate and provision.

1.10 STRUCTURE OF THE THESIS

Chapter 1: Serves as an introductory chapter. It contains the problem, background to the research problem/preliminary literature study, statement of the problem, research aims, definitions of terms, theoretical frameworks and its limitations, significance of the research, conceptual framework, research methodology, scope and limitations of the study, and programme of the study.
Chapter 2: Provides reviewed literature and summarises the investigation into the phenomenon of hearing loss related to MDR-TB treatment, exposition of prevention and support services.

Chapter 3: Discusses the research design and methods. It includes; sources of data indicating the locale of the study, population, and sampling; instrumentation and data collection; and tools for data analysis.

Chapter 4: Presents the results of the empirical research in form of analyses, presentation, and interpretation of the data. The results are presented in the form of text, tabular presentations, pie charts, and/or any other analysis suitable for the collected data.

Chapter 5: Presents and independent reflection of the researcher on the entire research process and findings and summarises the whole research process (describes the problem, research design, and the findings (answers to the questions raised), and discussion of research results.

Chapter 6: Presents the process to develop and validate the best practice guidelines to monitor and prevent hearing loss associated with MDR-TB treatment.

Chapter 7: Presents the conclusions of the study, describes its limitation, and makes recommendations for practice and for further research.

1.11 CONCLUSION

This chapter introduced the study. It provided a background describing the problem of MDR-TB and cochleotoxicity resulting in permanent SNHL in a proportion of patients on MDR-TB treatment. Despite evidence supporting the importance of early identification of ototoxicity, lack of guidelines, tools and experts hamper the routine practice of ADR monitoring programmes in the country. The purpose, the objectives and the theoretical foundations of the study are stated. Key concepts are defined as
well as the ethical considerations and measures to ensure validity and reliability of the study findings.

Chapter 2 discusses the literature review.
CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

This chapter presents the review of the literature on the concepts of sound, hearing and hearing loss associated with MDR-TB, with special focus on aminoglycoside cochleotoxicity, mechanisms for the hearing loss, impact of hearing impairment and best practices for ototoxicity monitoring and prevention. The chapter describes Neuman Systems model and the application of the model in prevention and monitoring hearing loss and hearing preservation.

While the emergence and spread of MDR-TB threatens global ability to treat infectious diseases, and the costs related treatments are draining available meagre resources in developing countries, the use of ototoxic medications in the current MDR-TB treatment regimens contributes to an escalating incidence of SNHL hearing loss (Laxminarayan, Bhutta, Duse & al 2006:1031; World Health Assembly 1995; World Health Organization 2008, 2011b). In 1994, the WHO reported a median prevalence of primary and acquired MDR-TB as 1.4% and 13% respectively (Prasad, 2010:180). However, by the end of 2013, the median prevalence of MDR-TB had risen to 3.5% among new TB cases and 20.5% among previously treated cases (Chiang, Van Weezenbeek, Mori & Enarson 2013:596; World Health Organization 2014b). The critical, urgent, and necessary expansion of MDR-TB treatment as a measure to curb the scourge of MDR-TB directly contributes to increased MDR-TB treatment related to hearing loss. Sensorineural hearing loss is sometimes referred to as the “invisible” impairment because usually, no obvious external signs of the damage are exhibited (Chiang et al 2010:413; Chiang et al 2013:596; Prasad 2010:180).
2.2 THE EAR, SOUND AND HEARING IMPAIRMENT

This section provides a brief background of the anatomy of the ear and the auditory system, the mechanism of sound, and the mechanism of hearing as a preamble to the discussion on hearing impairment.

2.2.1 Anatomy of the Ear and Auditory System

Three parts form the ear and they are described and shown schematically in Figure 2.1.

i) The outer ear, which is made up of the pinna (auricle) and ear canal (external auditory meatus). The pinna is made up of folds of cartilage surrounding the ear canal and the pinna plays an important role in trapping sound waves.

ii) The middle ear, which consists of the tympanic (middle ear) cavity; the ossicular chain (malleus, incus, stapes) with its associated muscles, tendons, and ligaments; and the eustachian (auditory) tube. The middle ear begins at the eardrum (tympanic membrane), the membrane that separates the outer and middle ear.

iii) The inner ear is made up of the sensory organs of hearing (the cochlea) and of balance (the semi-circular canals, utricle, and saccule) and begins at the oval window.
Figure 2.1: Anatomy of the ear showing the outer ear, the middle ear and the inner ear. The Cochlear and semi-circular canals are shown as the snail line structure in the inner ear and are connected to the cranial nerves.


2.2.1.1 The Cochlea

The auditory nerve connects the organ of hearing (the cochlea) to, and within, the central nervous system (Gelfand 2007:20). The cochlea sits within the inner ear and it is a snail-shaped organ and enables sound transmission via a sensorineural route (Figure 2.4). Three layers of fluid make up the cochlea, namely: the scala vestibuli separated by Reissner’s Membrane from the scala media, which in turn is separated from scala tympani by the basilar membrane. The scala vestibuli and scala tympani are filled with perilymph-filled and are above and below the endolymph-filled scala media respectively. The scala media contains the organ of Corti, which is further described in Section 2.2.1.2. Figure 2.2 shows a schematic that illustrates the complex layout of the compartments and their divisions:
2.2.1.2 The organ of Corti

The organ of Corti has the hair cells that are the sensory receptors for hearing and is supported by the basilar membrane (Gelfand 2009). There are approximately between 15 000 and 16 000 of these hair cells in one ear (Plewes 2006). Figure 2.3 shows the position of the organ of Corti and the composition.

Inner hair cells are the mechanoreceptors for hearing: they transduce the vibration of sound into electrical activity in nerve fibres, which is transmitted to the brain (Furness, Hackney & Evans 2010:765). Outer hair cells are a motor structure. The organ of Corti forms a ribbon of sensory epithelium, which runs lengthwise down the cochlea’s entire scala media (Gelfand 2009). The basilar membrane widens as it progresses from base to apex. Hence the amplitude of a sound wave travelling
through the basilar membrane varies as it travels through the cochlea, responding in a wave-like manner as the a vibration is carried through the fluid within the three compartments and causes the basilar membrane to move.

Afferent neurons innervate cochlear inner hair cells, at synapses where the neurotransmitter glutamate communicates signals from the hair cells to the dendrites of the primary auditory neurons. There are far fewer inner hair cells in the cochlea than afferent nerve fibres – many auditory nerve fibres innervate each hair cell. The neural dendrites belong to neurons of the auditory nerve, which in turn joins the vestibular nerve to form the vestibulocochlear nerve, or cranial nerve number VIII. Sound information, now re-encoded, travels down the vestibulocochlear nerve followed by processing in the brain through intermediate stations such as the cochlear nuclei and superior olivary complex of the brainstem and the inferior colliculus of the midbrain, being further processed at each waypoint. The information eventually reaches the thalamus and relayed to the cortex. The primary auditory cortex is the first region of cerebral cortex to receive auditory input, and is responsible for the sensation of basic characteristics of sound such as pitch and rhythm and is located in the temporal lobe (Lincoln, [Sa]b).

2.2.2 Physiology of the Ear and Auditory System

The auditory periphery and the central auditory system make up the functioning of the auditory system. The auditory system changes a wide range of weak mechanical signals into a complex series of electrical signals in the central nervous system (Furness et al 2010:765). Sound is a series of pressure changes in the air. Sounds often vary in frequency and intensity over time and, in man, the first stage of transduction is the ear (Lincoln, [Sa]a). While not part of the nervous system, its components feed directly into the nervous system, performing mechanoelectrical transduction of sound pressure-waves into neural action potentials (Lincoln, [Sa]b).

Reflection and attenuation of sound waves occur when they hit the pinna. These changes provide information to the brain to determine the direction from which the sounds came. This is followed by amplification of the sound in the ear canal before
hitting the tympanic membrane of the middle ear. The sound wave hitting the eardrum causes wave information to travel across the air-filled middle ear cavity via a series of delicate bones: the malleus, incus, and stapes. These ossicles act as a lever, converting the lower-pressure eardrum sound vibrations into higher-pressure sound vibrations at another, and smaller membrane called the oval (or elliptical) window. Higher pressure is necessary at the oval window than at the tympanic membrane because the inner ear beyond the oval window contains liquid rather than air. The stapedius reflex of the middle ear muscles helps protect the inner ear from damage by reducing the transmission of sound energy when the stapedius muscle is activated in response to sound. While the middle ear still contains the sound information in wave form, it is converted to nerve impulses in the cochlea in the inner ear (Plewes 2006).

A sound presented to the human ear will travel through the cochlea in only 5 milliseconds (Plewes 2006). The placement of vibration on the cochlea depends upon the frequency of the presented stimuli: the lower frequencies mostly stimulate the apex and higher frequencies stimulate the base of the cochlea. When stimulated by sound energy, hair cells change in the shape, which serves to amplify sound vibrations in a frequency specific manner in order to initiate activity in the auditory nerve fibres with which they are in contact. Outer hair cells have stereo cilia projecting towards the tectorial membrane, which sits above the organ of Corti. Stereocilia respond to movement of the tectorial membrane when a sound causes vibration through the cochlea as shown in Figures 2.2 and 2.4. When this occurs, the stereocilia separate and a channel is formed that allows chemical processes to take place (Fettiplace & Kim, 2014:951). A signal travels to reach the auditory nerve. The auditory nerve leaves the inner ear through the vestibulocochlear nerve, through the internal auditory canal, to enter the brain at the angle of the pons and cerebellum, and terminates in the brainstem at the cochlear nuclei in the central auditory system (Gelfand 2009; Lincoln, [Sa]b; Plewes 2006).
2.2.3 Development of the auditory system

The auditory system is complete and possesses normal adult sensory function approximately halfway through prenatal development (Whitfield 2015:116). However, the advancement of the auditory neural system capacity to process signals continues for several years. Frequency, intensity, and type of stimulus help babies to differentiate sounds but, over the first few months, they learn to localise, associate hearing with their own vocal productions, and gradually to better imitate the vocal sounds of others. By one year of age, they are able to process the meaning of approximately 50 words. By age four, children can process and understand just
about everything they hear. Auditory sensitivity reaches its peak at adolescence and then begins a very gradual decline (Litovsky 2015:55).

Barring any insult that would accelerate the decline (such as noise, drugs or disease), the reduction in sensitivity is not generally clinically measurable until at least the third decade of life. After about age 60, hearing sensitivity decreases by an average of about 10 dB per decade. The decrease in hearing sensitivity begins at the highest frequencies and gradually progresses to include the middle and low frequencies. Hearing loss due to age-related changes is known as presbycusis (Mitchell, Gopinath Wang, McMahon, Schneider, Rochtchina & Leeder 2011:251).

2.2.4 Sound Evaluation/Characterisation

Sound may be characterised along three main parameters: frequency, intensity, and complexity (Fausti et al 2005:49).

2.2.4.1 Frequency

Frequency is the rate of the sound pressure waves, or how often the molecules are displaced in a given period. Frequency is measured in Hertz (Hz), or cycles per second, and is perceived as pitch. Lower-pitched sounds (such as the rumble of traffic or a man’s speaking voice) are lower in frequency; higher-pitched sounds (such as a whistle or a baby’s cry) have higher frequencies (Berke 2014).

Humans can hear sounds waves with frequencies between 20 and 20 000 Hz. The ears contain structures for both the sense of hearing and the sense of balance. Table 2.1 compares frequencies heard by different animals.
Table 2.1 Hearing range frequencies for different animals

<table>
<thead>
<tr>
<th>Animal</th>
<th>Lowest frequency limit</th>
<th>Highest frequency limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elephant</td>
<td>17</td>
<td>10 000</td>
</tr>
<tr>
<td>Human</td>
<td>20</td>
<td>20 000</td>
</tr>
<tr>
<td>Cow</td>
<td>23</td>
<td>35 000</td>
</tr>
<tr>
<td>Horse</td>
<td>55</td>
<td>33 500</td>
</tr>
<tr>
<td>Dog</td>
<td>60</td>
<td>45 000</td>
</tr>
<tr>
<td>Monkey</td>
<td>110</td>
<td>45 000</td>
</tr>
<tr>
<td>Rat</td>
<td>650</td>
<td>60 000</td>
</tr>
<tr>
<td>Mouse</td>
<td>1 000</td>
<td>90 000</td>
</tr>
<tr>
<td>Bat</td>
<td>3 000</td>
<td>120 000</td>
</tr>
</tbody>
</table>


2.2.4.2 Intensity

The pressure of a sound that is just barely audible to a young, normal-hearing listener is approximately 20 μPa (the μPa—micropascal—is a unit for measuring pressure). The pressure of a sound that is painfully loud could be about 200 000 000 μPa. The pressure measurements are converted to a logarithmic scale decibel (dB).

In decibels, the human ear is responsive to intensities from 0 dB to 140 dB (Gelfand 2007:5). Intensity refers to the amplitude of the pressure waves, or how far the molecules are displaced from their original position. Amplitude is measured in decibels and is perceived as volume, or loudness. Low amplitude sounds (in which the molecules are displaced only a little bit) are perceived as “quiet” and high amplitude sounds (in which the displacements are larger) are perceived as “loud.” Loudness is measured in decibels (dB), which is the force of sound waves against the ear. The louder the sound, the more decibels intensity level the sound will be.

Intensity expressed in decibels is called intensity level (IL), and sound pressure in decibels is called sound pressure level (SPL) (Gelfand 2007:5). When measuring an individual’s hearing thresholds, the hearing level scale is used; results are recorded in dB HL. Just like temperature of 0°C, a measurement of 0 dB does not mean that there is no sound at all, just as if a temperature of 0°F does not mean that there is no heat at all. There are sounds that are quieter than 0 dB, and these sounds are measured in negative decibels in the same way that temperatures colder than 0°C are.
measured in negative degrees. Table 2.2 provides approximate decibel levels for some everyday sounds (National Institute on Deafness and Other Communication Disorders, [Sa]).

**Table 2.2 Sound decibel level for some everyday sounds**

<table>
<thead>
<tr>
<th>Sound</th>
<th>Intensity (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticking of a Watch</td>
<td>20</td>
</tr>
<tr>
<td>Whisper</td>
<td>30</td>
</tr>
<tr>
<td>Normal Speech</td>
<td>50-60</td>
</tr>
<tr>
<td>Car Traffic</td>
<td>70</td>
</tr>
<tr>
<td>Alarm Clock</td>
<td>80</td>
</tr>
<tr>
<td>Lawn Mower</td>
<td>95</td>
</tr>
<tr>
<td>Chain Saw</td>
<td>110</td>
</tr>
<tr>
<td>Jackhammer</td>
<td>120</td>
</tr>
<tr>
<td>Jet Engine</td>
<td>130</td>
</tr>
</tbody>
</table>


### 2.2.4.3 Complexity

Complexity refers to the interaction of the various frequencies and intensities that make up a sound; for example, a pure tone is a sound that is made up of only one frequency and one intensity. Most sounds are made up of many frequencies at different intensities combined, to make a very complex signal. Complexity is perceived as sound quality or timbre. If a flute and violin are playing the same note at the same volume, complexity is the parameter of sound that allows us to distinguish between the two instruments.

### 2.2.5 Hearing

According to the Merriam-Webster Dictionary hearing is defined as "the process, function, or power of perceiving sound: specifically, the special sense by which noises and tones are received as stimuli" (Merriam-Webster Medical dictionary, [Sa]). As described above, the sound of characteristics of frequency, intensity, and complexity determine hearing (Fausti et al 2005:49) A hearing person is one who
can perceive sounds that have frequencies between 20 and 20 000 Hz, with the most important frequencies being the 250–6 000 Hz range. On the other hand, speech includes a mix of low- and high-frequency sounds (Patel & Merrick 2011:8). The Webster Dictionary’s medical definition of hearing is “the act or power of apprehending sound” (Merriman-Webster [Sa]).

2.2.6 Hearing impairment/loss

Hearing loss exists when there is diminished sensitivity to the sounds normally heard at appropriate intensity (Patel & Merrick 2011:8-9). The severity of a hearing loss is categorised according to the increase in volume above the usual level necessary before the listener can detect it (Feldman, Salinas & Tang 2012:602). The term “hard of hearing” refers to people with hearing loss ranging from mild to severe/profound, who mostly communicate through spoken language. Quite often, these people lost hearing gradually. Such people often benefit from hearing aids and cochlear implants (Action on hearing loss 2015; World Health Organization 2012a). Conversely, deafness is defined as a degree of impairment that is so severe such that a person is unable to process or understand speech even in the presence of amplification. In profound deafness, even the loudest sounds produced may not be detected. In total deafness, no sounds at all, regardless of amplification or method of production, are heard (Feldman et al 2012:602; Mackenzie & Smith 2009:565-71; World Health Organization 2012a:8).

Hearing impairment can be characterised in many ways: i) based on the source of the dysfunctions along the auditory pathway can cause hearing loss. Hearing losses may be divided into several categories based on where in the ear the impairment is located (the type of hearing loss); ii) based on how severely the impairment affects a person’s hearing sensitivity (the degree of hearing loss); and iii) may be based on which ears are affected (the laterality of the hearing loss). Other considerations include the nature of the hearing impairment, especially onset; association with other conditions; or duration and reversibility of hearing loss (Feldman et al 2012; Mackenzie & Smith 2009:565-71; Shield 2006:10-12).
2.2.6.1 Characterisation according to where impairment is located (type of hearing loss)

Hearing loss could be conductive, sensorineural, or mixed. The schematic in Figure 2.5 illustrates the mechanism for the main categories of hearing loss.

Main hearing loss categories


2.2.6.1.1 Conductive hearing loss

This type of hearing loss occurs when there is a problem in the outer or middle ear. Sound is not able to travel properly through the ear canal to the eardrum and ossicles and the difficulty lies in the conduction of sound to the cochlea. One of the most common causes of conductive hearing loss is excessive wax in the ear canal, fluid in the middle ear brought on by an infection, or a discontinuity between the ossicles, which prevents sounds from reaching the inner ear efficiently. These may lead to a temporary hearing loss that can be treated medically or surgically.
2.2.6.1.2 Sensorineural hearing loss

Sensorineural hearing losses occurs when there is a problem in the inner ear or along the auditory nerve, because the difficulty lies in the ability of the cochlea to sense the sound or the ability of the nerve to carry the signal to the brain. Patients with SNHL can have a varying amount of hearing loss (slight to profound) and may have difficulty hearing and understanding speech clearly. Sensorineural hearing loss is typically treated with the use of hearing aids or other hearing technologies; it cannot be medically or surgically corrected.

2.2.6.1.3 Mixed hearing loss

This type of hearing loss occurs when a person has both conductive hearing loss and SNHL. People with mixed hearing loss may have damage to the outer ear, the middle ear, the inner ear, and/or the nerve that connects the inner ear and the brain (Smith, Bale & White 2005:880).

2.2.6.2 Characterisation of hearing loss according to severity (grade of hearing loss)

Severity of hearing impairment is categorised differently by different organisations (Shield 2006:10; World Health Organization 2012a). One hearing scale used a qualitative self-rated scale (SRS), and people rate the hearing ability of each ear without the use of hearing aids on a four-point scale, ranging from “good” to “deaf.” Another qualitative scale is the Gallaudet Hearing Scale (GHS). This is a five-point or eight-point scale that rates how well a person can usually hear and understand speech without the use of hearing aids, and it ranges from the “ability to hear and understand whispered speech” to the “inability to hear or understand any speech” (Barnett & Franks 2002:106; Kochkin 2007:3-4).

An eight-point scale was used in which the respondent indicates whether they can understand speech under the following conditions:
1. whisper across a quiet room;
2. normal voices across a quiet room;
3. shouts across a quiet room;
4. loud speech spoken into their better ear;
5. not able to understand loud speech in their better ear;
6. tell noises from each other;
7. hear loud noises at all;
8. Hear any sound or any noise.

While an individual's score ranges from 1-8, typically the scores are classified into one of five groups:

1. hear whisper;
2. hear normal voice;
3. hear shouts;
4. hear speech in loud ear;
5. cannot hear speech (Kochkin 2007:3-4).

From the quantitative point of view, below are examples of the grading of hearing impairment by individual institutions.

2.2.6.2.1 World Health Organization Grading system

The WHO defines disabling hearing impairment in adults as a permanent unaided hearing threshold level (average for frequencies 0.5, 1, 2, 4 kHz) for the better ear of 41 dB or greater (World Health Organization 2013). In children under 15 years of age, disabling hearing impairment is defined as permanent unaided hearing threshold level (average for frequencies 0.5, 1, 2, 4 kHz) for the better ear of 31 dB or greater.

The WHO grades hearing impairment into four grades in better ear and provides qualitative description:
• Grade 0 is no impairment; 25 dB or better refers to no or very slight hearing problems.
• Grade 1 refers to slight impairment, and 26 - 40 dB the person is able to hear and repeat words spoken in normal voice at 1 metre.
• Grade 2 is moderate impairment with a 41 - 60 dB range and the person is able to hear and repeat words using raised voice at 1 metre.
• Grade 3 is severe impairment with a threshold of 61 - 80 dB and the person is able to hear some words when shouted into better ear.
• Grade 4 is profound impairment including deafness and a threshold of 81 dB or greater. The person is unable to hear and understand even a shouted voice.

2.2.6.2.2 European Commission Grading system

The European Commission proposed definitions of grades of hearing impairment for use in Europe (European Group on genetics of hearing impairment, 1996) as cited in Shield (2006). In these definitions, the better ear hearing loss (BEHL) is defined as the pure tone average of the four frequencies 0.5, 1, 2 and 4 kHz for the better ear as follows:

• Normal -20dB(BEHL);
• Mild-21-39 dB (BEHL);
• Moderate-40-69dB (BEHL);
• Severe-70-94 dB (BEHL); and
• Profound-95 or more dB (BEHL)

A reason for including the frequency 4 kHz was that it is often a significant frequency in noise induced hearing loss and age related loss (Shield 2006:12)

2.2.6.2.3 American National Standards Institute Grading system

The American National Standards Institute (ANSI) defines 5 categories of hearing impairment, starting at a hearing level of 27 dB (Shield 2006:12):
- Normal hearing level - less than 27 dB;
- Mild hearing loss is 27 - 40 dB hearing level;
- Moderate hearing loss is 41 - 55 dB hearing level;
- Moderate-severe hearing loss is 56 - 70 dB hearing level;
- Severe hearing loss is 71 - 90 dB hearing level; and
- Profound hearing loss is 91 dB and above.

2.2.6.2.4 The Royal National Institute for Deaf and Hard of Hearing People Grading system (RNID)

The Royal National Institute for Deaf and Hard of Hearing People (RNID) on the other hand has defined deafness in four categories (Action on hearing loss, 2015) which relate to the quietest sound that can be heard in the better ear as follows:

- Normal hearing is below 25dB;
- Mild hearing loss is 25 - 39 dB and there is difficulty in following speech;
- Moderate hearing loss is 40 - 69 dB and there is difficulty in following speech without a hearing aid;
- Severe hearing loss is 70 - 94 dB with great reliability on lip reading, even with a hearing aid;
- Profound hearing loss is 95 dB or greater and communication is by lip reading, the British Sign Language or the preferred language.

The RNID defines ‘deafened’ people as people who are not pre-lingual deaf but become profoundly deaf later in life because of trauma, infection or ototoxic drugs.

2.2.6.2.5 The British Society of Audiology (BSA) grading system

In the United Kingdom, four audiometric descriptors used are based on the average pure tone thresholds at 0.25, 0.5, 1, 2 and 4 kHz. Averages do not imply any particular configuration of hearing loss and do not exclude additional terms (e.g.
profound high frequency hearing loss) (British Society of Audiology 2011:22). According to the BSA:

- Mild hearing loss is 20 - 40 dB;
- Moderate hearing loss is 41 - 70 dB;
- Severe hearing loss is 71 - 95 dB; and
- Profound hearing loss is in excess of 95 dB.

2.2.6.2.6 The National Institute on Deafness and Other Communication Disorders Grading System

The National Institute on Deafness and Other Communication Disorders (NIDCD) in the US defines hearing handicap in terms of the pure tone average hearing loss at speech frequencies 0.5, 1, 2, and 3 kHz:

- Normal hearing is 25 dB or less;
- Functional handicap is around 40 dB and some form of amplification is beneficial;
- Severe to profound hearing loss is 75 dB or greater and hearing aids provide limited benefit.

From the above descriptions, it is clear that there is no global consensus on the standards used to determine the thresholds of hearing loss. Each institutions has made their own recommendations for grading severity of hearing loss as summarised in Table 2.3.
Table 2.3 Summary of hearing status grading by different institutions

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Moderate to Severe</th>
<th>Severe</th>
<th>Profound</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO (avg. 0.5, 1, 2, 4 kHz)</td>
<td>≤ 25</td>
<td>26-40</td>
<td>41-60</td>
<td>61-80</td>
<td>≥ 81</td>
<td></td>
</tr>
<tr>
<td>European Commission (avg. 0.5, 1, 2, 4 kHz)</td>
<td>≤ 20</td>
<td>21-39</td>
<td>40-69</td>
<td>70-94</td>
<td>≥ 95</td>
<td></td>
</tr>
<tr>
<td>ANSI</td>
<td>≤ 26</td>
<td>27-40</td>
<td>41-55</td>
<td>56-70</td>
<td>71-90</td>
<td>≥ 91</td>
</tr>
<tr>
<td>RNID</td>
<td>≤ 26</td>
<td>25-39</td>
<td>40-69</td>
<td>70-94</td>
<td>≥ 95</td>
<td></td>
</tr>
<tr>
<td>BSA (avg. .25, .5,1,2,4 kHz)</td>
<td>≤ 20</td>
<td>20-40</td>
<td>41-70</td>
<td>71-95</td>
<td>&gt;95</td>
<td></td>
</tr>
<tr>
<td>NIDCD (avg. 0.5, 1, 2, 3 kHz)</td>
<td>&lt;25</td>
<td>~40</td>
<td></td>
<td></td>
<td>≥75</td>
<td></td>
</tr>
</tbody>
</table>

2.2.6.3 Characterisation of hearing loss by the laterality of the hearing loss

Hearing losses may be classified as either unilateral (affecting only one ear) or bilateral (affecting both ears). Bilateral hearing losses may be symmetric (approximately the same in each ear) or asymmetric (worse in one ear than the other). Hearing losses from environmental causes (such as noise, ototoxic chemicals, and ageing) are generally bilateral and symmetric. Hearing losses from medical causes (such as ear infections, mumps, and acoustic tumours) are often unilateral or asymmetric. A substantial difference in hearing sensitivity between ears can be indicative of a medically significant condition.

2.3 IMPACT OF HEARING LOSS

The loss of hearing can be very devastating and a life-changing experience. It has far-reaching consequences that may encompass the way one communicates, relates, perceives self, earns a living and and/or is perceived (Ask et al 2010:271-275; Morris et al 2013:954; Wallhagen 2004:S190-119; Wallhagen 2010:66-75). Groce, Yousafzai, Dlamini, Zalud and Wirz (2006: 319) found that in Swaziland, the majority (99%) of the deaf report difficulties in communicating with healthcare facility staff affecting their utilisation of health preventive and curative services. In another study, the deaf population in Swaziland was reported to be significantly more likely (p<0.05) to believe in incorrect modes of HIV transmission than the normal hearing (Groce et al 2006:319-324; Groce 2003:1401-1402).
2.3.1 Impact of diagnosis on the patient

If hearing loss develops in the young, it impedes speech and language development and could affect the educational and vocational attainment, including an increase in physical, emotional and psychological abuse (Mason & Mason 2007:407-26; Olusanya 2008:S3-13; Olusanya, Neumann & Saunders 2014a). Increased mental problems have been reported among deaf people (Fellinger, Holzinger & Pollard 2012:1037-38). After adjusting for confounding factors, hearing impairment negatively impacted on the independence of the affected by increasing reliance on community or family support (Schneider, Gopinath, Karpa, McMahon, Rochtchina, Leeder & Mitchell 2010:458-60). Hearing-impaired persons had a 3-fold higher risk of developing social and emotional deficits in everyday life (Gopinath, Hickson, Schneider, McMahon, Burlutsky, Leeder & Mitchell 2012:618-23). Hearing loss causes impairment of the exchange of information, thus significantly impacting everyday life, causing loneliness, isolation, dependence, and frustration (Ciorba, Bianchini, Pelucchi & Pastore 2012:159-63). People with hearing impairment have barriers to health care (Groce et al 2006:319-24; Scheier 2009:4-10). In principle, persons with MDR-TB treatment related hearing loss have the same right on diagnosis and treatment of sensory loss as other people have to other medical and surgical conditions.

2.3.2 Effects of hearing loss on the family

Hearing disabilities, due to their interactive nature, strongly affect intimate relationships (Hetu, Jones & Getty 1993-81), placing a considerable strain on relationships and increasing their vulnerability to failure (Hallam, Ashton, Sherbourne & Gailey 2008:369-88). Hearing loss affects the whole family, as communication is a key part of maintaining healthy relationships with family members. Failure to communicate, or when people with hearing loss fail to correctly guess the words, they miss a range of reactions, ranging from laughter, to confusion, to anger, and social withdrawal. Ultimately, the whole family misses out, including children and adolescents (Mason & Mason 2007:407-26). Spousal impact is high and ranges from the effects of the hearing impairment on the spouses’ everyday lives; the spouses’
need to constantly adapt to their partners' hearing impairment; and the effect of acceptance of the hearing impairment on the spouse (Scarinci, Worrall & Hickson 2008:141-50). Spouse hearing loss increases the likelihood of subsequent poorer physical, psychological, and social wellbeing in partners, although the negative impact of husbands' hearing loss on wives' wellbeing appears stronger than the reverse (Wallhagen, Strawbridge, Shema & Kaplan 2004:S190-6). Mental health of the spouse could be affected (Ask et al 2010:271-5).

2.3.3 Impact on informal and professional networks

Most work places rely on verbal communication and hence hearing is a critical sense for effective communication in the work force. The quality of life of people with hearing loss is significantly affected in the following ways: reduced earning power (especially the more severe hearing losses); reduced interpersonal relationships (especially for mild-to-moderate losses), including lesser intimacy and increasing of negative dysfunctional communication in the informal and professional networks and the hearing impaired may be unintentionally left out. The hearing impaired are also challenged by the physical aspects of the work environment, the need to use telephones or videoconferencing, the difficulty of group communication situations, and difficulties presented by various speaker characteristics. Employer attitudes could be another barrier and unsupportive supervisors could be among the difficulties encountered by many deaf and hard-of-hearing workers causing them to make mistakes on the job, which may negatively impact job performance (Dobie & Van Hemel 2004).

2.3.4 Hearing Loss and self-esteem, self-image and communication

Positive self-concept is associated with higher levels of positive adjustment and lower levels of psychosocial problems, especially internalizing problems. Communicative deprivation amongst the hearing impaired, and sometimes, even isolation, may be particularly troublesome during adolescence. Intimate attachments with parents and peers are especially important for the development of a sense of competence and for identity or ego development (van Gent, Goedhard, Knoors, Westenberg & Treffers 2012:331-51). Increased self-criticism; and reduced cognitive
functioning (primarily severe-to-profound hearing loss) could result because of isolation and being misunderstood, with a severe blow to self-concept in the social domains (van Gent et al 2012:333-351). Hearing loss can also cause decreased health status and more incidence of pain, and reduced group social activity because of a negative self-image (Olusanya et al 2014a:367-73). Hearing loss also associated with increase in the incidence of depression and depressive symptoms; reduced emotional stability; increase in paranoid feelings and increased anxiety symptoms as well as increased social phobias (primarily severely impaired respondents); and reduced belief that the subject is in control of their lives (locus of control).

2.3.5 Economic and social costs

While no studies have been undertaken in Swaziland to assess the economic and societal costs of SNHL, anecdotal evidence suggests that MDR-TB patients who develop hearing loss lose their jobs because of the permanent loss of hearing. Consequently, if they are the breadwinners, the family loses income. Based on report on hearing loss, Shield (2006:140) posits that the socio-economic costs of hearing impairment arise from loss of earnings and medical costs related to hearing health, either on an individual or total population basis. Jung and Bhattacharyya (2012:771-5) states that adults with hearing loss are more likely to be unemployed and on average earn significantly less wage income than adults without hearing loss. (Jung & Bhattacharyya 2012). Kochkin (2005) shows that hearing loss negatively impact household income on average up to US $12 000 per year in the US depending on the degree of hearing loss and it can projected some degree of household income is affected in Swaziland too.. Emmett & Francis (Emmett & Francis 2015) affirm that that although hearing loss is also associated with low educational attainment, even after controlling for education and important demographic factors, hearing loss is independently associated with economic hardship, including both low income and unemployment/underemployment.
2.4 DRUG RESISTANT TUBERCULOSIS

Multi-drug resistant tuberculosis (MDR-TB) is caused by *Mycobacterium tuberculosis* that is resistant at least to Isoniazid and Rifampicin, the main first-line drugs in the treatment of tuberculosis. On the other hand, extensive drug resistant tuberculosis (XDR-TB) by mycobacteria is resistant to Rifampicin and Isoniazid, any fluoroquinolone, and one of the three injectable drugs, Capreomycin, Kanamycin, and Amikacin (Ahmad & Mokaddas 2013:1-5, Gandhi et al 2010:1830; WHO 2013, World Health Organization 2011c, 2012). While DR-TB is a global emergency and poses a major threat to control of TB worldwide, more than 50% of the estimated cases are in India and China (Chiang et al 2010:413). Globally, however, major diagnostic and treatment gaps of MDR-TB exist: 55% of reported TB patients estimated to have MDR-TB were not detected. Of those detected, less than 60% were in 10 high MDR-TB burden countries in 2013 with the lowest in Myanmar (34%), South Africa (41%), and Tajikistan (30%) who were started on treatment: 136 000 MDR-TB patients were diagnosed and notified and 97 000 MDR-TB patients were started on treatment out of the estimated 480 000 cases globally (World Health Organization 2014).

2.4.1 Global Control of Multi-drug resistant tuberculosis

The WHO has characterised MDR-TB as a public health crisis, synonymous with a global health security risk and with grave consequences for those affected. The five prioritised global control priority actions to accelerate the response against the MDR-TB epidemic are: i) Prevent MDR-TB as a first priority; ii) Scale-up rapid testing and detection of all MDR-TB cases; iii) Ensure prompt access to appropriate MDR-TB care, including adequate supplies of quality drugs and scaled-up country capacity to deliver services; iv) Prevent transmission of MDR-TB through appropriate infection control; and v) High level political commitment, strong leadership across multiple governmental sectors, ever-broadening partnerships, and financing for care and research (Chiang et al 2010:413; Chiang et al 2013-604; Gandhi et al 2010:1830-43; World Health Organization 2014b).
2.4.2 Burden of MDR-TB in Swaziland

In Swaziland, 7.7% of the new TB patients have MDR-TB and 33.4% of the previously treated patients are estimated to have MDR-TB (Sanchez-Padilla et al 2012:29-37). In 2013, Swaziland had 491 laboratory confirmed MDR-TB cases but only initiated 199 cases on treatment (WHO 2013).

2.4.3 Mechanism for development drug resistant tuberculosis

Resistance to anti-tuberculosis drugs can be primary or acquired (Laxminarayan et al., 2006). Drug resistance primarily arises because of spontaneous mutations in the genome of \textit{M tuberculosis}. These resistant-conferring mutations occur at predictable rates for each antituberculosis drug (for example, Isoniazid 10–6, Rifampicin 10–8) (Gandhi et al 2010:1830-43). Thence, subpopulations of resistant mycobacteria arise spontaneously, and can emerge as the dominant strain in the presence of drug-selection pressure (Ahmad & Mokaddas 2009:1777). Many activities of the health care workers, patients and health system in the management of tuberculosis and anti-tuberculosis medicines may be responsible for sub-therapeutic serum concentrations, hence a cause of the current predicament of DR-TB. Isoniazid monotherapy selects for Isoniazid-resistant mutants and allows them to multiply (Figure 2.5) and become the dominant strain.

Resistance to additional tuberculosis drugs can be added in a step-wise manner to create tuberculosis strains that are resistant to several drugs; for example, treatment of Isoniazid mono-resistant tuberculosis with Isoniazid and Rifampicin selects for spontaneous Rifampicin-resistant mutants (Gandhi et al 2010:1830-43). This process is referred to as acquired resistance. Once created, drug-resistant strains can be transmitted giving rise to DR-TB in individuals never previously exposed to anti-tuberculosis drugs (primary resistance) (Gandhi et al 2006:1575–80)
2.4.4 Treatment of MDR-TB

MDR-TB is treated with combination chemotherapy. In 2011, the WHO released an update of the programmatic guidelines (Falzon, Jaramillo, Schunemann, Arentz, Bauer, Bayona, Blanc, Caminero, Daley, Duncombe, Fitzpatrick, Gebhard, Getahun, Henkens, Holt, Keravec, Keshavjee, Khan, Kulier, Leimane, Lienhardt, Lu, Mariandyshev, Migliori, Mirzayev, Mitnick, Nunn, Nwagboniwe, Oxlade, Palmero, Pavlinac, Quelapio, Raviglione, Rich, Royce, Rusch-Gerdes, Salakaia, Sarin, Sculier, Varaine, Vitoria, Walson, Wares, Weyer, White & Zignol 2011:516-28) recommending that the intensive phase of MDR-TB treatment should consist of at least 8 months of injectable second-line anti-tuberculosis drugs (TB SLD) and total treatment duration of a minimum of 20 months. Hence, treatment of MDR-TB may require at least 2 years or more to treat (Ahmad & Mokaddas 2013). Shorter treatment regimens are currently being explored but these two require injectable TB SLDs (Piubello, Harouna, Souleymane, Boukary, Morou, Daouda, Hanki & Van Deun 2014:1188-94).

The drugs used in the treatment of MDR-TB are referred second-line drugs and are generally more toxic than the first-line drugs (Bardien, de Jong, Schaaf, Harris, Fagan & Petersen 2009a; Bardien, Human, Harris, Hfke, Veikondis, Schaaf, van der Merwe, Greinwald, Fagan & de Jong 2009). Aminoglycosides constitute one of the oldest classes of antimicrobials. Despite their toxicity, mainly nephrotoxicity and ototoxicity, aminoglycosides are valuable in current clinical practice, since they retain good activity against multidrug-resistant Gram-negative pathogens, such as Pseudomonas aeruginosa and Acinetobacter species (Arbex, Varella Mde, Siqueira & Mello 2010:626-640; Pagkalis, Mantadaki, Mavros, Ammari & Falagas 2011:2277-94).

In Swaziland, MDR-TB treatment consists of a backbone of an injectable agent Kanamycin (Amikacin or Capreomycin) and oral second-line medicines. Formulation of an MDR-TB treatment regimen is based on the following principles:
1. The recommended regimen in the treatment of MDR-TB is the combination of at least four drugs to which the *Mycobacterium tuberculosis* isolate is likely to be susceptible.

2. Drugs are chosen with a stepwise selection process through five groups based on efficacy, safety, and cost and the injectable medicines form the backbone of MDR-TB treatment (Caminero et al 2010:621):

   a) Group 1: the oral first-line drugs including high-dose Isoniazid, Pyrazinamide, and Ethambutol are adjunct for the treatment of MDR and XDR tuberculosis.

   b) Group 2: the fluoroquinolones including Moxifloxacin and high-dose Levofloxacin.

   c) Group 3: the injectable drugs: Capreomycin, Kanamycin, and Amikacin.

   d) Group 4: the second-line drugs should be used in the following order: Thioamides, Cycloserine, and then Aminosalicylic acid.

   e) Group 5: includes drugs that are not very effective, or for which there are sparse clinical data, should be used in the following order: Clofazimine, Amoxicillin with Clavulanate, Linezolid, Carbapenems, Thioacetazone, and then Clarithromycin.

The full treatment regimen used is recommended by the Swaziland National Tuberculosis Control Programme and abbreviated as Km-Lfx-Eto-Cs (Trd)-PAS-Z; in full the abbreviation stands for: Kanamycin, Levofloxacin, Ethionamide, Cycloserine, Para Amino-Salicylate, and Pyrazinamide). The injectable agents are used for the first 8 months before a continuation treatment of 12 months on oral medicines giving a total treatment duration of 24 months (Kingdom of Swaziland Ministry of Health 2012).
2.4.5 Adverse drug reactions: definition, grading and monitoring

2.4.5.1 Definitions related to adverse drug reactions

In section 1.6.1, the term adverse drug reaction (ADR) is defined as “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product” (Davies et al 2009; Edwards & Aronson 2000:1255-59; Mammi, Citraro, Torcasio, Cusato, Palleria & di Paola 2013:S33-7). However, WHO (1969) provides a more precise definition stating intention and dosage as important components of the definitions: an ADR is a “response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.” The European Union, however, further clarifies that all noxious and unintended effects may be due to: i) the use of medicines according to the marketing authorisation instructions; uses not complying with the wording marketing authorisation: ii) authorised use of medication (off-label use), abuse, misuse, medication errors, overdose and adverse reactions associated with occupational exposure.

The terms adverse drug reaction (ADR) or adverse drug effect (ADE), sometimes referred to only as adverse events (AEs), are used synonymously and are broad terms referring to unwanted, uncomfortable, or dangerous effects that a drug may have (Forster et al 2011:576; Nebeker, Barach & Samore 2004a:975; Thomas & Petersen 2003:61). Nebeker et al (2004:795) delineates these terminologies. In that regard, an ADR (as defined above) is part of a bigger term, adverse drug event. An adverse drug event (ADE) is an injury resulting from the use of a drug. Under this definition, the term ADE includes harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug (including dose reductions and discontinuations of drug therapy). About 25% of adverse drug events are due to medication errors as shown in Figure 2.8 (Nebeker et al 2004b:801).
While adverse drug reactions result from intended use, adverse drug events may result from medication errors. Medication errors are mishaps that occur during prescribing, transcribing, dispensing, administering, adherence, or monitoring a drug. Examples of medication errors include misreading or miswriting a prescription. Medication errors that are stopped before harm can occur are sometimes called “near misses” or “close calls” or more formally, a potential adverse drug event (Naranjo et al 1981:240-245; Nebeker et al 2004b:795).

On the other hand, a side effect is an expected and known effect of a drug that is not the intended therapeutic outcome of medication. The term “side effect” tends to normalise the concept of injury from drugs and adverse drug reaction is a more accurate expression. Medication errors are more common than adverse drug events, but less than 1% of the time result in harm (Naranjo et al 1981:240).

2.4.5.2 Grading of adverse drug reactions

Adverse reactions can be graded as mild, moderate or severe or grades 1-5, each with a unique clinical description of severity (US Department of Health and Human Services 2010:1):

- Mild ADRs require minimal therapeutic intervention such as discontinuation of drug(s);
- Moderate ADR requires active treatment of adverse reaction, or further testing or evaluation to assess extent of non-serious outcome.
• Severe ADRs include any serious outcome, resulting in a life- or organ-threatening situation, significant or permanent disability, requiring intervention to prevent permanent impairment or damage, or requiring/prolonging hospitalisation. MDR-TB related hearing loss falls in this category.
• Death related to the ADR.

2.4.5.3 Adverse drug reactions monitoring

Pharmacovigilance is the term used for routine monitoring of adverse drug reactions. It is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems. It can be linked to the risk reduction strategies for adverse drug reactions that require a reporting system that enables reporting on the frequency, magnitude, and impact of adverse events (WHO 2005:7).

However, in general, in spite of spontaneous adverse drug reaction reporting being the cornerstone of PV, adverse drug reactions are inadequately reported (Lopez-Gonzalez, Herdeiro & Figueiras 2009a:19-31). Below are some illustrations in literature that implicate potential under-reporting of ototoxic hearing loss, which can be a “silent” condition. In Nigeria, Ohaju-obodo and Iribhogbe (2010:191) report that although 92.6% of medical doctors had observed adverse drug reactions at the four large teaching hospitals, only 25.5% had reported them. Inadequate knowledge about adverse drug reaction reporting (73.1%) among the doctors was the commonest reason. However, in Oshikoya and Awobusuyi (2009), ADR reporting was encouraged if the reaction was serious (77, 77.8%) and unusual (70, 70.7%) and education and training was the most recognised means of improving ADR reporting. Voluntary reporting (41.66%) was the most preferred form of reporting ADRs in India (Pimpalkhute, Jaiswal, Sontakk, Bajait & Gaikwad 2012:55-61).

2.4.5.4 Adverse drug reactions associated with MDRTB treatment

Many studies have documented adverse drug reactions (ADRs) associated with MDRTB treatment (Bloss et al 2010:275-81; Furin, Mitnick, Shin, Bayona, Beccerra,
may include the following:

- psychiatric disorders manifesting as depression, anxiety, nightmares or psychotic symptoms;
- gastrointestinal effects consisting of nausea, vomiting, abdominal pain, hematemesis, melena, diarrhoea and positive endoscopic findings;
- skeletal effects like arthralgia, arthritis with pain or swelling in the joints and limitation of movement;
- central nervous system disorders like seizure activity of any type as reported by the patient or witnessed by another individual;
- hepatitis evidenced by any elevation of serum transaminases in the presence of symptoms or elevation of serum transaminases to five times normal values without any symptoms;
- peripheral neuropathy manifesting as numbness, tingling or burning in the trunk or extremities; diminished or absent reflexes; and
- Ototoxicity manifesting as cochleotoxicity and/or vestibulotoxicity. Symptoms of ototoxicity include partial or profound hearing loss, vertigo, and tinnitus.

2.5 AMINOGLYCOSIDE RELATED HEARING LOSS AND OTOTOXICITY

2.5.1 Structure and Chemistry

Aminoglycosides are a class of antibiotics, discovered in 1944 by Selman Waksman and, because they are cost effective, they are widely used in the treatment of tuberculosis. Aminoglycosides are naturally occurring compounds produced by the soil actinomycetes and their semi synthetic derivatives. Streptomycin, Neomycin, Gentamycin, Kanamycin, Tobramycin and Amikacin are all examples of aminoglycosides. They were part of the miracle drugs in treatment of tuberculosis. Although Streptomycin was abandoned as a first-line drug for treating new TB patients, it plays an important role in the re-treatment regimen for previously treated
patients. The other aminoglycosides, Kanamycin and Amikacin are used in the treatment of DR- TB (Arbex et al 2010:641; Guthrie 2008:91).

2.5.2 Antibacterial activity of aminoglycosides

Aminoglycosides inhibit protein synthesis by irreversibly binding to the 30S ribosomal sub-unit of M. tuberculosis, interfering with the integrity of the cell membrane. The aminoglycosides are bactericidal antibiotics that bind to the 30S ribosome and inhibit bacterial protein synthesis (Arbex et al 2010:642). Resistance is due to mutations in the *rrs* gene, which encodes 16S ribosomal RNA, and in the *rpsL* gene, which encodes the S12 ribosomal protein gene.

2.5.3 Pharmacokinetics of aminoglycosides

Oral absorption of aminoglycosides is minimal, and the drugs are administered parenterally. Absorption is complete when aminoglycosides are administered intramuscularly and the serum levels of the drugs peak within 30-90 minutes after their administration; however, intramuscular absorption can be slower, requiring successive injections at the same site. It is recommended that intravenous administration of aminoglycosides be carried out over a period of 15-30 minutes in order to reduce the risk of adverse effects, such as neuromuscular blockade. The binding of aminoglycosides to plasma proteins is low (approximately 10%). Over a 24-hour period, 80-98% of the drug is excreted, unaltered, by the kidneys (glomerular filtration), 1% is excreted in bile, and 1% is excreted in faeces. The half-life of Streptomycin is 2-3 hours, and the half-life of Amikacin is 2 hours, although the latter can be as long as 86 hours in patients with kidney failure (Arbex et al 2010:642).

2.5.4 Aminoglycoside Ototoxicity

Ototoxicity refers to poisoning of the inner ear by medication, by a toxin or a poisonous reaction damaging the cochlea, vestibule, semi-circular canals, or the auditory/ vestibulocochlear nerve. Symptoms of ototoxicity include partial or profound
hearing loss, vertigo, and tinnitus (Roland 2004). The damaged structure then produces the symptoms the patient presents with and ototoxicity defined as a) 20dB or greater decrease in pure tone threshold at one frequency, b) 10dB or greater decreased at 2 adjacent frequencies, or c) loss of three consecutive test frequencies in which responses were previously obtained when OAR or Auditory Brainstem Responses (ABR) is used ((American Speech-Language-Hearing Association 1994).

Aminoglycoside antibiotics used in MDR-TB treatment may cause hearing loss resulting from cochlear toxicity. Cochlear toxicity usually begins in the high frequencies and is secondary to irreversible destruction of outer hair cells in the organ of Corti, predominantly at the basal turn of the cochlea (Rybak & Ramkumar 2007). This type of hearing loss is induced by selective inner ear sensory hair cell death caused by the aminoglycoside cleared more slowly from inner ear fluids than from serum, and therefore latency exists to the ototoxic effects of aminoglycosides (Alharazneh, Luk, Huth, Monfare, Steyger, Cheng & Ricci 2011). This latency can result in progression of hearing loss or onset of hearing loss after cessation of aminoglycoside treatment. Continuing to monitor the patient for cochleotoxic and vestibulotoxic effects up to 6 months after cessation of aminoglycoside treatment is recommended (Fausti et al 2005:52).

2.5.5 Mechanism of aminoglycoside ototoxicity

The cellular basis for aminoglycoside hearing loss is a destruction of cochlear hair cells, specifically the outer hair cells, and ototoxicity is mediated by disruption of mitochondrial protein synthesis and the formation of free oxygen radicals. Aminoglycoside uptake is mediated through the mechanotransducer (MET) Channels (Alharazneh et al 2011). Damage to the hair cells progresses from the base of the cochlea that is an area for high frequency sound detection to the apex and low frequency sound detection (Chen et al 2007:178). Sha, Taylor, Forge and Schacht (2001) have suggested that the base is more vulnerable than the apex which could be due to an intrinsic difference in sensitivity to damage along the cochlear spiral. Since hair cells do not regenerate in the mammalian cochlea, their losses are irreversible and cumulative, and result in permanent damage to sensory
cells and neurons. Coupled with damage to sensory cells and neurons is the retrograde damage to the auditory nerve.

2.5.6 Characteristics of individual aminoglycosides

Ototoxicity is a grade 4 ADR and is one of the most severe ADR of MDR-TB treatments because it causes permanent disability (US Department of Health and Human Services 2010:17). Ototoxicity consists of one, or a combination of tinnitus, hearing loss and presence of disequilibrium. The anti-TB aminoglycosides vary greatly in their differential effects on the vestibular and cochlear systems. Kanamycin, Amikacin, Neomycin, and Dihydrostreptomycin are preferentially cochleotoxic. Gentamicin affects both cochlear and vestibular systems. Streptomycin, Tobramycin, and Netilmicin are primarily vestibulotoxic (Guan 2011:237; Guthrie 2008:91-6; Huth, Ricci & Cheng 2011:1-6).

2.5.6.1 Streptomycin

Streptomycin was the first clinically applied aminoglycoside and was used successfully against tuberculosis. Streptomycin preferentially affects the vestibular system rather than the auditory system. Vestibular damage due to Streptomycin is common with prolonged use and in patients with impaired renal function. However, Streptomycin use has risen for treatment of tuberculosis (Arbex et al 2010:626-40).

2.5.6.2 Kanamycin

Kanamycin is quite ototoxic. Kanamycin has a propensity to cause profound cochlear hair cell damage, marked high-frequency hearing loss, and complete deafness (Brennan & Young 2008:89-169; Perletti, Vral, Patrosso, Marras, Ceriani, Willems, Fasano & Magr 2008:3-13). The damaging effect is primarily to the cochlea, while the vestibular system is usually spared injury (Perletti et al 2008:3-13; Zhang, Yu, Liu, Tian, Wang, Lai & Zhou 2011:171-6).
2.5.6.3 Amikacin

Amikacin is a derivative of Kanamycin and has very little vestibular toxicity. Its adverse effects primarily involve the auditory system; however, it is considered less ototoxic than Gentamicin (Brennan & Young 2008:89-169; Perletti et al 2008:3-13).

2.5.6.4 Polypeptides (Capreomycin)

Capreomycin is a cyclic polypeptide antimicrobial and not an aminoglycoside and the chemical structure of Capreomycin is different from that of aminoglycosides. Capreomycin is obtained from Streptomyces capreolus and has been used as an anti-tuberculosis drug since 1959 (Akbergenov, Shcherbakov, Matt, Duscha, Meyer, Wilson & Bottger 2011:4712-7; Arbex et al 2010:626-40). The MIC of Capreomycin for M. tuberculosis is 10 μg/mL. However, Capreomycin and aminoglycosides are quite similar in terms of their antibacterial activity and adverse effects (Akbergenov et al 2011:4712). Resistance is associated with ribosomal changes in the 16S rRNA. There is cross-resistance between Capreomycin and Streptomycin and certain strains resistant to Amikacin and Kanamycin (Brennan & Young,2008:89). The mechanism of action of Capreomycin has yet to be fully understood. It is believed that the drug is active because it interferes with bacterial protein synthesis.

Capreomycin is not absorbed when taken orally. Capreomycin is administered by intramuscular injection and absorption can be delayed in cases in which the same site of application is used repeatedly. Tissue distribution has yet to be fully understood. After the administration of the drug, the serum levels of Capreomycin peak within 1-2 hours. The plasma half-life of Capreomycin is 4-6 hours in patients with normal renal function, and it can be as long as 55 hours in patients with kidney failure. Most of the dose (50-60%) is excreted through glomerular filtration 12 hours after administration and a small proportion is excreted via the biliary tract (Brennan & Young 2008:88-90).
STUDIES ON INCIDENCE AND RISK FACTORS FOR MONITORING MULTI DRUG RESISTANT TB RELATED HEARING LOSS

2.6.1 Global incidence of hearing loss related to MDR-TB treatment

The incidence of ototoxicity among patients receiving the standard MDR-TB treatment varies greatly, according to some of the studies reviewed. Refer to Table 2.4.

Table 2.4 Studies on the incidence of MDR-TB treatment induced hearing impairment

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Prevalence/incidence</th>
<th>Rate</th>
<th>Source</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>India</td>
<td>incidence</td>
<td>52.9%</td>
<td>WHO (1995:4)</td>
<td>Patients treated with Streptomycin</td>
</tr>
<tr>
<td>2001</td>
<td>Peru</td>
<td>incidence</td>
<td>6.7</td>
<td>Furin (2001:650)</td>
<td>Community based study</td>
</tr>
<tr>
<td>2002</td>
<td>Netherlands</td>
<td>incidence</td>
<td>18.5%</td>
<td>de Jager (2002:622-7)</td>
<td>Investigated ototoxic and nephrotoxic effects</td>
</tr>
</tbody>
</table>


2.6.2 Incidence of hearing loss related to MDR-TB treatment by continent

2.6.2.1 Europe

In the Netherlands, de Jager (2002:622-7) found that 18% of the patients treated with injectable aminoglycoside developed hearing loss, while Bloss et al (2010:275) reported the hearing loss incidence of 19% in Latvia among 1,027 patients, while other researchers in Latvia found an incidence of 28.4% among 204 patients

2.6.2.2 Latin America


2.6.2.3 Middle East and Asia

Masjedi, Baghaei, Mirsaeidi, Farnia, Javanmad, Mansoiri and Velayati (2011:752) in Iran, reported a hearing loss incidence of 46% and Duggal and Sarkar (2007:1) reported a hearing loss incidence rate of 18.75% in India which compares closely with the incidence of 14% in another study in India (Singla, Sarin, Khalid, Mathuria 2009:976).

2.6.2.4 Sub-Saharan Africa

Among children in South Africa, the incidence of hearing loss was 24% (Seddon et al 2013:320-9). Van der Walt et al documented a hearing loss incidence of 38% among ART naïve HIV positive patients (Van der Walt, Lancaster, Odendaal, Davis, Shean & Farley 2013:[1]), while Harries et al (2012:363-6) documented a hearing loss incidence of 37.8%. Ramma and Ibekwe (2012) found a prevalence of 47%.

2.6.2.5 North America

Peloquin found a hearing loss incidence of 37% among patients on aminoglycosides in the USA (Peloquin, Berning, Nitta, Simone, Goble, Huitt, Iseman, Cook & Curran-Everett 2004:1538-44).
2.6.3 Risk Factors and Determinants of Aminoglycoside Related Ototoxicity

A risk factor as any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury, (adverse health outcomes) (World Health Organization 2004). On the other hand, a determinant is a variable associated with either increased or decreased risk. Risk factors and determinants are correlational and not necessarily causal, because correlation does not prove causation. In this section, risk factors for developing ototoxicity are grouped as health system related or patient related.

2.6.4 Health system related risk factors

There are a number of health system related risk factors for MDR-TB treatment related ototoxicity such as type of drug, dose, frequency and administration route, treatment duration, dosage, co administration with other drugs and bioavailability, and so on.

2.6.4.1 Dose of aminoglycoside drug

Some studies show that the dose is a risk factor for MDR-TB treatment ototoxicity. Gatell, Ferran, Araujo, Bonet, Soriano, Traserra and SanMiguel (1987:1387) showed that patients enrolled in three prospective randomised trials patients who developed auditory toxicity, had a significantly higher (P = 0.04) percentage of trough levels Amikacin above 5 mg/liter on univariate analysis. Rybak and Ramkumar (2007:933) contend that the degree of hair cell damage and hearing loss is directly proportional to the dose of the drug to which the hair cells are exposed. However, de Jager and Alterna (2002:622) found that factors such treatment duration, total aminoglycoside doses or first serum creatinine concentration were not associated with hearing loss.
2.6.4.2 Frequency of dosing

One meta-analysis of once-daily versus multiple-daily dosing rates of clinically reported hearing loss were 0.4% for once-daily dosing and 0% for multiple daily dosing. Hearing loss rates determined audiometrically were 5.1% and 7.8%, respectively (Turnidge 2003:503). According to Barclay, Kirkpatrick and Begg (1999:89), at least 30 controlled clinical trials have compared once daily dose versus conventional multiple daily dose administration and it appears that aminoglycoside regimens that use the same total daily dose have the same incidence of ototoxicity as multiple dosing. Aminoglycosides appear to rapidly enter the cochlea after systemic administration, but the distribution within inner ear tissues does not correlate with their preferential toxicity to particular cells in the cochlea and vestibular system (Dulon, Aran, Zijic et al 1968:96). Perletti (2008:13) questioned what seems to be paradoxical. Although single dose drugs induce higher peak serum concentrations, lower ototoxicity was observed when compared to multiple dose drugs. The inner ear uptake of AGs is a saturation process. Single dose drugs inner ear cells are saturated only once, whereas with multiple drug saturation occurs 2-3 times within 24 hours thus increasing the cellular aminoglycoside load.

2.6.4.3 Duration of exposure and previous exposure

MDR-TB patients with previous exposure to Streptomycin could be prone to hearing loss. Repeated exposure to aminoglycosides leads to an additive damage to hair cells and other structures, and subsequently to deafness (Rybak & Ramkumar 2007:933). It appears that the aminoglycosides persist in the inner ear tissues for 6 months or longer after administration, and is the main cause for enhanced susceptibility of patients to the ototoxicity of aminoglycosides when they have a history of previous aminoglycoside treatment. The susceptibility does not seem to arise from drug accumulation within the inner ear, given that the inner ear concentration of aminoglycosides does not exceed that of the plasma.
2.6.4.4 Concurrent exposure to ototoxic drugs

Prescription of ototoxic drugs concomitantly, especially loop diuretics, platinum-based antineoplastic drugs, salicylates and NSAID, anti-malarial drugs (especially Quinine), HIV protease inhibitors and NRTI may be associated with increased MDR-TB treatment hearing impairment. Antineoplastic agents most commonly associated with ototoxicity are the platinum-based compounds cisplatin and, to a lesser degree, carboplatin (Xia, Chen, Su, Yin & Wang 2014:376-85). These agents are widely used in gynaecologic, lung, central nervous system, head and neck, and testicular cancers (Yasui, Adachi, Kato, Koh, Asanuma, Sakata & Hanada 2014:1).

Platinum compounds damage the stria vascularis in the scala media and cause outer hair cell death beginning at the basal turn of the cochlea (Xia et al 2014). The mechanism of platinum ototoxicity is mediated by free-radical production and the free radicals generated by this mechanism then lead to mitochondria-mediated and caspase-mediated apoptotic cell death, and ultimately permanent hearing loss. The following risk factors have been identified for development and potentiation of platinum-induced ototoxicity: (1) high dose and increasing number of cycles, (2) concurrent or past cranial irradiation, (3) age extremes, (4) dehydration, (5) co-administration of other ototoxic agents, and (6) renal failure (Langer, am Zehnhoff-Dinnesen, Radtke, Meitert & Zolk 2013:558-69; Mudd 2012).

Loop diuretics are a class of medications used to treat congestive heart failure, renal failure, cirrhosis, and hypertension. These include several different chemical groups, including sulfonamides, phenoxyacetic acid derivatives, and heterocyclic compounds. The most effective and frequently used diuretics; ethacrynic acid, furosemide, bumetanide can cause ototoxicity (Vilayur, Gopinath, Harris, Burlutsky, McMahon & Mitchell 2010:661-9). The ototoxic effects of loop diuretics seem to be associated with the stria vascularis, which is affected by changes in the ionic gradients between the perilymph and endolymph (Xia et al 2014:376-85). These changes cause oedema of the epithelium of the stria vascularis. Overall, ototoxicity attributed to this group of medications is usually self-limited and reversible in adult patients, although irreversible hearing loss has been reported in neonates.
Ototoxicity is estimated to occur in 6-7 % of patients taking loop diuretics. Occurrence of loop diuretic ototoxicity depends on several factors, including dose, infusion rate, history of renal failure, and co-administration of other ototoxic agents like those used in treatment of MDR-TB (Sinxadi 2009:372-73). Potentiation and synergism of ototoxic effects of aminoglycosides and loop diuretics is well documented, and co-prescription of these drugs is not recommended (Hirose & Sato 2011:108-18; Xiong, Chu, Huang, Cui, Zhou, Chen, Li, Wang, Chen & Li 2010:222-8). If used, the lowest doses of loop diuretics is possible to achieve desired effects, avoiding rapid infusion rates and use in renal failure.

2.6.5 The patient related risk factors

From the literature reviewed, patient characteristics include age, sex, ethnicity, coexisting disorders, and genetic or geographic factors.

2.6.5.1 Age above 60 years

Gatell, Ferran, Araujo, Bonet, Soriano, Traserra, and SanMiguel (1987:1387) studied records of 187 patients enrolled in three prospective randomised trials. The patients who developed auditory toxicity were significantly older (P = 0.01) and only age was retained as independently influencing the development of auditory toxicity on logistic regression. It appears that damage is more significant in the elderly who may have fewer hair cells at the beginning of treatment or lower endogenous protective mechanisms than other individuals with compromised auditory function (Rybak 2007:364-9; Rybak & Whitworth 2005:1313-21); Rybak & Ramkumar 2007:933). On the converse, de Jager and Alterna (2002:622-7) did not find that factors such as sex or age were associated with hearing loss in a prospective study. These findings are also corroborated in Moore, Smith and Lietman (1984:30) who analyzed risk factors for the development of auditory toxicity in patients receiving aminoglycosides from patients enrolled in three prospective randomised double-blind clinical trials of Gentamicin, Tobramycin and Amikacin, found that age and sex did not increase risk for hearing loss among the patients.
2.6.5.2 Renal impairment and/or hepatic impairment

Individuals with renal insufficiency are more susceptible to aminoglycoside ototoxicity, because of reduced renal excretion that can result in higher serum levels and prolonged half-life. This could lead to increased exposure of the inner ear to toxic concentrations of aminoglycosides resulting in more severe hearing loss (Meena, Aseri, Singh & Verma 2012:356). Vilayur, Gopinath, Harris, Burlutsky, McMahon and Mitchell (2010:661-69) and (Vilayur et al 2010:661) show that moderate and severe grades of chronic kidney disease (CKD) are significant risk factors even after adjusting for age; sex; noise exposure; education; diabetes, hypertension, and stroke histories; and smoking. Respondents with eGFR 45 mL/min/1.73 m2 had the highest prevalence of hearing loss (73%) compared with those with eGFR 90 mL/min/1.73 m2 (19%). Pandey, Gore, Valame and Mehta (2011:131-6) demonstrated that hearing loss in patients with CRF has a distinct audiologic pattern and significant differences in the degree of hearing loss were observed among patients with different stages of CRF.

2.6.5.3 Smoking and Alcohol abuse

Current smoking status is significantly associated with the prevalence of hearing loss (Gopinath, Flood, McMahon, Burlutsky, Smith & Mitchell 2010:277-82) and noise induced hearing loss (Agrawal, Platz & Niparko 2008:1522-30). Teens who are regularly exposed to second-hand smoke are nearly twice as likely to have hearing loss as teens who live in smoke-free environments (Lalwani, Liu & Weitzman 2011a:655-662). Lalwani, Liu and Weitzman (2011:655) postulate that nicotine is neurotoxic. Conversely, cross-sectional analysis also demonstrated a significant protective association between the moderate consumption of alcohol (1 - 2 drinks/day) and hearing function in older adults (compared with non-drinkers), OR 0.75 (95% CI, 0.57 to 0.98).

2.6.5.4 Genetic predisposition and family history of ototoxicity

Genetic variations, including mitochondrial mutations and inherited haemoglobin gene disorders are important contributors to hearing loss, especially in children, and
newborn genetic screens for hearing loss mutations and gene disorders could be useful.

Mitochondrial mutations have been linked with ototoxic responses to common antibiotics, therefore understanding the association of these mutations with hearing loss is of special importance (Jing, Zongjie, Denggang, Na, Bin, Aifen, Xijiang, Cong, Yunping, Ring & Ring 2014:1-4). Genetic predisposition where some mutations of genes coding for mitochondrial 12S r RNA confer higher susceptibility to aminoglycoside-induced ototoxicity and such mutations are transmitted to all children by maternal lineage and recessive SCD gene. Mutations in the mitochondrial 12S ribosomal rRNA renders patients highly susceptible to aminoglycoside ototoxicity. The first described mutation was an A1555G mutation in the 12S rRNA. There are at least six mutations described to date (A1555G, T1095C, C1494T, A827G, 961delT, and T1291C). The A1555G mutation has been described in numerous populations worldwide, including Chinese, Spanish, and Arab-Israeli (Peng, Zheng, Fang, Wu, Liang, Zheng, Nan, Yu, Tang, Zhu, Lu, Chen & Guan 2013:62). This mutation has also been found in a South African family in which 11 family members were diagnosed with aminoglycoside-induced hearing loss following Streptomycin treatment for TB. Persons with this mutation may incur hearing loss after a single dose of aminoglycoside. However, one case has been reported who did not develop hearing loss after repeated aminoglycoside exposure (Al-Malky, Suri, Sirimanna & Dawson 2014-73). Since these are mitochondrial DNA mutations, all maternal relatives harbour the mutation, and mutation-positive mothers will transmit the mutation to all of their children (Bardien et al 2009a:1).

Sickle cell disease also predisposes to a significant incidence of SNHL in SCD patients (36.95%), although the patients maybe clinically asymptomatic (Al Okbi, Alkindi, Al Abri, Mathew, Nagwa & Pathare 2011:392-6). According to the study by Al Okbi et al (2011:392-6) the hearing loss was worse in the right ears and had a female preponderance. Also, the hearing loss was more severe at the higher frequencies, 2,000-8,000 Hz in SCD patients. HbS, HbF, or low haemoglobin levels did not discriminate SCD patients with SNHL, and the role of haemoglobin F in the cochlea is still not clear.
2.6.5.5  *Work or environment exposure to noise*

Excessive sound (unprotected exposure above 95dBA) damages the hair cells and the blood supply in the cochlea (Dobie 2008:565, 2005a:630; Rabinowtz 2012:14, Thurston 2013:367). The damage may directly result from the noise, or indirectly from very high levels of continuous sound, that causes vasoconstriction of the vessels of the stria vascularis in the cochlea blood supply. This renders the hair cells relatively anoxic and thus secondarily damaged. The amount and type of direct hair cell damage depends on the intensity of the sound. Noise exposure increases hearing thresholds, resulting in threshold shifts toward higher values (poorer hearing).

During each overexposure to noise, the ear develops a temporary reduction in sensitivity called temporary threshold shift. This shift reverses over a period of hours or days if the ear is allowed to rest in a quieter environment. However, if the exposure is high enough, or if exposures are repeated, the temporary threshold shift may not reverse completely, and a permanent threshold shift begins to develop. Hearing losses from different causes are additive and interaction can occur between noise exposure and chemicals such as toluene, or antibiotics such as the aminoglycosides (Li & Steyger 2009a:26-32). Whenever hazardous noise exists in the workplace, patients on MDR-TB treatment are vulnerable to the additive effect and measures should be taken to reduce noise levels as much as possible to protect exposed workers and to monitor the effectiveness of hearing loss prevention programmes at the workplace. Noisy environments potentiate susceptibility to noise induced cochlear damage (Fausti et al 2005).

2.6.5.6  *Co-Morbid conditions*

In co-morbid conditions like diabetes mellitus, neuromas, hypertension and cardiovascular diseases, Bainbridge and Cowie (2009) found a six-fold increased risk of high-frequency hearing loss associated with both peripheral neuropathy and coronary heart disease. Suboptimal glycemic control was also associated with a nearly threefold increased risk of high-frequency hearing impairment (Akinpelu,

It is postulated that some of the mechanisms by which hearing is affected in diabetic patients include thickened vessels of the stria vascularis and the internal auditory artery, as well as demyelination of the eighth cranial nerve (Carrasco, Prazma, Faber, Triana & Pillsbury 1990:411-7; de Moraes Marchiori, de Almeida Rego Filho & Matsuo 2006:533-40). Evidence about hypertension as a risk factor for hearing loss is not as definitive. Agrawal et al posit that hypertension is an independent risk factor, mainly due to age (Agarwal, Mishra, Jagade, Kasbekar & Nagle 2013:614-8), Oh et al (2014) showed that on multivariate analysis, diabetes mellitus (DM) was an independent predictor of hearing loss (p<0.05).

2.6.5.7 Acoustic neuromas

Acoustic neuromas are intracranial, extra-axial tumours that arise from the Schwann cell sheath investing either the vestibular or cochlear nerve. Unilateral hearing loss is overwhelmingly the most common symptom present at the time of diagnosis and is generally the symptom that leads to diagnosis (Walsh, Bath, Bance, Keller, Tator & Rutka 2000:21-6). The tumour can produce hearing loss through at least two mechanisms, direct injury to the cochlear nerve or interruption of cochlear blood supply. Progressive injury to cochlear fibers probably accounts for slow progressive neurosensory hearing loss observed in a significant number of patients with acoustic neuromas (Gonzalez-Orus Alvarez-Morujo, Alvarez-Palacios, Martin-Oviedo, Scola-Yurrita & Aristegui-Ruiz 2014:275-82). Sudden and fluctuating hearing losses are more easily explained on the basis of disruption of cochlear blood supply (Kutz 2012).

2.6.6 HIV/AIDS and Hearing loss

Evidence of HIV as a cause of hearing loss has been scanty and so there is no consensus on the role of HIV and the role of anti-retroviral medicines in the causation of hearing loss among people living with HIV (Assuiti , Lanzoni , Santos , Erdmann & Meirelles 2013:448; Kakuda 2000a:685; Schouten, Lockhart, Rees,
Collier & Marra 2006:1-4). Schouten et al (2006) found no association between hearing loss with treatment with AZT. Another study did not find a clear association nucleoside analogue therapy and hearing loss, and posited that the pathophysiology of less common adverse effects of nucleoside analogue therapy, such as diabetes, ototoxicity, and retinal lesions, may be related to mitochondrial dysfunction cause by NRTIs (Kakuda 2000b:685-708).

Direct action of the virus on the central hearing systems has been muted. This is in way to undermine the potential action of ARV medications on the ear, which may have potential ototoxic effects and cause hearing loss. The possible association with hearing loss in the central hearing system caused by the direct action of the virus, is suggested by the fact that in many cases there are otoneurological signs and symptoms presented by or reported by the patients, such as hearing loss, tinnitus and dizziness (Khoza-Shangase 2011; Schouten et al 2006). Recent studies in South Africa that included PLHIV showed high rates of hearing loss associated with MDR-TB treatment among PLHIV but did provide direct evidence on the role of HIV and ARV in the hearing loss (Harris et al 2012:363-6; Seddon et al 2013:320-9).

2.6.7 Time to hearing loss

No studies reporting on time-to-hearing loss in MDR-TB patients were found during the literature search.

2.7 PREVENTION, TREATMENT AND MANAGEMENT OF HEARING LOSS

2.7.1 Basic concepts of natural history of disease occurrence

Primary, secondary, and tertiary prevention programmes focus on different aspects of the natural history of disease. The concepts of primary, secondary, and tertiary prevention make use of these prevention concepts. Primary prevention aims at inhibiting the development of disease before it occurs. Secondary prevention aims to
identify and detect disease in its earliest stages before it is noticeable, when it is possible to prevent progression or minimise complications (sometimes referred to as “screening”). The purpose of tertiary prevention is to improve the quality of life for people by rehabilitation (therapy to restore functionality and self-sufficiency) among people already affected by a disease in order to mitigate catastrophic outcomes (Figure 2.11 shows key milestones in natural disease progression).

Figure 2.7: Natural disease progression and the milestones of detection.


From the onset of disease, until clinical symptoms occur, there is a pre-clinical phase without overt symptoms and the individual who has the disease may not know it. Within the preclinical phase, there may be an interval between the onset of the disease and the occurrence of clinical symptoms during which disease can be detected with certain tests. This is called a detectable pre-clinical phase. If treatment (and/or preventive action) is more effective when disease is in the preclinical stage, screening for disease during the detectable pre-clinical phase offers an advantage. See Figure 2.12.
2.7.2 Basic concepts of Years lived with Disability

According to the World Health Report of 2003, adult onset hearing loss was the second leading cause of years of lived with disability (YLDs) in 2000 (Mathers, Smith & Concha 2010). Early detection may prevent hearing loss that requires rehabilitation and hence, YLDs as illustrated in Figure 2.11.

Figure 2.9: Model for adult onset hearing loss.
2.7.3 Application of the prevention concepts to MDR-TB treatment hearing loss

Primary prevention involves avoidance of the ototoxic drugs and hence prevention of MDR-TB, and rational prescription of aminoglycosides and polypeptides.

Effective management by secondary prevention includes the early detection and treatment. Early detection and monitoring of ototoxicity as a standard of care can reduce the impact of ototoxic-induced hearing loss, ultimately improving treatment options for patients and preserving post treatment quality of life (Wilmington, Konrad-Martin, Helt, Dille, Gordon & Fausti 2011:248). That can be achieved through pharmacovigilance (PV) which is responsible for monitoring the safety of medicines in normal clinical use and during clinical trials (Mammi et al 2013:S33-4).

Tertiary prevention refers to the management and rehabilitation of hearing loss and includes the provision of good-quality, appropriate hearing aids, essential support services, access to appropriate communication, improvements in the acoustic environment, special education and social integration at all levels (Smith, 2002, World Health Organization 1996).

2.7.4 Monitoring hearing loss as part of a MDR-TB treatment related hearing loss prevention strategy

The main purpose for monitoring is to enable early identification and prevention.

"Should we care about early changes enough to take the time to measure them?"
- Campbell (2007)

The answer is yes. Reasons to monitor cochlear and vestibular function are enumerated as:

i) cochlear function is affected by almost all aminoglycosides;
ii) even slight ototoxic cochlear dysfunction is noticeable, particularly via high frequency audiometry and otoacoustic emissions; and

iii) slowly progressive vestibular dysfunction may go undetected for some time. Cochlear and vestibular ototoxicity may be variable in terms of onset and progression.

The American Speech-Language-Hearing Association (1997) states that:

“Audiologic screening serves a secondary prevention function; that is, if a hearing disorder, impairment, or disability is detected and treated early, potential hearing-related problems can be prevented or ameliorated”.

The benefits of monitoring include early detection may prevent hearing damage that requires amplification/rehabilitation; if change is observed, treatment modification can prevent further hearing loss. However, if no change is observed, continued treatment is warranted, monitoring provides an opportunity for counselling and rehabilitation during and post treatment, and finally, monitoring provides the basis for informed medical decision-making.

2.7.5 Establishing an ototoxicity monitoring programme

According to the ASHA recommendations (1997), a basic audiological ototoxicity-monitoring programme requires:

a. specific criteria for identification of toxicity;

b. timely identification of at-risk patients;

c. pre-treatment counselling regarding potential cochleotoxic effects;

d. valid baseline measures (pre-treatment or early in treatment);

e. monitoring evaluations at sufficient intervals to document progression of hearing loss or fluctuation in sensitivity; and

f. follow-up evaluations to determine post-treatment effects.
2.8 APPLICATION OF THE NEUMAN SYSTEMS MODEL FOR HEARING PRESERVATION IN PATIENTS ON MDR-TB TREATMENT

The model provides a comprehensive flexible holistic and system based perspective for nursing and health care. Developed by Betty Neuman, the Neuman System Model (NSM) is a nursing theory based on following key concepts:

i) the client system (which maybe an individual, family group or community);
ii) interacting variables of the client system which are the physiological, psychological, spiritual, developmental and sociocultural;
iii) client’s response to actual or potential environmental stressors (internal, external and created environments), the reaction to it, and reconstitution factors that are dynamic in nature (Freese & Lawson 2010:309-33; Geib 2002:237);
iv) emphasis on prevention, as intervention for retention, attainment, and maintenance of optimal client system wellness; and
v) the purpose of the nurse is to retain of the client system's stability through the three levels of prevention; which are:

- Primary prevention to protect the normal line and strengthen the flexible line of defence. Primary prevention relates to good clinical practice that is applied in client assessment and intervention, in identification and reduction of possible or actual risk factors.
- Secondary prevention to strengthen internal lines of resistance, reducing the reaction, and increasing resistance factors. Secondary prevention also relates to symptomatology following a reaction to stressor, appropriate ranking of intervention priorities and treatment to reduce their noxious effects.

Tertiary prevention to re-adapt and stabilise and protect reconstitution or return to wellness following treatment. Tertiary prevention also relates to adjustive processes taking place as reconstitution begins.
2.8.1 The Client system in Neuman Systems Model

The client system includes physiological, psychological, sociocultural, developmental, and spiritual aspects as variables. The central core of the model consists of energy resources (normal temperature range, genetic structure, response pattern, organ strength or weakness, ego structure, and known or commonalities) that are surrounded by several lines of resistance, the normal line of defence, and the flexible line of defence. The lines of resistance represent the internal factors that help the patient defend against a stressor, the normal line of defence represents the person’s state of equilibrium, and the flexible line of defence depicts the dynamic nature that can rapidly alter over a short period.

NSM provides a comprehensive, flexible, holistic, and system-based perspective for medical practice including monitoring and prevention of hearing loss for patients on MDR-TB treatment. It also provides a structure for critical thinking (an active process that guides action). The review of literature is cognizant of the four paradigms of Neuman’s System model.

i) The person

The model views the human being as a total person, as a client system, and the person is a layered multidimensional being physiological (physicochemical structure and function of the body); psychological (has mental processes and emotions); has relationships and social/cultural expectations and activities; has spiritual beliefs and undergoes processes related to development over the lifespan;

ii) The environment:

The model considers the environment with the totality of the internal and external forces (intrapersonal, interpersonal, and extra-personal stressors) which surround a person and with which they interact at any given time);
iii) Health:

The model equates health to wellness where the condition in which all parts and subparts (variables) are in harmony with the whole of the client and the client system moves toward illness and death when more energy is needed than is available;

iv) Medical practice/nursing:

The Medical/Nursing profession is a unique profession that is concerned with all of the variables, which influence the response a person might have to a stressor. While a person is seen as a whole, it is the task of nursing to address the needs of whole person through actions, which assist individuals, families and groups to maintain a maximum level of wellness. The primary aim for wholist action is stability of the patient/client system, through nursing interventions to reduce stressors by the use of primary, secondary, and tertiary interventions.

2.8.2 Nursing Diagnosis, Goals and Outcomes

Neuman’s System model guides a framework for the development of comprehensive diagnoses, determination of appropriate interventions and evaluation of outcomes. We can apply the nurse-client partnership to identify a stressor(s) that may penetrate the flexible defence and lead to variance from wellness as in the case of MDR-TB treatment related hearing loss. The variation from wellness is of interest in the study of hearing loss.

2.8.2.1 Nursing diagnosis

According to Neuman’s System model, clinical care of MDR-TB starts with assessment of the physiological, psychological, developmental, sociocultural and spiritual dimensions for the following components of the client’s system (MDR-TB patient) in order to conceptualise and analyse the client’s system (Gei, 2002:345-357):
• Basic structure and function: the central or core structure consists of basic survival factors (normal temp range, genetic structure, response pattern, organ strength/weakness (and this includes hearing health assessment) and ego structure (Geib 2002:235-259).

• Potential or actual environmental stressors (interpersonal, intrapersonal and extra personal stressors) to help in identifying the majors areas of stress, changes in the patterns of living, previous coping behaviours, anticipated consequences and expectations for self, from health care systems and from others. Early signs of hearing loss, fears, and worry about potential hearing loss with MDR-TB treatment and pre-existing risk factors for hearing loss from various aspects are assessed according to the five interacting variables.

• Characteristics of the cleanest flexible line and normal lines of defence, lines of resistance, degree of potential and actual reaction and reconstitutions. This model is used in defining parameters that enable provision of care in a comprehensive manner.

2.8.2.2 Nursing Goals

After diagnosis, the next step is synthesis. Reasoning is applied to the findings, the variances from wellness identified, and applicable and nursing theories appraised. The identified diagnosis based on the data from the client system, level of the system or subpart of the response, variables, stressor source. The healthcare specific outcome goal prioritised as and primary, secondary and tertiary prevention-as-intervention modalities is done based on the related risk factors found, client perceptions, and resources to promote optimal stability, that is, hearing preservation.

2.8.2.3 Nursing Outcomes

In the development of the nursing outcomes, the synthesis, analysis, and evaluation of the prevention-as-intervention modalities and perceived efficacy are processed in partnership and with the validation of the client.
2.8.2.4 *Optimal Wellness Stability*

Optimal wellness is the greater possible degree of system stability at a given point in time and the optimal client system stability means the highest possible health condition achievable at a given point in time (Neuman 2002).

2.8.3 *The Lines of defence in Neuman systems model*

The client is also conceptualised as having an inner core or basic structure (basic energy resources) that is protected by concentric circles representing a normal line of defence and a flexible line of defence. The usual level of health is identified as the normal line of defence that is protected by a flexible line of defence and it can be affected by tension producing intrapersonal, interpersonal, and extrapersonal stressors, which arise from the internal, external, and created environments respectively.

When stressors break through the flexible line of defence, the client system is invaded and the lines of resistance are activated with the client system moving into illness on a wellness-illness continuum. If adequate energy is available, the system will be reconstituted with the normal line of defence restored at, below, or above its previous level (Freese & Lawson 2010:315-323).

2.8.4 *Critical thinking and Neuman Systems Model of Clinical Practice*

The healthcare model adapted in the theoretical framework in the study of MDR-TB treatment related hearing impairment is the Neuman System’s model of nursing and table (Neuman 2002:10-12). See Table 2.5.
2.8.5 Critical thinking and Neuman Systems Model of Prevention-as-Intervention

From a hearing preservation perspective, the model suggests that clinical and nursing care interventions occur through three prevention modalities based on Caplan's concept of level of prevention (Caplan, 1964). Primary prevention occurs before the stressor invades the system; secondary prevention occurs after the system has reacted to an invading stressor; and tertiary prevention occurs after the system has reacted to an invading stressor.

Table 2.5: Application of the theoretical framework (Neuman's model) to hearing loss related to MDR-TB treatment

<table>
<thead>
<tr>
<th>Model component</th>
<th>Application to MDR-TB treatment related hearing impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Care worker/client relationship</td>
<td>Mutual partnership developed during the initial assessment with baseline tests and audiology. The HCW perceives the physiological stressors (injectable MDR-TB drugs and hearing impairment) as very important. Throughout the process of care, planning the HCW team assesses possible discrepancies in perception.</td>
</tr>
<tr>
<td>Physiological</td>
<td>Stressors: <strong>Intrapersonal</strong>: - (injectable aminoglycoside antibiotics and other medicines, adverse drug reactions, compromised hearing); <strong>Interpersonal</strong>: - (role of family support, perceptions of the caregiver); <strong>Extra-personal</strong>: - (nutrition and strong medications and home situation during the long treatment duration).</td>
</tr>
<tr>
<td>Psychological</td>
<td>Stressors: <strong>Intrapersonal</strong>: - (fear of the future, fear of hearing impairment and the serious impact on communication and self-esteem); <strong>Interpersonal</strong>: - (fear about children's future, lack of support from family and relatives); <strong>Extra-personal</strong>: - (Isolation during MDR-TB treatment, effect of the situational stress such as finances and job security during the long treatment duration).</td>
</tr>
<tr>
<td>Developmental</td>
<td>Stressors: <strong>Intrapersonal</strong>: - (productive life); <strong>Interpersonal</strong>: - (roles as parent, husband, wife and so on).</td>
</tr>
<tr>
<td>Sociocultural</td>
<td>Stressors: <strong>Intrapersonal</strong>: - (image of self); <strong>Intrapersonal</strong>: - (unsupportive family); <strong>Extra-personal</strong>: - (reduced income).</td>
</tr>
<tr>
<td>Spiritual</td>
<td>Stressors: <strong>Interpersonal</strong>: - (fears illness is punishment)</td>
</tr>
</tbody>
</table>
| Affected boundaries   | The client's flexible lines of resistance have been penetrated by the injectable MDR-TB antibiotics and lines of defence activated. Defence lines are augmented by all the primary prevention (proper hydration while on MDR-TB treatment, temperature control, good nutrition, use of medical techniques to identify and prevent of risk factors for HL in the client, information of TB medications and ototoxicity, and baseline hearing screening). The secondary prevention - regular monitoring of hearing status, blood chemistry while on treatment, dose and drug change modifications when risk is discovered) and the tertiary prevention (provision of assistive hearing aids, training for sign language, family
counselling and support for the hearing impaired) modes of prevention-as-interventions should be implemented to meet the client’s needs. Promote hearing conservation; promote wellness; prevention as intervention is evaluated for the defensive enhancement; as needed goal reformulation.

Clients have lines of resistance that protect their client’s basic core structure energy resources of the client (described in 2.8.1 (i) and 2.8.2.1). Ineffective lines of defence can be seen when an individual receives extensive MDR-TB chemotherapy (external stressor) with a result that the hearing system is severely compromised. The hearing loss is an example of the system energy being depleted and this disrupts optimum health. Mobilisation of external resources (assisted hearing aids) helps the client's internal resources and strengthens the lines of resistance. The outcome is a more physiologically and psychologically stable client (Alligood 2010:240).

Accordingly, the health professional plays an important role in creating connections among the client, environment, health and health care service that lead to system stability (Freese & Lawson 2010:309-334). Neuman considers a “client” as an individual, group, family, or community system, and each client has five variables that act synergistically to each other (physiological, psychological, developmental, socio-cultural, and spiritual) and reciprocally with the internal, external, and created environment in which the client exists. Multi-drug resistant TB exists in the external environment and the sufferer develops MDR-TB through the mechanisms explained in Chapter 2, section 2.2. The treatment of MDR-TB also exists in the external environment and is categorised as a “stressor” to the client, which the client reacts to.

Neuman’s model regards the normal line of defence as the usual or standard client level of wellness that protects the basic structure as the client reacts to the stressors. However, beyond, and in addition to the normal line of defensive, the Neuman’s model points out a flexible line of defence that expands protection to the client. The paragraphs highlight the application of the lines of defence to MDR-TB:
the flexible line of defence may include healthy life styles such as a diet free from saturated fats where Rosen, Olin and Rosen (1970:242) demonstrated that low saturated fat diet prevents coronary heart disease and may arrest progression of hearing loss.

- minimizing modifiable risk factors for hearing loss such as voluntary exposure to loud noise, failure to use hearing protection when necessary, smoking, lack of exercise, and failure to avoid tooth decay/tooth loss (Daniel 2007:225);

- a lifestyle that avoids diabetes and cardiovascular disease may buffer the client from the stressors that invade the client, thereby freeing the client from reactions to those stressors (Daniel 2007:225)

Client system stability and normal health are affected by the internal and external environmental and the created environment, the third distinct aspect of the environment (made up of factors in the environment) and are defined as stressors in the Neuman’s System model.

When the stressors penetrate the flexible and normal lines of defence and the lines of resistance are activated, energy depletion and system instability occurs. When applying MDR-TB and MDR-TB treatment on the one hand and resultant MDR-TB treatment related hearing loss on the other hand to the model, as the stressors and system instability respectively, MDR-TB treatment can influence the client in three ways: intrapersonal, interpersonal, and extrapersonal dimensions.

First, intrapersonal stressors are internal stressors that will occur within the patient system boundary such as atherosclerosis, hypertension, diabetes mellitus, Human immune deficiency syndrome, and Acquired immune deficiency syndrome (HIV and AIDS).

Second, interpersonal stressors are external stressors that occur in the external environment outside but proximal to the client system boundaries. The client’s role in
the family as a breadwinner, perceptions of the caregiver, and friend relationships are examples of these forces.

Third, extrapersonal stressors occur distally to the client boundary and examples include employment of the individual client, and financial status.

All the three stressors may be exhibited and observed by health professionals in the management of MDR-TB. Data should be collected, analysed during diagnosis and goals, outcomes and interventions, in conjunction with the client. Monitoring of hearing loss during MDR-TB treatment provides an opportunity for prevention of hearing loss as an intervention jointly agreed upon by the health professional and the client.

Primary prevention for hearing loss occurs before the client system reacts to a stressor, which is MDR-TB disease and MDR-TB treatment as below:

- MDR-TB (individual is free from potential need for MDR-TB treatment),
- Second line anti-tuberculosis drugs (MDR-TB treatment after the stressor invasion-MDR-TB disease).

Health professional actions implemented as primary prevention interventions of hearing loss aims at strengthening the flexible lines of defence. The pre-emptive actions promote the retention of the client’s wellness to enable the person to better deal with stressors that make the client susceptible to hearing loss.

Prevention interventions against stressor invasion (MDR-TB) include promotion of health, maintenance of wellness, preventing acquired drug resistance among patients on first line TB treatment (“turning off the tap”) and prevention of MDR-TB transmission at household, in health care settings, and congregate settings. Once created, drug-resistant strains can be transmitted, giving rise to DR-TB in individuals never previously exposed to anti-tuberculosis drugs (Gandhi 2010). Patients with tuberculosis, with and without HIV co-infection, can be infected with MDR-TB strains, but those co-infected with HIV are much more likely than are their counterparts to
progress to active tuberculosis disease after initial infection (Selwyn, Hartel, Lewis et al, 1989:545). Hence, prevention of HIV is an indirect primary prevention intervention for hearing loss.

On the contrary, primary prevention-as-interventions for hearing loss occurs before the client system reacts to a stressor (MDR-TB treatment) and include dealing with the risk factors and determinants for MDR-TB related hearing loss outlined in section 2.6. Primary prevention-as-interventions for MDR-TB related hearing loss includes actions such as:

- careful aminoglycoside dosing,
- judicious use of aminoglycosides in high risk patients such as
  - the elderly,
  - those with pre-existing renal insufficiency,
  - those with pre-existing hearing problems,
  - those with family history of ototoxicity,
  - those receiving loop diuretics or other ototoxic or nephrotoxic medications, and
- Lifestyle measures to avoid noisy environments that potentiate susceptibility to noise induced cochlear damage, and healthy diets for prevention of hearing loss (Rosen, Olin & Rosen 1970:242-7).

Secondary prevention-as an-intervention is implemented as a prevention of ototoxicity once a patient who develops MDR-TB is initiated on MDR-TB treatment and his system (client system) has reacted to a stressor (MDR-TB treatment). While primary prevention refers to inhibiting development of hearing loss, secondary prevention, also known as screening, refers to measures that detect the disease before it is symptomatic and attempt to reduce the resultant hearing loss (disability and restore functionality).
Secondary prevention entails early detection of ototoxicity by detecting the earliest signs of hearing impairment and effective management to stop further deterioration through treatment and clinical interventions.

According to Neuman’s System model, the focus of intervention is for the client system to attain reestablishment (reconstitution) through use of internal and external resources. Re-stabilisation prevents further damage to the basic structure of the client system, and strengthens the internal lines of resistance (against hearing loss) and/or removing the stressor (offending MDR-TB treatment) (Freese & Lawson 2010:243). Management of early hearing loss involves removing offending drug and risk factors as an example of secondary prevention. Monitoring hearing status during MDR-TB treatment is one of the interventions that assists in detecting hearing impairment early, hence enabling change in the offending drugs. Monitoring of hearing status during treatment provides an opportunity to identify and provide interventions such as use of assistive hearing devices in order to preserve hearing and communication.

Tertiary prevention-as-intervention occurs after the system has developed hearing loss (been treated through secondary prevention strategies) and offers support to the client and attempts to add energy to the system or reduce energy needed in order to facilitate reconstitution (Freese & Lawson 2010:243; Neuman 2002). Such interventions include use of hearing aids, and cochlear implants.

2.9 CONCEPTUAL FRAMEWORK

The overarching goal of clinical management of the MDR-TB patients is highest level of care and best treatment outcomes for the patients. The national goal of universal treatment and prevention coverage can be achieved through improving the processes of nursing care; medical care and treatment; monitoring and timely management of and prevention of adverse drug reactions. However, availability and compliance with the appropriate guidelines, policies, and protocols for the allied professionals, nurses and doctors enables standardised care.
Neuman Systems model provides a framework that outlines the stages of the medical process as a continuum:

- at diagnosis, the diagnosis of stressors is done as well as the dynamic interaction with the five variables (physiological, psychological, developmental, socio-cultural and spiritual);
- at enrolment, treatment goals are negotiated with the patient, taking into account of patient's and nurse’s perceptions of variance from wellness (Table 2.5);
- during care, continuous monitoring of wellness ensures timely interventions to promote attainment of the treatment goals.

The conceptual framework for the monitoring and prevention of hearing loss related to MDR-TB treatment adopted by the current study, is, in addition to NSM, enriched by the conceptual model on medication monitoring and adverse event proposed by Steinman et al (2011). According to the authors, the uncertainty in how adverse drug events will happen needs to be addressed, not only by the appropriateness of the initial prescription, but also on detecting and mitigating the adverse events once they have started to occur, requiring a framework of team-based approaches for patient management. The enhanced monitoring framework proposes integrating monitoring in clinical practice, use of health information technology, systems redesign including tracking laboratory tests and timely notification of physician, and use of risk assessment tools for enhanced patient participation (Steinman et al 2011).
Figure 2.10: Paradigm for primary, secondary and tertiary hearing preservation as intervention
2.10 REFLECTIONS FROM THE LITERATURE

The literature review provides a theoretical framework for this study. The study investigated the following two hypotheses. No published studies directly address the issue of MDR-TB treatment-related hearing loss and the impact of HIV on hearing impairment incidence in an HIV high prevalence setting. Although there is some evidence that HIV, or even anti-retroviral drugs, could cause hearing loss there is no consensus on the magnitude. The literature review suggests that many drugs may have synergistic effects that potentiate ototoxicity among patients receiving MDR-TB treatment.

2.11 CONCLUSION

Irreversible hearing loss related to treatment regimens in MDR-TB is common and various studies conducted in different continents reveal that unless there changes to the current regimen, the incidence of MDR-TB treatment related hearing loss will continue to increase. Various studies identify some risk factors but no uniform guidelines exist for prevention and monitoring of hearing loss in MDR-TB patients. The ASHA (1997) recommendations for establishment of ototoxicity monitoring programs are largely unimplemented in resource-limited settings as evidenced from the literature. The NSM provides a model nurses and doctors treating patients with MDR-TB to facilitate conservation of hearing as part of preservation of the wholeness of the individual so that his or her participation and place in the family, community and society can be preserved using prevention as an intervention (three levels). Neuman Systems model also provides a framework for development of the best practice guidelines for monitoring and prevention of hearing loss related to MDR-TB treatment in Swaziland.

The next chapter discusses the research design and methods to investigate the incidence of hearing loss among MDR-TB patients in Swaziland. It also provides a framework for the development of best practice guidelines for prevention and monitoring hearing impairment in the patients on treatment for MDR-TB.
CHAPTER 3
RESEARCH DESIGN AND METHODS

3.1 INTRODUCTION

“Every successful research project requires two things: a meaningful research question and an appropriate way to answer that question”

-(Morgan 2013:59)

The purpose of the current chapter is to provide the practical and relevant details of how the study’s intentions were realised. The study intentions (purpose and objectives), as stated on page 8, influenced and shaped the research design and methods. Whereas research design refers to the broader plan for management of the study, encompassing plans for data collection, utilisation, measurement and analysis, the research methods refers to data collection using the specific instruments and techniques to achieve the outcomes of the study (Curtis & Drennan 2013a:131, Mouton 2001:55-56). The details of data collection and analysis, study population and sample, sampling techniques, research instruments, and measures taken to ensure validity and reliability, and the ethical considerations are presented.

3.2 RESEARCH DESIGN

Research design refers to the structure of an enquiry. Research design plays a central role in ensuring that the study minimises the chance of drawing incorrect causal inferences from data. In addition, it ensures that the evidence collected enables the researcher to answer questions, and/ or to test theories, as unambiguously as possible. Research design also specifies direction for
procedures in the study design (Lincoln, Lynham & Guba 2011).

3.2.1. Quantitative research designs

According to (Krauss 2005:759), quantitative research on how we acquire knowledge (epistemology) is closely linked to the philosophy and study of reality (ontology) and the specific practices to acquire knowledge (methodology). Quantitative research designs aim to produce findings that are: objective, reliable, valid, and reproducible, and associated with an objectivist ontology, a positivist epistemology, and use of quantitative methods (Curtis & Drennan 2013a:133). In order to determine incidence of SNHL in MDR-TB patients, determine the risk factors and the time to hearing loss, the current study used analytical study design, which falls under the quantitative research design. Donmoyer (2008) refers to quantitative research as approaches to empirical inquiry that collect, analyse and display numerical data in numerical rather than narrative form.

The following factors influenced the choice of the quantitative design:

- In epidemiology and statistics, analytical observational studies draw inferences about the possible effect of exposure or treatment. The researcher observes what happens to people under exposure conditions that have been self-selected or have been determined by influences outside the control of the researcher. The researcher can choose what exposures to study, but does not influence them. Observational studies can either be descriptive studies that describe how things are; or analytical, in that they are set out to test hypotheses predicting an association between the two, an exposure and the independent variable (AFMC Primer on Population Health, [Sa]; Curtis & Drennan 2013c). The latter suited this study. The aim of the current study was to determine whether there was a relationship between hearing loss and duration on MDR-TB treatment, and whether HIV status of the patients influenced the incidence of hearing loss, and hence suited the study design as an observational analytical study.
- This study sought to understand the relationships, type of the relationships, and quantify the strength of the relationships, akin to correlational studies (Grove, Burns & Gray 2013:87). In order to establish such associations, a deductive approach was necessary (Curtis & Drennan 2013a:134). A literature search preceded the choice of theoretical concepts and theories most relevant to the causes of hearing loss in MDR-TB patients and the hypotheses developed. A quantitative design was the best option for the hypothetico-deductive approaches.

- Time was a variable in this study. In order to analyse time-to-event, an analytical survey approach using multiple timed data collection points was necessary. Repeated measurements of hearing sensitivity at timed intervals during follow up on the patients who initiated treatment within the prescribed period were necessary for the derivation of time to hearing loss from initiation of MDR-TB treatment. This type of longitudinal data collection, requiring collection of data from the same unit at two or more different points in time is one of the quantitative methods that can suggest the direction of cause and effect associations(Curtis & Drennan 2013d:178; Mathew & Farewell 2007:160; Todem 2007).

- The common characteristic of this study population was enrolment into MDR-TB treatment. The objectives of the study necessitated the gathering of data in form of numbers to enable evidence be presented in quantitative form on the study cohort. Cohort studies are typically quantitative and collect empirical data. While experiments can provide empirical data, in this study, observation was the source of the empirical data (Donmoyer 2008:2-3).

The differentiating characteristic between observational and experimental study designs is that, in the latter, the presence or absence of an intervention defines the groups. In an observational study, the investigator does not intervene but simply “observes” and assesses the strength of the relationship between an exposure and health outcome variable, that is, observe and measure the effects on disease rates of exposures of interest as they occur in the target population (Song & Chung
On the other hand, experimental designs have an intervention and control arm. To describe and measure the degree or association (or relationship) between the exposure and the health outcome of interest in analytical studies, investigators use the correlational statistics (Creswell 2012). Therefore, results of the current study were analysed to produce quantifiable, statistical data to shed more light on such cause-and-effect relationships between independent variables and SNHL related to MDR-TB treatment (Polit & Beck 2008:338).

3.2.2. Cohort study design

A cohort study design is one of the three observational analytical study designs, the other two being, cross-sectional studies and case control studies. However, the cohort studies and case-control studies can aid in evaluating associations between diseases and exposures. As in other cohort studies, the identification, and establishment of the exposure was done before the outcome, and hence the temporal framework was used to assess causality. Cohort studies yield the more reliable results in observational epidemiology when compared to case control studies. They are used in epidemiology to describe the distribution of disease incidence, and prevalence of disease or health outcomes, and the exposure-disease association (Hseih, Feng & Wang 2007). Cohort studies collect data through longitudinal research. Ruspini (2003:182-88) characterises longitudinal research in which: (1) data are collected for two or more distinct periods; (2) the respondents or cases analysed are the same, or at least comparable, from one period to the next; and (3) the analysis involves some comparison of data between or among periods. The longitudinal studies have the ability to collect data over a period, and hence monitor and record change in life events. By recording events over time, longitudinal studies are better placed to disentangle temporal and sequential occurrence and facilitate understanding of causal mechanisms and relations (Curtis & Drennan 2013d:178, Ruspini 2003:182-88).

In the study, the main variable that was uniquely different among the study respondents was HIV status. Hence, in the current study, the “exposed” cohort was constituted by the HIV positive group while the “unexposed” cohort was composed of the HIV negative group making it possible to compare the rate and risk hearing loss
between the HIV exposed and the HIV unexposed which was expressed by the proportions as cumulative incidence relative risk.

The cohort study design was relevant to the study as follows:

i) The cohort studies are able to measure the risk of disease in the exposed and the unexposed. While all the patients were exposed to second line MDR-TB drugs, the study measured risk of hearing loss in the HIV positive (exposed) and in the HIV negative (unexposed) in order to compare the risk ratio for SNHL. The temporal sequence between putative cause and outcome in prospective cohorts is usually clear; and

ii) Investigation of multiple outcomes that might arise after a single exposure is possible with cohort studies. The study had potential to document multiple outcomes such grade of hearing loss, change medications because of adverse drug reactions, other incidental complications associated with hearing loss.

The limitations of cohort studies include:

i) Sensitivity to selection bias due to drop outs and loss to follow-up of cases and controls whereby the validity of the study can seriously be affected by the differential losses to follow-up between those exposed and unexposed because of the bias in results that this causes;

ii) Over time, the exposure status of study respondents can change, for instance, the HIV status changes from negative to positive during the study;

iii) Confounding and bias and hence need to control for potential confounding at the design stage and in the analysis; and

iv) Prospective cohorts can be expensive and time consuming because of the long-time of follow-up and if the condition is rare, a large group of people have to be followed up.
3.2.3. Case-cohort design

The current study also adopted a nested case-cohort design where, instead of obtaining the exposure information on all the individuals constituting the denominators in the exposed and unexposed cohorts on on-going basis, the data was only continuously collected on a sample of the cohort save for the hearing sensitivity. This innovative design uses a sub sampling technique in survival data for estimating relative risk of disease in the cohort study without collecting data from the entire cohort.

Data from all respondents becoming cases (case sample) and a randomly selected sample of the cohort (referred to as; reference cohort, reference sample, sub cohort, or control- cohort or control group) are used in the study. The sub cohort may contain some cases (see Figure 3.2). The purpose of the reference sample is to estimate the relative size of the exposed and the unexposed components of the source population (the proportion of the exposed in the source population at the beginning of the cohort). The case-cohort allows efficient analysis where the population size is large to collect detailed data on all the respondents. Thence, the sub cohort is selected from the original sample at entry and data was analysed only on all the members of the sub cohort and all the cases. Case-cohort studies can be thought of as nested with the cohorts of the exposed and unexposed people, hence as nested from the source population (Kulathinal, Karvanen, Saarela & Kuulasmaa 2007; Pfeiffer et al 2005:982; Zhang, Schaubel & Kalbfleisch 2011:18).

Benefits of case-cohort design as applied to the study include:

i) the selected sub-cohort was able to serve as a comparison group for multiple endpoints (Kang & Cai 2009:887);

ii) Given that, at baseline, all cohort member information was collected rather than only that from sub cohort, analysis can be performed on the full cohort (Breslow, Lumley, Ballantyn, Chambless & Kulich 2009).
3.3  RESEARCH METHOD

A research method is a general framework guiding a research project and methods that are used to tackle different research questions. It involves the specific forms of data collection, analysis, and interpretation that researchers propose for their studies (Creswell 2014:17). Quantitative research methods were used to collect data and analyse the problem. Methodological standards adhered to in order to assure that the evidence provided is reproducible and reliable knowledge, included: sampling, measurement validity, internal validity and external validity.

3.3.1  Population

A population is a complete set of people with a specialised set of characteristics and a sample is a subset of the population. However, there are three closely linked types of population in a study, and these are target, study and sample population.

3.3.1.1. Target population

In the current study, the target population and hence the group to whom generalisation is intended were all the individuals on MDR-TB treatment in Swaziland. Any inferences from a sample only refer to this defined population from which the sample was properly selected (Banerjee & Chaudhury 2010:60-65).

The main characteristics of interest to the researcher that defined the target population in the current study was that all these patients were using aminoglycoside treatments for MDR-TB. Swaziland has a high MDR-TB/HIV capita burden setting, albeit the population of about 1.2 million inhabitants. The HIV prevalence is 31% among 18-49 year olds (Bicego et al 2013) and among MDR-TB patients, the HIV prevalence was about 75% of the patients. In 2010, the nationally representative drug resistance study found that MDR-TB is also prevalent with 7.7% of the new TB cases (NTC) patients and 33.9% of previously treated TB cases (PTC) having MDR-TB. HIV co-infection is independently associated with MDR-TB (Sanchez-Padilla et al., 2012:32-33). At the time of cohort enrolment (November 2012-December 2013),
a total population of 353 MDR-TB patients were initiated on treatment, constituting the target population.

3.3.1.2 Study population

The study population is the subset of the target population available for the study. In the current study, the accessible population was that of the individuals who enrolled into MDR-TB treatment at the MDR-TB treatment sites in Swaziland. Before selecting the health facilities relevant to be included in the study, health facilities offering MDR-TB treatment were visited to ascertain enrolment practices of MDR-TB patients, patient loads, and availability of audiology services for MDR-TB patients and willingness of the MDR-TB health facilities to participate in the study. One health facility has audiology services on site and the other sites receiving outreach services form the department of ENT. The findings showed that all the six MDR-TB treatment sites were clustered into three: TB hospital in Manzini was linked with Piggs Peak Hospital in the Hhohho region, Mankayane Hospital in Manzini region was linked to MSF comprehensive clinic in Manzini, and Nhlangano MDR-TB centre in Shiselweni linked to Matsajeni MDR-TB treatment site. The Lubombo region did not have an MDR-TB treatment site at the time of the study commencement, and hence its patients managed at the TB hospital.

The TB hospital in Manzini had a national representation with patients visiting from all the other regions and had onsite audiology services.

3.3.1.3 Sample population

Due to practical reasons and creditable data management, it was not possible to study all the patients from the six MDR-TB sites. The derivation of the sample population was done in two stages.

- Study sites: The TB hospital and Piggs Peak hospital were selected to participate in the study in a two stage multistage sampling method. The sampling frame was consisted of all patients in the master MDR-TB register maintained at the TB and Piggs Peak hospitals. All patients referred for
treatment at these two sites were included in the sampling frame (Curtis & Drennan 2013d:181).

- Study cohorts: patients enrolled into the study were categorised and followed based on HIV status. The HIV positive patients constituted in the HIV exposed cohort and the HIV negative patients constituted the unexposed cohort. All the patients received injectable MDR-TB TB medication during the study. The internal comparison group of the HIV negative patients was used because its characteristics were mostly similar to the exposed group. In addition, using an internal comparison group was the most feasible approach to testing the hypothesis evaluating incidence of hearing loss in the HIV positive and HIV negative MDR-TB patients and would make follow up more feasible (Purty 2011:176).

The primary objective of the analysis of the cohort data was to compare the occurrence of hearing loss in the HIV positive (exposed) and the HIV negative (unexposed), and the occurrence of the outcome measured using incidence rates and the relationship between the exposure and the outcome quantified using the relative difference between the rates.

### 3.3.1.2 Sampling

Sampling is the process of selecting a group of respondents for a study in such a way that the individuals represent the larger group from which they were selected (Curtis & Drennan 2013a:135-136). Probability sampling was considered ideal for this study because it increases the likelihood of obtaining samples that are representative of the population. In a random sample, each individual in the population of interest has an equal likelihood of selection. The rationale of sampling is selecting a representative subset of the population because it is impractical and very costly to survey the whole population (Curtis & Drennan 2013d:180). Hence, selection of the sample is done according to specific criteria.

In first stage of the multistage sampling, two health facilities were selected out of the six facilities providing MDR-TB treatment in Swaziland (see section 3.3.1.1.3). In the
second stage of the multistage sampling the sample from the sample was selected from the available lists. The listing of all patients enrolled at the two health facilities was done. All consecutive patients fulfilling the eligibility criteria, attending the participating MDR-TB sites between November 2012 and December 2013, and registered for MDR-TB treatment were approached for enrolment into the study. According to Polit and Beck (2008:338) eligibility criteria as is that which designates the specific attributes of the target population by which people are selected for the study. This study used the following criteria to select the study population at the study sites:

i) Patients who were diagnosed with MDR-TB (bacteriologically or clinically on empirical criteria) between November 2012 and December 2013 (13 months);
ii) Patients who had been notified of the intention to start them on MDR-TB treatment;
iii) Patients who were free of the outcome of interest (hearing loss) at the beginning of the study;
iv) Had not initiated on MDR-TB treatment or had initiated on treatment within a period of less than 72 hours;
v) Were males and females aged 15 -65 years;
vi) Clinically stable; and
vii) Consented to the study or, in case of minors, where the guardian has consented to enrolment in the study and assent from the minor obtained.

The following exclusion criteria applied for non-eligibility:

i) Patients with serious forms of drug resistance like extremely resistant drug resistant TB (XDR-TB) and totally drug resistant TB (TDR-TB) because these posed extremely serious infection control risk to the data collectors. These patients also have very high mortality rates and hence are unsuitable for long term follow up;
ii) Very sick patients and patients with pre-existing psychiatric conditions and dementia;
iii) Patients with pre-treatment clinical assessment of infective pathology in ear;
iv) Patients with pre-existing sensori-neural hearing loss (prevalent hearing loss).
The schematic in Figure 3.1 shows the steps in sampling included in the identification of the target population, identification of the study population, and the selection of the sample.

![Figure 3.1: Study Population Selection and Follow up](image)

In order to nest the case cohort study, two distinct samples comprised the study cohorts. (i) The random subsample of the original cohort (sub-cohort), selected independently of the definition of cases of hearing loss (respondents developing the event of interest) and, (ii) respondents outside the sub cohort developing hearing loss (respondents outside the sub cohort developing event of interest) during the follow up (Kulathinal et al 2007). The full cohort observation conducted from November 2012 to October 2014 identified respondents who developed hearing loss, that is, the cases. The cases emerged from the full cohort (that is from both in and out of the sub-cohort); while the controls were respondents in the sub-cohort, who
were not cases.

In this study, the following notation are used:

\[
\begin{align*}
N &= \text{the size of the sampling frame} \\
n &= \text{the size of the sample} \\
n_c &= \text{the size of the full cohort C} \\
n_{sc} &= \text{the size of the sub-cohort SC} \\
E &= \text{respondents developing hearing loss in the Event subset E} \\
d &= \text{the size of the set E respondents of hearing loss with the event E} \\
f &= n/N = \text{the sampling fraction}.
\end{align*}
\]

By definition, all of the respondents in E are in C. The union of (i) and (ii) is referred to as the case-cohort set (Kulathinal et al 2007). Detailed data was collected only for cases experiencing the event of interest in a cohort and for members of a randomly selected sub-cohort.

### 3.3.1.2.1 Sub Cohort Selection process

Use of simple random sampling techniques achieved the sub cohort sample from the full cohort. A simple random sample is a subset of a statistical population in which each member of the subset has an equal probability of being chosen and simple random sample is meant to be an unbiased representation reflecting characteristics of a group (Mathew & Farewell 2007:3). The calculated size of the sub cohort was obtained randomly using random numbers generated from an internet based software developed by Social Psychology Network (Social Pyschology Network, [Sa]). Source: [http://www.randomizer.org/form.htm Retrieved 14 Nov 2012](http://www.randomizer.org/form.htm). Random numbers were allocated to the respondents with the registration serial number matching the random number.

### 3.3.1.3 Ethical Issues related to sampling

Before and during the conduct of the study, ethical considerations were adhered to in order to protect the rights of the respondents. These included the respect for the human person, who has the right not to be injured or mistreated, right to give
informed, un coerced consent to participate in a particular piece of research, the right to privacy, and the right to confidentiality and/or anonymity, commonly summarised as the ethical principles of: autonomy, justice, beneficence and non-maleficence (Curtis & Drennan 2013f:77-85).

3.3.1.3.1 Research approval

When the proposal was fully developed, the researcher applied to the Department of Health Studies of the University of South Africa (UNISA) for ethical clearance (Annexure C1)(University of South Africa, 2015:71-74). Once approval was received from UNISA, the proposal was submitted to the Swaziland Ministry of Health (MOH) Scientific and Ethics committee for country level approval (Annexure C2) and a research reference number (Creswell 2014a:95). Approval was also obtained from the Ear Nose and Throat department of Mbabane National Referral hospital and the National Tuberculosis hospital (Annexures C3 and C4).

3.3.1.2.2 Respect for the human person

It is the duty of the research team not to expose the research respondents to significantly burdensome, unreasonable, known or predictable risks (Curtis & Drennan 2013f:81). As the duty of the researchers, the respondents were provided with the information on the purpose, procedures and rights, risks, discomforts and constraints of participation in the study. The research assistants were trained to provide adequate information to all prospective eligible patients. The information sheet and consent form provided information on the researcher, sponsoring institutions, purpose of the study, benefits of participating, notation of the risks to the respondent, assurance of withdrawal anytime and provided names of persons to contact if questions arose (see Annexure B1).

3.3.1.3.2 Voluntary informed consent

Informed and voluntary consent was sought from each of the study respondents (Annexure B1). Informed consent refers to the respondents being fully aware of the research they are involved in (Boynton, 2005:91). As autonomous beings, individuals
have the right to make decisions about themselves and their life. Participation in the study was voluntary. The study respondents were adequately and properly informed about the nature and the extent of the proposed participation in the study, including information that their participation, responses, results of the medical examination would be sued for purposes identified in the study only. Before enrolment into the study, the following steps were taken to ensure that their participation was not only informed, but also voluntary:

- The capacity to understand the information that was being provided, the implications of their participation and that they had the cognitive ability to exercise consent (Curtis & Drennan 2013f:79). This was also embedded in inclusion and exclusion criteria;
- The participants were free from coercion (Creswell 2014:97). The respondents were assured that they had the right to refuse participation and that would not affect care provided in any way. The study respondents were also made aware of their right to withdraw from the study at any time without any jeopardy to their medical care as well as the right not to respond to any question of their choice or partake any procedure.
- Patients who initially consented to the study but found not to be eligible after the preliminary evaluation were given the reasons for removal from the study.
- In order to include minors in the study, the minor secured the informed consent of the guardian in addition to assent.

3.3.1.3.3 Anonymity and Confidentiality

Research subjects need to know that they will not be identified through the research and that their information is going to be private and remain anonymous in a study in order to be protected from unwarranted risk of personal information becoming publically available(Boynton 2005:101). Respondents' responses were obtained in private and medical examinations such as audiometry and biophysical measurements were conducted in private. They were assured that their identity and personal information would not be divulged, except for medical care purposes and
only to their physicians, and that the data handling and storage processes would protect anonymity and confidentiality (Curtis & Drennan 2013f:81). Respondents were also assured that the researcher would not reveal potentially identifying information and materials when presenting the research findings. The research assistants were also trained to provide privacy and keeping research information confidential according to the established procedures.

3.3.1.3.4 Justice

The principle of justice can be viewed as having two components: i) fair treatment in research activity, including fairness to the least advantaged who should be benefited rather than forgotten, and ii) participation without exclusion based on vulnerability or vulnerable persons taken advantage of with enrolment into research which is not responsive to their health needs. All groups in the socio and economic structure were eligible to partake in this study. There were no grounds for discrimination and denial of enrolment because of belonging to one group of the other. The hard-to-reach category or had limited resources to participate in the follow visits to the hospital during the data collection period were supported with transport reimbursements. The age group 15-18 participated in the study based on assent provided by them in addition to the guardian’s consent. The risk of selection bias and error were dealt with through rigor in defining the target population, inclusion of all cases meeting the eligibility criteria, not omitting “hard to find or potential non-adherent” persons. The study assistants were provided with skills to increase acceptance rate and lower dropout rate, and the following measures were implemented to minimise loss to follow up and hence compromise the sample representativeness:

Respondents likely to be lost (planning to move or were non-committal) were provided with additional counselling to stay in touch;

- Information to allow future tracking was collected including subject’s contact information such as physical addresses and telephone numbers. During follow-up, periodic contact was made by telephone;
- Transport allowance provided for those having challenges to return for appointments ensured that respondents returned for appointments.

3.3.1.3.5 Beneficence and non-maleficence

Article 5 of the World Medical Association declaration of Helsinki of 1964 (as amended in Fortaleza, Brazil in 2013) declares that medical progress is based on research that may involve human subjects. Similarly, however, article 7 articulates the need for medical research to be subjected to ethical standards that promote and ensure respect for all human subjects and protect their health. In the same vein, risk must be minimised, monitored and documented according to article 17 (World Medical Association, 1964, 1975, 1983, 1989, 1996, 2000, 2002, 2004, 2008, 2013). The two principles of beneficence (do good) and non-maleficence (do no harm) require that health practice and research fulfil the duty of doing good, preventing harm, as well being vigilant. While the current study did not pose significant discomfort, risk and burden on the respondents, it is important that scientific studies benefit the patient directly and/or society as a whole (WMA, 2013).

In summary, the researcher took the necessary steps to address the ethical principles in general but also during sampling in the following manner:

- Ensuring that the selected research question was legitimate, an hence it was not a waste of time and that the design would answer the research question;
- Self-identification of the researcher, and assurance to the effect that the researcher was not responsible for the clinical care of the patients and hence minimising the fear that refusal to participate in the study would adversely affect the patients care;
- Providing clear information and guidance as to the purpose of the study and information on the potential inconvenience and risks;
- Adequately addressing anonymity and confidentiality of the respondents;
- Ensuring that there was no discrimination in the selecting of study respondents.
3.3.1.4 Sample

3.3.1.4.1 Sample Size considerations

According to (Faber & Fonseca 2014:27-9), the purpose of estimating the appropriate sample size is to produce studies capable of detecting clinically relevant differences, protection of human subjects and good stewardship of fiscal, physical and staff resources. The reasons for performing sample size calculations in the planning phase of a study were:

i) to assure confidence in the study results and conclusions;
ii) ensure that the study is adequately powered because inadequately-powered studies are waste resources and have ethical considerations to the study respondents, given that they may not produce clinically meaningful results;
iii) achieve adequate power to enable the testing hypothesis testing;
iv) facilitate development of sound evidence for the best practice guidelines given that inadequately powered may produce results that are unable to alter clinical practice.

According to Grove et al (2013:704) power is the probability that a statistical test will detect a significant difference or relationship that exists, and in so doing, the capacity to correctly reject a null hypothesis. A number of factors affect power of the study: $\alpha$, $\beta$, effect size, variability (baseline incidence), n

- The level of significance ($\alpha$) is the probability of a Type I error. The researcher is willing to accept a 5% level of risk of declaring the null hypothesis false when it is actually true.
- The effect size ($\beta$) is the deviation from the null that the researcher wishes to be able to detect. The researcher powered the study so as to be able to detect a relative risk of two or greater.
- Design effect (DEFFs) is the effect of a non-simple random sampling that needs to be accounted for by the researcher because of the risk of misestimating the effects and increasing the probability of type 1 errors. Without correcting for design effects, standard errors could be
underestimated, leading to significant tests that are inappropriately sensitive (Osborne 2013:74).

Two sample sizes were calculated:

a) the sample size of the study cohort, Lwanga and Lemeshow (1991:18-19);
b) the sample size for the case cohort, Kubota and Wakana (2011:279).

They provided minimal sample sizes of 81 for the full cohort and 20 for the sub cohort.

3.3.1.4.2 Assumptions of sample size calculation for the full cohort

Because of lack of studies with incidence rates in Africa, the current study assumed incidence MDR-TB related hearing loss of 20% among the HIV negative patients based on the prevalence reported in the literature for studies in the United Kingdom and India (Bisht & Bist, 2011:255-9; Bitner-Glindzicz & Rahman 2007:784-5; Blakley, Hochman, Wellman, Gooi & Hussain 2008-3; Bloss et al 2010:275; Duggal & Sarkar 2007:1-7; Sturdy et al 2011:1815). The study assumed the incidence for MDR-TB treatment induced hearing loss was double (40%) among HIV positive patients (lack of studies of MDR-TB treatment related hearing loss in HIV positive patients).

According to Lwanga and Lemeshow (1991:18-19) hypothesis testing for two incidence rates in cohort studies can be derived from the sample size formula:

\[
n = \left\{ \frac{Z_{1-\alpha/2} \sqrt{[(1+k)f(\lambda)]} + Z_{1-\beta} \sqrt{[k(\lambda_1) + f(\lambda_2)]}}{/(\lambda_1 - \lambda_2)^2} \right\}^2 \text{ Equation 1}
\]

Where k is a ratio of the sample size for the second group of respondents (HIV positive) and the first group (HIV negative).

Hence, assuming the null hypothesis of no difference between the incidence between the exposed (HIV positive) and the unexposed (HIV negative), the following information was assumed:
Test value in the difference in incidence... .........................................................0
Anticipated incidence rates (20% among HIV negative and 40% among HIV positive)...20%
Level of significance .................................................................5%
Power of the test.................................................................80%
Alternative hypothesis.............................................................$\lambda_1 \neq \lambda_2$
Duration of study..........8 months follow up during the injectable phase of treatment
The minimum sample size per group (HIV positive and HIV negative) was 28
according to the tables (Lwanga & Lemeshow, 1991:80) assuming sample size ratio
of 1.

However, given the high HIV rates in the target population are 75% HIV positive to
25% HIV negative, the number per group was adjusted to reflect a ratio of HIV
prevalence in MDR-TB patients which stands at 3:1 (HIV+: HIV- = 3:1). The adjusted
minimum sample size for the study was 112. Although the rule of thumb for lost to
follow up not to exceed 20%, we provided for 30% attrition rate in the study because
of high mortality among MDR-TB patients and hence the adjusted the sample size
was 149 respondents (Song & Chung 2010).

3.3.1.4.3 Assumptions of sample size calculation for the sub cohort

In order to determine the adequacy of sample size for case cohort study, the
formula proposed by Kubota and Wakana which derives the sample size calculation
for case cohort studies from formula of the sample size of the cohort study was used
(Kubota & Wakana 2011:279). Kubota and Wakana (2011:279) proposed a sample
size formula for the case-cohort study for a binary exposure variable with the
exposed respondents ($N_1$) and total respondents ($N$) in the entire cohort for the case-
cohort study with the same $\alpha$, $\beta$, $K$, $RR$ and $P_0$ as full cohort.

$$N = N_1f_{ult}(1 + K)(1 + \frac{1}{m}) = N_f_{ult}(1 + \frac{1}{m})$$  \hspace{1cm} (1)
N is full cohort (112) and \( N_{\text{full}} \) number exposed (84), \( m \) is the ratio of the number of respondents in the sub cohort to the expected number of cases (0.5) in the entire cohort and K ratio of unexposed to exposed (0.5). The value of \( m \) was assigned by the researcher as 0.5 and the required size of the sub cohort, \( n \), is

\[
n = m P_D N_1 (RR + K) = m P_D N
\]

Assuming \( m \) as 0.5; \( P_D \) as 20% (Duggal, 2007) and \( N \) as 112

The calculated Sub cohort sample size \( n=20 \)

3.3.1.4.4 Description of final sample

A study sample is chosen from the study population. In the current study, the study sample was the group of patients attending two of the six MDR-TB treatment sites from November 2012 to December 2013. One hundred and ninety-four (194) respondents were evaluated for eligibility and of these 173 fulfilled the inclusion criteria and were enrolled into the study. Figure 3-3 summarises time of the baseline assessment in relation to commencement of MDR-TB treatment. About 84% had pre-treatment assessments and 9% assessment within 72 hours and 7.5% within 4-7 days of initiation on treatment. A small proportion had the pre-treatment assessment after the recommended 72 hours cut-off but hearing status was still within normal range at the time of the baseline audiology.

![Figure 3.2: Pre-treatment baseline assessment (number of days of treatment at baseline audiological evaluation)](chart.png)

<table>
<thead>
<tr>
<th>Duration on DR-TB treatment regimen at audiological evaluation</th>
<th>Number of Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>≤72 hours</td>
</tr>
<tr>
<td>Count</td>
<td>145</td>
</tr>
<tr>
<td>Percent</td>
<td>83.8%</td>
</tr>
</tbody>
</table>
3.3.2 Data Collection

3.3.2.1 Data collection approach and method

The WHO defines data collection as an ongoing systematic collection, analysis, and interpretation of health data necessary for designing, implementing, and evaluation of public health programs (World Health Organization, [Sa]-a). On the other hand,
Grove et al (2013:690) define data collection as the systematic gathering of information relevant to the research purpose or specific objective, question of hypothesis. In the current study, quantitative methods were used to collect numerical data or data that could be converted into numbers using a longitudinal survey method. The data required was collected on a number of variables that would be used to describe the incidence patterns, and predict the time-to-hearing loss among the cases.

Advantages of longitudinal surveys:

- As an observational study with the aim of understanding cause-effect relationships, determination of sequencing and timing can be done readily, using this method. Prospective data collection also reduces recall bias and allows examination of expected and unexpected outcomes (Curtis & Drennan 2013d:178).
- Quantitative data collection methods produce results that are easy to summarise, compare and generalise.
- The longitudinal survey method enables the determination of incidence, risk ratio and time-to-event analysis (see section 3.2.2) (Curtis & Drennan 2013b:19). According to Singer and Willet (2003), in the framework for investigating event occurrence, identify three methodological features:
  - a well-defined “event” whose occurrence is being explored;
  - a clearly defined “beginning of time”; and
  - a substantially meaningful metric for clocking time. In line with the above criteria; the event being investigated was hearing loss; the beginning time was assessed for each individual MDR-TB patient at the entry of the cohort (recruited between November 2012-December 2013); and the metric for clocking time was the monthly follow up during the intensive phase of treatment until exit of the cohort.

Based on the above considerations for cohort studies, collection of socio-demographic information and risk factors, HIV status, determinants and risk factors
in the previous medical, family and occupational history as well as biophysical characteristics was conducted. The method also enabled the follow up of self-selected cohorts to the HIV positive (exposed) or HIV negative (unexposed). The metric for clocking time was the monthly follow up during the intensive phase of treatment until exit of the cohort. The longitudinal survey also enabled recording of repeated measurements of hearing sensitivity and to collect and record event occurrence up to eight months (injectable phase of treatment) and determine occurrence of hearing loss as the outcome of interest (hearing loss).

The key disadvantage of longitudinal studies is that they are expensive and possibility of missing data due to loss to follow up is high. These challenges have the potential of cause threats to internal validity. Section 3.4 explains the measures that were used to minimise any threat to internal and external validity.

3.3.2.2 Development and testing of Face-to-Face Interviewer-administered questionnaire

3.3.2.2.1 Defining Face-to-Face Interviewer-administered questionnaire

According to the SAGE Dictionary of Social Research Methods, a questionnaire is, “A set of carefully designed questions given in exactly the same form to a group of people in order to collect data about some topic(s) in which the researcher is interested” (McLean 2006). Face-to-face Interviewer-administered standardised questionnaire were administered by the researcher/ research assistant in the hospital setting in a private space to consenting patients.

The Wikipedia, however, includes other prompts in the definition - “a questionnaire is a research instrument consisting of a series of questions and other prompts for the purpose of gathering information from respondents” (Wikidepia., ibid-c). While some researchers reserve this term exclusively for self-administered or postal questionnaires, others would include interview schedules (personally administered face-to-face) under the general rubric of ‘questionnaire’. The researcher used the latter definition (Curtis & Drennan 2013d:183).
Advantages of face-to-face interviewer administered questionnaires include:

- The questionnaire format and sequence is the same for all although pre-determined, no directive prompts maybe used.
- The interviewer is able to build rapport and confidence with the respondent
- Observation of body language is possible and enable clarification where the respondent does not seem to understand
- Interviewer structured interviews/ questionnaires are a useful tool to obtain information from disabled respondents or those who are unable to read.

The disadvantages of the face-to-face interviewer-structured interviews include:

- Could be time consuming and may involve travel of either the respondent or the research assistant.
- Could be more costly than questionnaires sent through the post or administrated online

3.3.2.2.2 Developing the Face-to-Face Interviewer-administered questionnaire

In the formulation of the questionnaire, the researcher complied with the following best practices for developing questionnaires:

- The questions were arranged in a set format, measuring separate variables and some aggregated into either a scale or index;
- Open-ended questions were used for the respondent to formulate their own answer while the closed-ended questions were used to enable respondents to pick an answer from a given number of options, and having standardised answers that make it simple to compile data;
- In order to address a limitation with questionnaires where the respondents must be able to read the questions to respond appropriately to the limitation, conducting face-to-face questionnaire administration was done as a mitigation measure. In addition, translation of the questionnaire into SiSwati made it easier for some patients who can read the local language.
3.3.2.2.3 Pilot Study

Grove, Burns and Gray (2013:523) define a pilot study as a smaller version of a proposed study conducted to develop or refine methodology such as treatment, instrument or data collection. Hence a pilot study was conducted with a subset of the respondents (Sproull 2004). The purpose of the pilot study was to replicate the large study, as a trial, to test the consent forms, data collection forms and questionnaires and recruitment process, and to identify if there was need to alter the big study based on the pilot study (Curtis & Drennan 2013d:185).

According to Curtis and Drennan (2013d: 185), the following rationale is provided for pilot studies:

- development of rigorous data collection tool and evaluation of workability;
- development and pre-testing questionnaires and other instruments;
- to establish validity, reliability, practical utility and issues affecting respondents' response;
- identification of logistical problems that could mar data collection.
- evaluating data analysis techniques;
- establishing communication networks with key stakeholders, and
- determination of resources are needed for the main study.

Thirty respondents for the pilot study were recruited in the same way as the proposed study and respondents completed the same informed consent and instrumentation procedures. The primary feasibility outcomes of the pilot were:

- establish the recruitment rates of the study patients,
- establish the informed consent rates,
- determine follow-up return rates for the first three months of follow-up period, formulate a questionnaire that is clear and comprehensible, and
- establish adequacy of data handling system.
The secondary feasibility outcomes were optimised human resources for the study and establishment of an external quality assurance.

**Summary of the results of the pilot**

Assessment of the methodological quality, validity, reliability of the measurement instruments and data management was conducted during the pilot. The questionnaires were easy to complete consistently, and there was evidence of difficult questions that needed to be modified. The calibration of the audiometers was immediately verified and all audiometers, tympanometers and otoscopes were validated and the produced reproducible measurements, passing internal quality and external quality assessments. HIV exposure was assessed by a documented result of an HIV test obtained according to the national algorithm.

Training to support research and data entry assistants to assure consistency across the data collectors and reliability of data collected and entered was over a three-day period. On-going support provided post training ensured that the research assistants became proficient within two weeks. The test-retest by the same and/or different data collectors was consistent. A change to patient flow was necessary after the analysis of pilot data. The systems for managing longitudinal files were available but strengthened. A “cross-sectional” file was also maintained where the longitudinal data had been cleaned.

### 3.3.2.3 *Types of data collection instruments*

Questionnaires and audiograms were used for data collection in this study.

#### 3.3.2.3.1 Questionnaire

The structured questionnaire was divided into the following sections:

1) The first section comprised the biographic data, medical information and lifestyle characteristics:
the socio-demographic and patient characteristics data including patient's age, gender, and region of origin, educational achievement, employment, profession and job types as well as marital status, race and religious affiliations.

- relevant medical information including concurrent medical conditions such as hypertension, diabetes mellitus, HIV/AIDS, cancer as well as any medical treatments for these conditions as applicable.

- data on life style characteristics such as history and quantity of smoking, drinking alcohol, exercise, and daily fluid and water intake.

b) The second component of the questionnaire captured responses from self-assessment of the following variables:

- hearing acuity and history of hearing problems in the family and by the patient, as well as physical assessments like external and middle ear examinations,

- audiometric screening hearing status,

- clinical measurements such as blood pressure, temperature, weight, and height for calculation of body mass index and hydration status. The physiological assessment was used to determine the participant's health status prior to and during the study.

- results of laboratory tests including HIV sero-status, blood chemistry tests including random blood glucose, haemoglobin A1c, serum urea, creatinine, electrolytes, and liver function tests.

3.3.2.3.1 Collection of audiometry results using Audiograms

Hearing sensitivity results from audiometry were recorded in both the graphic and tabular audiograms. The audiogram is a picture of how a person hears at a given place and time under given conditions. Graphic representation is probably the most common form for reporting pure tone, audiometric results. The American Speech-Language-Hearing Association recommends a set of symbols to allow for efficient
and uniform transfer of information using audiometric symbols (American Speech-Language-Hearing Association 1990, 2002-129; British Society of Audiology-2011:22-23). Audiometric symbols are used to record the results of conventional pure tone threshold audiometry and the audiogram to describe the hearing of a person for the various frequencies tested (Figure 3.5 and Figure 3.6). An audiogram maybe used to calculate the amount of hearing handicap a person has. In addition, it may be used as a tool to determine the cause of a person’s hearing loss (Frank 2007).

![Hearing loss grading](image1)

**Figure 3.4 Hearing loss grading;**

Audiograms are graphic presentations shown as a grid with frequency, in Hertz (Hz), represented logarithmically on the abscissa and hearing level (HL), in decibels (dB), represented nearly on the ordinate.

### 3.3.2.4 Data collection process

#### 3.3.2.4.1 Questionnaire administration

Two locations were selected for administration of the face-to-face Interviewer-administered questionnaires; one in each of the study sites near the audiology room. For each of the consenting respondents, the research assistant or audiologist filled in the general questionnaires and audiologist administered questionnaire filled in by the audiologist in a private setting within the hospital. On average completion of both
questionnaires lasted about 20-25 minutes. The completed questionnaires were then kept in individual respondents longitudinal files, secured together with the consent form. Results of the audiological evaluation and audiometric tests were also added to the respondents which were then stored away in a lockable cupboard accessed only by the researcher and research assistants. At the end of follow up of each patient, files were checked for completeness before being transported to the researcher’s office data entry into a password-protected computer. In the researcher’s office, files were stored under lock and key, and accessible only to the researcher.

3.3.2.4.2 Ear, Hearing health and sensitivity screening

Case history was obtained including history of hearing loss, unilateral hearing loss, sudden or rapid progression of hearing loss, unilateral tinnitus, acute or chronic dizziness, recent drainage from the ear(s), and/or pain or discomfort in the ear(s), recreational noise exposure, family history and exposure to ototoxic drugs was the first hearing health screening activity.

3.3.2.4.3 Ear examination

Ears (auricle, ear canal, and eardrum) were examined visually using an otoscope (see Figure 3.7):

- to identify abnormalities requiring alternate audiometric procedures or could influence the results obtained; and
- to identify conditions requiring medical referral. Patients with cerumen impaction were assisted through cerumen management (ASHA 1997).
3.3.2.4.4 Tympanometry/Acoustic immittance measurement

Acoustic impedance is a collective term that refers to measurements of eardrum compliance. There are two types of acoustic impedance measures: tympanometry and acoustic reflex testing. In the current study, the function of the middle ear was tested using tympanometry. Tympanometry tests the mobility of the eardrum, from which information regarding the function of the middle ear system can be inferred. A picture of a tympanometer is shown in Figure 3.7.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{tympanometer.png}
\caption{Figure 3.7: Picture of a Tympanometer}
\end{figure}

\textit{a. Diagnostic audiometry}

An audiometer (see Figure 3.8) was used to obtain air conduction thresholds on all examinees. The audiometry protocol tested the participant’s hearing threshold (in decibels, dB) at six frequencies in a soundproof room (see Figure 3.9). Baseline measurements were taken pre-treatment of within 72 hours of treatment. Follow up audiometry was done either two weekly or monthly.
A patient was instructed to respond in a specified manner (conventional audiometric techniques) each time auditory stimuli are perceived. Pure tone signals are then presented to each ear through earphones and the intensity of the signals is varied until the level is identified at which the person is just able to hear the sound. After the baseline measurements, the hearing status is measured periodically during follow up at specified periods: month 1, 2... month N... Hearing loss was graded according to the WHO grading: 0-25 dB Normal hearing; 26-40 dB Slight/Mild hearing loss; 41-60
dB Moderate hearing loss; 61-80dB severe hearing loss; and 81+ dB Profound hearing loss.

**Instructions to respondents**

Instructions were as follows:

> “I am going to test your hearing by measuring the quietest sounds that you can hear. As soon as you hear a sound (tone), press the button (or raise your finger). Keep it pressed (or raised) for as long as you hear the sound (tone), no matter which ear you hear it in. Release the button (or lower your finger) as soon as you think you no longer hear the sound (tone). Whatever the sound and no matter how faint the sound, press the button (or raise your finger) as soon as you think you hear it, and release it (or lower it) as soon as you think it stops.”

**False Responses**: false responses may be of two types: (a) false positive, a response when no tone is present; or (b) false negative, no response to a tone that the audiologist believes to be audible to the participant. Either type complicates the measurement procedure. Reinstruction was done to reduce the occurrence rate of either type.

### 3.3.2.4.5 Audiometry results recording

Pre-treatment diagnostic audiology was conducted to document baseline pure tone average (PTA) for conventional frequencies, \( \text{PTA}_{250\text{Hz}-4000\text{Hz}} \) as well as high frequency averages \( \text{PTA}_{4000\text{Hz}-8000\text{kHz}} \) using a conventional audiometer. Recording was done in a graph that shows the audible threshold for the standardised frequencies.
call and audiogram. Audiograms were used to record hearing status of each of the two ears for each patient at baseline (pre-treatment or within 72 hours after start of MDR-TB treatment) and during the scheduled follow up hearing evaluation. For each ear tested, results of the hearing threshold (in decibels) at frequencies of: 250 hertz; 500 hertz; 1 000 hertz; 2 000 hertz; 3 000 hertz; 4 000 hertz; 8 000 hertz were recorded. Standard symbols were used for recording hearing sensitivity, which was shown as a grid with frequency, in Hertz (Hz), represented logarithmically on the abscissa, and hearing level (HL), in decibels (dB), represented nearly on the ordinate (ASHA, 1990: 32-35).

3.3.2.4.6 Hearing loss case definition

In order to define a case of hearing loss and to grade the extent of the hearing loss, the pure tone averages at baseline were compared with follow up hearing sensitivity pure tone averages. Significant threshold shifts during the follow up were used to define a case of SNHL. According to WHO, hearing sensitivity is graded as follows: 0-25 dB Normal hearing; 26-40 dB Mild hearing loss; 41-60 dB Moderate hearing loss; 61-80 dB severe hearing loss; 81+ dB Profound hearing loss. However, based on threshold shift criteria, a case of hearing loss was confirmed when baseline measurements were compared with follow up measurements and ototoxicity defined as any of: i) a 20 dB decrease at any one frequency, ii) a 10 dB decrease at any two adjacent frequencies (American Speech-Language-Hearing Association 1994:11-19).

3.3.2.4.7 Results confirmation

A person was considered at risk of incident hearing loss during the follow-up period if the Pure-Tone average (PTA) 0.5–4 kHz in the better ear was ≥26 dB HL). The incidence of any level of hearing loss was defined as a PTA0.5–4 kHz ≥26 dB HL, mild hearing loss as PTA 0.5–4 kHz ≥26 to 40 dB HL, and moderate hearing loss as PTA0.5–4 kHz ≥41 to 60 dB. Respondents with hearing loss at baseline were considered at risk of progression of hearing impairment if the PTA0.5–4 kHz in the better ear was ≥26 dB HL. Progression of hearing impairment was defined as a PTA0.5–4 kHz at follow-up that was >20 dB HL than at baseline at a single frequency or 10 dB in each of the
adjacent frequencies. Low-frequency hearing loss was defined as a PTA 0.5, 1, 2 kHz ≥26 dB HL in the better of the two ears. Conventional frequency hearing loss PTA 0.25, 0.5 1, 2, 4 kHz ≥26 dB HL. High-frequency hearing loss was defined as a PTA 4, 8-kHz≥26 dB HL in the better of the two ears. The audiometric ISO values calculated as an average of 250, 500, 1000, 2000 and 4000 Hz in the better ear (Mitchell et al 2011).

3.3.2.4.8 Interventions post audiometry for patients with early hearing loss

A referral for hearing amplification was made if no response is observed at any frequency in either ear. The referral involved counselling regarding hearing impairment and recommendations for further management.

Figure 3.11: Respondents’ recruitment, data collection, and follow-up process

All data was checked for completeness and doubly entered into ©Microsoft Office Access 2013 database (Microsoft Corporation 2013 (15.0.4420.1017) by trained data capturers. Errors and disparities between the databases were rectified before that
was exported to Microsoft® Excel® (version 14.4.7), SPSS version 17 and STATA/MP (StataCorp LP, Texas, USA) version 12 where data cleaning was done by the principal investigator before statistical data analysis commenced.

### 3.3.2.5 Ethical considerations related to data collection

The principles of autonomy, beneficence, non-maleficence, and justice were explained in section 3.3.1.3. Data collection is a critical point in the study process and has some ethical considerations that needed to be taken into account:

- Obtaining permission from the institution where the data were to be collected. Management of the institutions was briefed about the study and formal approval was granted prior to the commencement of the study (Annexure C).
- Obtaining permission for data collection from the clinical staff and from the patients. The respondents were provided with information on the purpose, procedures and rights and other information as part of the ethical considerations of autonomy, justice, beneficence, and non-maleficence (see details in section 3.3.1.3).
- Guaranteeing appropriate behaviour from the researchers during the data collection period.
- In line with the principle non-maleficence, the potential risks and discomforts/constraints were explained to the respondents. While no significant psychological or social risks were anticipated to occur, other forms of inconvenience that were likely. Respondents were informed of potential discomfort, embarrassment, mild fatigue, anxiety, or frustration while completing the items in the questionnaires or undergoing procedures, as well as their right to skip any questions that they did not wish to answer without having to explain their response for non-response.
- The respondents were informed of their right if any unforeseen risks are noted, to notify the principal investigator and/or Swaziland Scientific and ethics committee.
• Benefits: For some respondents, completing the questionnaires and participating in the research could have provided an opportunity for them to think about their overall well-being in a more concentrated structured manner. Some would potentially benefit from close monitoring of their hearing status because of the possibility of earlier detection of ototoxicity and action to preserve hearing but, for others, there may not have been direct benefits from participating in this study.

3.3.2.5.1 Involvement of Audiologist, Statistician, Clinicians, Nurses and the Researcher

The researcher was responsible for the overall supervision and coordination; collection of data, safety and confidentiality of all data collected, management of the data derived from ototoxicity monitoring training all personnel involved in data collection, data entry and data analysis. The audiologist participated in the designing and implementing the audiology procedures and in the design and implementation of ototoxicity monitoring protocol. She administered the monitoring test(s), interpreted audiometry results and participated in the follow-up management when clinically significant, especially when handicapping degrees of hearing loss were detected. The Audiologist received technical supervision from the Otorhinolaryngologist at the national referral hospital and from the researcher who is also a physician. Quality assurance was done in collaboration with the audiology department at the University of Pretoria. The statistician was involved in the calculation of sample size, development of the data analysis plan and detailed data analysis. The clinical team of doctors and nurses were involved in referring patients for the study, following recommendations by the audiologist to prevent aggravation of hearing loss, and referring cases of hearing loss to the audiologist for rehabilitation.

3.3.3 Data Analysis

Data analysis is the process of developing answers to questions through the examination and interpretation of data. The basic steps in the analytic process consist of identifying issues, determining the availability of suitable data, deciding on which methods are appropriate for answering the questions of interest, applying the
methods and evaluating, summarizing and communicating the results. In this section, the study hypothesis and objectives are recapped because they influence the analysis plan. The study design allows for three major analytic approaches, namely: analysis as a cohort study, analysis as a case-cohort study and analysis as a nested case control. Data analysis was done per objective and the main analysis methods used were:

- Descriptive analysis;
- Explanatory analysis of longitudinal data;
- Predictive analysis of survival data;
- Hypothesis testing.

**a. Descriptive analysis**

The first objective was analysed using descriptive data analysis to address each sub problem statistically using measures of central tendency (mean, standard deviation and median) calculated from the continuous data. The following rates and proportions were also calculated:

i) Incidence rate presented as the number of new cases of hearing loss per 1,000 person-days observation;

ii) Incidence odds presented as the ratio of number of people who developed hearing loss (outcome) to the number of people who do not experience the event;

iii) Risk ratio or Relative risk presented as ratio of the incidence rate of hearing loss among those who are HIV positive and HIV negative respondents (Mathew & Farewell 2007:263-281);

iv) Cumulative incidence (incidence proportion) was presented as an estimate of the risk that a person will develop hearing loss during a specified period of time and calculated as the number of new cases of hearing loss that develop in a population at risk during the follow-up time interval. Cumulative incidence allowed the researcher to predict risk of a hearing impairment over 8 months of MDR-TB treatment for patients.
**Explanatory Analysis**

Explanatory analysis was conducted for the second and third objective. Analytic tests were applied and statistical methods were used to establish the risk factors and determinants for hearing loss among the cases. Risk factors are variables with a lower likelihood of a positive outcome and higher likelihood of undesirable outcomes; while determinants are any variable that affect the frequency with which disease occurs in the community. Measures of association were used to identify relationships between the dependent variable and one or more variables and statistics used to measure the relationship when it exists. The Spearman rank-order correlation coefficient (Spearman rho) was used to measure the strength of a monotonic (in a constant direction) association between level hearing impairment and risk factors measured in the ranked scale. The $2 \times 2$ (‘two-by-two’) table used to analyse data with two levels of exposure (HIV exposed, not exposed), and the chi-square test for association (contingency) used to measure for association between two categorical variables and the significance of the association (Haug 2007). Logistic regression modelling was applied to remove the confounding effect in an estimate of the association and to identify significant factors (Mathews & Farewell 2007:263; Bednarczyk & McNutt, 2007). The results were reported by relative risk with 95% confidence intervals.

The endpoint of interest was hearing loss at the end of the time of follow up logistic regression and the proportional hazards regression used to study the effect of HIV and ARV on hearing status among patients receiving MDR-TB treatment. The covariates considered as indicator variables $X_1 = 1$; if the patient has a positive HIV status and 0 otherwise, and two indicators for level of immune suppression, $X_2 = 1$ for CD4 levels less than 200, $X_2 = 0$ otherwise, and $X_3 = 1$ for CD4 levels above 500, $X_3 = 0$ otherwise. The lowest CD4 level was the reference group. We also used the covariates indicators related to ARV treatment. We considered the indicator variables $X_4 = 1$; if the patient has a positive HIV status and on ARV and 0 otherwise (Larsen 2005:1049-55; Kulathinal et al 2007; Mathews & Farewell 2007:152-159; Grimes 2002a: 248-52).
b. Predictive analysis and Survival data analysis

Objective 4 was achieved by analysis of time- to- event and to prediction probability of hearing loss after survival after time t. Through the calculation of the median and the interquartile range, the researcher was able to assess the optimal frequency for audiolologic testing for monitoring of patients on MDR-TB treatment in Swaziland. Proportional hazards regression, using the Cox regression, was used to model the incidence or hazard rate with adjustment to the standard partial likelihood. The hazard function is the probability that if a person survives to t, they will experience the event in the next instant. Data from the study was used to analyse earliest time for the event in order to recommend how frequently conducting audiology testing should be done to prevent the hazard of hearing impairment (Onland-Moret et al 2007:350; Kalbfleisch & Lawless 1988:149; Barlow 1999:1165; Mathews & Farewell 2007:263).

c. Hypothesis testing

*Study hypothesis 1:*

The incidence ratio of sensorineural hearing loss during the intensive phase of MDR-TB treatment increases proportionally with the duration of treatment.

If incidence ratio of sensorineural hearing loss is stated as \( a/b \) and the duration of treatment is stated as \( d \)

The study hypothesis can be stated as \( a/b \propto d \)

*Null hypothesis 1:*

“There is no relationship between the incidence of hearing loss among MDR-TB patients on MDR-TB treatment and the length of treatment during the intensive phase of MDR-TB treatment”

Likewise, the null hypothesis can be stated as \( a/b \ not \propto d \)
Study hypothesis 2

MDR-TB patients living with HIV infection have a higher incidence ratio of sensorineural hearing loss than HIV negative MDR-TB patients during the intensive phase of MDR-TB treatment.

- If the Incidence ratio of SNHL in HIV positive MDR-TB patients = $\lambda_1$
- And If the Incidence ratio of SNHL in HIV negative MDR-TB patients = $\lambda_2$
- Then study hypothesis can be restated as $\lambda_1 > \lambda_2$

Null hypothesis 2:

“There is no difference in the incidence ratio of sensorineural hearing loss in MDR-TB patients living with HIV and MDR-TB patients who are HIV free during the intensive phase of MDR-TB treatment.

- If the Incidence ratio of SNHL in HIV positive MDR-TB patients = $\lambda_1$
- And If the Incidence ratio of SNHL in HIV negative MDR-TB patients = $\lambda_2$
- Likewise the null hypothesis can be restated as $\lambda_1 = \lambda_2$

d. Grading evidence and best practice guidelines

Objective 5 aimed at assessing the existing literature and existing guidelines in order to develop best practice guidelines for prevention of aminoglycoside induced hearing loss. Mold (2003:131-134) defines best practices research as a systematic process used to identify, describe, combine, and disseminate effective and efficient clinical and/or management strategies developed and refined by practicing clinicians. The literature review for development of best practice guidelines analysed the following:

- definition of “best” based on values and standards;
- identification and evaluation of potentially effective methods;
- combination of most-effective methods, and testing of combined methods requiring methodological assessment of quality of the included studies, from
design, conduct and analysis as well as evaluation of the overall strength of that body of evidence (Harbour & Miller 2001:334-6; Polit & Beck 2008:348; Rehfuess & Akl 2013:1-5). Polit and Beck (2008) identify 7 levels of evidence-based practice:

- Level 1: Systematic reviews of randomised and non-randomised clinical trials
- Level 2: Single randomised and non-randomised clinical trials
- Level 3: Systematic review of correlational and observational studies
- Level 4: Single correlational and observational studies
- Level 5: Systematic review of descriptive, qualitative, and physiologic studies
- Level 6: Single descriptive, qualitative, and physiologic studies
- Level 7: Opinions from authorities, and expert committees.

3.4 INTERNAL AND EXTERNAL VALIDITY OF THE STUDY

3.4.1 Internal Validity of the Study

In scientific research, researchers try to establish as to whether one can draw meaningful and useful inference from the scores of the instrument (Creswell 2014:160). According to Curtis and Drennan (2013a: 136), internal validity refers to whether an instrument used in a study actually measures what it purports to measure. Lavrakas (2008: (1-4) on the other side refers to internal validity as the extent to which methodological research design used by the researcher is able to provide empirical data to test possible cause-effect relationship between the dependent and independent variables. Traditional forms of validity that can be applied to the instrument, the questionnaire are:

- Content validity identified as the extent to which the questions are representative of what is known about the specific topic,
• Criterion validity identified as the relationship between scores on the questionnaire and their correlation with an independent criterion
• Construct validity which refers to the attributes which underlie series of scaled measurements, that is do the items in the tool measure hypothetical constructs or concepts (Curtis & Drennan 2013a:136, 2013d:186; Donmoyer 2008, Lavrakas 2008).

In the current prospective cohort study, the potential threats to internal validity could arise from the following (Lavrakas 2008):

• The selection of the subjects to constitute different comparison groups in the study. If there is no controlled effort for random assignment of subjects to make the groups similar, the basis to draw valid inference about the causes of any observed difference between two populations is limited). In this study, we had internal controls. Although they self-selected on the basis of no HIV, all the other characteristics between the two groups were similar;
• Differential history effect causing observed differences among the respondents in the dependent variable. Hence, in other words, because of previous exposure the possibility that something in the past other than the independent variable may influence dependent variable. In the current study, previous exposure to second line anti-TB medicines used in the treatment of MDR-TB was taken into account. This history did not appear to be different between the HIV positive and HIV negative patients.
• Changes in the measurement instrument between the pre and post-period in wave panel studies can influence the observed changes in the dependent variable. The observed changes in the dependent variable of interest could solely be due to changes in the instrument in the post period as opposed to the real changes in the groups attributable of the intervention effect. In the current study, the same instrument was used consistently throughout the observation time.
• Mortality may undermine the research designs ability to support case-effect reasons especially if subjects were not randomly allocated in the current
study, mortality occurred during the follow up period but the proportion was less than 10% and occurred in both the exposed and unexposed cohorts.

In summary, the instrument's internal validity was addressed in the following ways:

i) A panel of experts in the area reviewed the content of the questionnaires to validate the questions. The experts included an Audiologist, an Otorhinolaryngologist, and a Senior Medical Officer managing MDR-TB and they provided independent views on the content.

ii) Interviews with a sub sample of the MDR-TB patients (population of interest) through a pilot study to further strengthen the validity of the instrument. The results of the pilot are presented in section 3.4.5.

iii) The questions chosen were a culmination of review of the literature and examination of what is known on the topic of MDR-TB treatment related hearing loss.

iv) Additionally, through the above three approaches, content validity was established. Patients were requested to provide self-reported assessment hearing sensitivity as part of the hearing health screening in the pre-intervention period. Qualitative measures of hearing loss were compared with audiometry measures and this helped in the determination of whether the results accurately predicted what audiometer (instrument's) results would be expected to predict. Through this approach, criterion and predictive validity was achieved (Curtis & Drennan 2013c:223-227; Donmoyer 2008).

3.4.2 External Validity of the Study

Conversely, external validity (which also is referred to as generalisability) refers to the likelihood that a study's findings will apply to the larger population represented by the study's sample (Kalaian & Kasim 2008). However, measuring a construct by means of an instrument, in the case of this study, a questionnaire, always poses a problem of validity because constructs cannot be measured directly (Gallestey 2008:1071-74). Gallestey (2008:1071) posits that validity can be assessed on two grounds, theoretical (thorough examination of the contents of the instrument so as to verify if it reflects the meaning attached to the construct it is intended to measure),
and empirical (which entails a careful testing of the properties that should respond in practice to the meaning). That is, the ontological and methodological dimensions. The study was based on probability sampling and the construction of the sampling framework ensured that sample size was large enough to overcome type 2 statistical error. The study also addressed the following potential threats to external validity that were likely to causes of a limitation to generalisation include:

- Sample characteristics: The sample was selected through multistage sampling, and all consecutive patients attending the treatment sites had an equal chance of being included in the study. The biographic characteristics closely matched those of the target population.
- Setting characteristics: The settings included an urban setting with referral of patients from all over the country, but also a rural hospital setting to reflect the general settings in the country. The intervention delivery methods were harmonised and synchronised at all the study sites and competencies of the personnel conducting the recruitment and testing of hearing sensitivity were the same at the study sites
- Temporal characteristics: The time variable was considered in the study. For instance, recruitment of the cohort was continuously done over 13 months. That type of enrolment overcomes the threat of seasonal fluctuations in any of the parameters
- Research study awareness and pre-testing effects: the Hawthorne effect or reactivity of respondents knowing that they are involved in a study can have potential impact on performance, achievement, attitude, behaviour. Most of the variables collected in the study, were not dependent on the variables listed in the previous paragraph. The measurements were rather objective. Audiometry is a behavioural test but measures were put in place to identify malingerers. In addition, ABR test was conducted, as an additional test to pure tone audiometry once there was a suspicion of “faking” responses.
- Multiple treatment interferences: the researchers worked closely with the management of the study sites to minimise any possibility of multiple
treatments, hearing sensitivity testing, and management algorithms’ interferences.

- High dropout rates attrition, in cases where individuals who drop out might have specific characteristics that are different from individuals who remain. Attrition rates were kept low and hence this was not a major problem in this study. Special training of the research assistant to motivate patients, provision of transport re-imbursement for patients who were likely to miss appointments and short text message reminders helped to reduce attrition.

- Low response rates where there could be considerable effects due individual’s nonresponse to certain items on the questionnaire: Out of the 194 patients approached for eligibility, 173 agreed to participate in the study. The response rate was actually much higher than we have anticipated being 50-70%.

In summary, the study addressed those weaknesses by:

- Ensuring that the sample is a representative of the target population. Respondents were selected from the largest MDR-TB treatment site with a national representation of patients attending the facility.
- The optimisation of statistical considerations in the calculation of sample size to achieve very high power for the study to increase the chances of generalizability.

### 3.4.3 Reliability

Another aspect of quantitative research related to validity is reliability. Reliability is viewed as a property of the instruments (for example, tests and observation schedules) that quantitative researchers used to measure the phenomena they are studying (Curtis & Drennan 2013c:314-322; Donmoyer 2008). An instrument is considered reliable if it consistently produces the same results when administered to the same or comparable individuals. Reliability was assured by the use of the standard operating procedures for the equipment including daily calibrations and
quality control manoeuvres. Translation of the questionnaires into SiSwati is another measure that the researcher took into consideration to ensure reliability.

- A pilot test of procedures, equipment, and questionnaires was done as reported in section 3.3.1 and 3.4.5. Procedure manuals detailing each step were used and staff involved in the study were trained. Scheduled progress meetings were conducted and troubleshooting was done timeously.


- The main potential confounders were identified prior to the study. However, the researcher dealt with those discovered later during the data collection. Methods used to eliminate confounders included restriction in participation in the study; stratified analysis within strata of the cofounding variable (for example, age) and intent-to treat analysis to address drop out and non-compliance.

- Information Bias (Error or bias in measurements) minimised strict observance of diagnostic criteria; testing for inter and intra observer variability; and implementing regular quality assurance procedures to ensure that there is no “drift” in the precision of the results (Enarson et al 2001:97-104). The exposure variables were defined *apriori* to make sure they are clear, specific, and measurable.

- The physician, audiologist and statistician, and other interested parties were invited to review the data collection tools, ensure content validity, and measurements were standardised for the exposed and unexposed.


3.4.4 Quality Control

Other quality control procedures were conducted at all different facets and stages of the study, and these included:

- review of sample selection procedures,
- supervision of interviewing,
- random checks that interviews have actually taken place,
- compliance with proper standards in recruitment and training of personnel, continual review, verification, and evaluation that all procedures and processes correspond to the study design.

- Training: Research assistants were trained for two weeks in the standard operating procedures of the study: basics in research methods, basics of research ethics, data collection, data entry, how to ensure data quality, actions to enhance adherence and reduce missing data. The audiologist also had an additional one-week attachment to the audiology-training centre at the University of Pretoria.
3.5 SUMMARY OF THE RESEARCH DESIGN AND METHODS

The table 3.1 summarises the research design and methods framework.

Table 3.4 Research design and methods summary framework

<table>
<thead>
<tr>
<th>Research Question</th>
<th>Time Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) What is the incidence of hearing loss among patients enrolled in the MDR-TB treatment programme in Swaziland? ii) Is there a difference in the incidence of SNHL, time to SNHL and risk factors in HIV positive and the HIV negative patients on MDR-TB treatment? iii) How can best practices for prevention and monitoring of MDR-TB treatment related hearing loss be developed?</td>
<td>2011</td>
</tr>
</tbody>
</table>

Problem Statement

The internationally recommended MDR-TB treatment regimens are complex and use aminoglycosides and polypeptide antibiotic injections that have known to be ototoxic.

There is paucity of data on impact of HIV infection on the incidence of hearing loss related to MDR-TB treatment. From existing studies, the influence HIV infection on incidence hearing loss in general is disputed. There is paucity of data for development of guidelines.

There are no guidelines for prevention and monitoring SNHL in MDR-TB patients; and the guidelines from WHO do not provide details on what should be done, how and when. There is a need for best practice guidelines for monitoring and preventing MDR-TB treatment related hearing impairment, but there is empirical evidence.

Research design and Methods


Areas Studied


Data Collection


Data Analysis

3.6 CONCLUSION

In conclusion, this chapter presented a detailed description of the research design and methodology used for the study, focusing on the prospective cohort design and longitudinal data collection. Chapter four will present the findings and provide a response to the problem statement and other research questions presented in chapter 1.
CHAPTER 4

ANALYSIS AND PRESENTATION OF RESULTS

4.1 INTRODUCTION

In Chapter 3, the research design and methods for the study and the plan for the analysis of data were discussed. Chapter 4 presents the results of the research conducted from August 2012 and October 2014. The presentation of the results is divided into five sections, closely linked to the study objectives.

In Sections A to F, results of the research are presented. The socio-demographic data are presented first, characterising the study respondents according to their age profile, level of educational attainment, occupational profile, past medical history and their clinical profiles. Section 1 covers the results of the descriptive and explanatory analysis. The incidence of hearing loss is presented first followed by the bivariate and multivariate analysis of risk factors for hearing loss associated with MDR-TB treatment. Results of the impact of HIV on hearing loss are presented next followed by the presentation of the time-to-event data, predictive analysis, and survival data analysis. Finally, the results of the hypothesis testing are presented. The logistic regression statistical model, cox proportional hazards regression, log rank tests, and Kaplan Meier survival curves are also represented.

4.2 DATA MANAGEMENT AND ANALYSIS

Data management is a process by which the required data are acquired, validated, stored, protected, and processed, and by which its accessibility, reliability, and timeliness is ensured to satisfy the needs of the data users (Business dictionary, [Sa]). Data management consists of:

- data capture which refers to any process that converts the information provided by a respondent into electronic format (Canad 2013), and
- data cleaning, which is the process of preventing and correcting these errors. Common tasks in data cleaning include record matching, deduplication, and column segmentation, identified and managed through a variety of analytical techniques (Osborne 2013).

The data were entered into the electronic form using an MS Access database by two trained research assistants/data clerks. The data were checked for completeness and errors, and finally cleaned before analysis.

Data analysis is the process of developing answers to questions through the examination and interpretation of data (Canada 2013). Data analysis as the process of reducing, organising and giving meaning to data. Data analysis involves systematically applying statistical and/or logical techniques to describe and illustrate, condense and recap, and evaluate data and transforming raw data into usable information (Grove et al 2013; Polit & Beck 2008:725) Data were analysed using STATA software (Texas, USA). In the current study, data analysis was conducted to achieve the objectives of the following objectives set for the research to:

- Establish the incidence of hearing loss among DR TB patients receiving DR-TB treatment in Swaziland.
- Identify risk factors for hearing loss associated with DR-TB treatment.
- Determine the extent to which HIV/AIDS influences the incidence of hearing loss in MDR-TB patients in Swaziland.
- Assess time-to-hearing loss and recommend the optimal frequency for audiology testing for monitoring of patients on DR-TB treatment in Swaziland.
- Develop best practice guidelines for prevention and monitoring MDR-TB related hearing loss in Swaziland.
4.3 RESEARCH RESULTS

SECTION A

4.3.1 Socio-demographic characteristics of the respondents

4.3.1.1 Age of respondents

The ages of the respondents ranged from 15 years to 68 years. The mean age was 33.9 years (95% CI: 32.1-35.7). More than half of the respondents (52%) were 34 years or younger. The mean age in the male was higher at 36.4 years (95% CI: 33.7-38.9) compared with the mean age in females which was 31.9 years (95% CI 29.6-34.7) (p value 0.0062). Table 4.1 provides the details of the age breakdowns.

<table>
<thead>
<tr>
<th>Age categories</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-19 (1)</td>
<td>04</td>
<td>2.37%</td>
</tr>
<tr>
<td>20-24 (2)</td>
<td>18</td>
<td>10.65%</td>
</tr>
<tr>
<td>25-29 (3)</td>
<td>36</td>
<td>21.30%</td>
</tr>
<tr>
<td>30-34 (4)</td>
<td>33</td>
<td>19.53%</td>
</tr>
<tr>
<td>35-39 (5)</td>
<td>36</td>
<td>21.30%</td>
</tr>
<tr>
<td>40-44 (6)</td>
<td>17</td>
<td>10.06%</td>
</tr>
<tr>
<td>45-49 (7)</td>
<td>06</td>
<td>3.5%</td>
</tr>
<tr>
<td>50-54 (8)</td>
<td>10</td>
<td>5.92%</td>
</tr>
<tr>
<td>55-59 (9)</td>
<td>09</td>
<td>5.45%</td>
</tr>
<tr>
<td>60+ (10)</td>
<td>04</td>
<td>2.37%</td>
</tr>
</tbody>
</table>
4.3.1.2 Item 2: Gender

Data from one hundred and seventy-three (173) respondents were analysed. Seventy-eight respondents (45%) were males and 95 females (55%). See Figure 4.1 for the details.

![Frequency of respondent's gender (N=173)](image)

**Figure 4.1: Frequency of respondent's gender**

4.3.1.3 Item 3: Nationality and Race

The majority of the respondents, 169 (97.6%) were black Swazis, while the white Swazis constituted 2 (1.68%) and black Africans of other nationalities, 2 (1.68%) as shown in Figure 4.2.
4.3.1.4 Item 4: Respondent’s Region of origin

The respondents from Manzini region constituted 71 (41%) of the study respondents. Respondents for Lubombo region constituted 51 (30%) and Hhohho 43 (25%) as shown in Figure 4.3. Respondents from Shiselweni region were the least 7 (4%). There were fewer respondents from Shiselweni because there is an MDR-TB treatment facility serving catchment area that covers most of the region. The two respondents who reported their ethnicity as black African did not state their nationality and region of origin. Except for Hhohho region, there were more female respondents than males in each of the regions as displayed in Figure 4.3.
Figure 4.3: Region and gender of the respondents

4.3.1.5 Item 5: Respondent’s highest educational attainment

About 59 (34%) of the respondents had completed secondary education, 40 (23.1%) completed tertiary education, and 39 (22%) had some secondary education. Only about 2 (1%) had no formal education (See Figure 4.5). Respondents from either Hhohho or Manzini were more likely to be more educated than those from either Lubombo or Shiselweni were (p value = 0.014). In addition, the male respondents were more likely to be more educated than female counterparts (p value = 0.014). This compares well with the country’s literacy level. Swaziland has a total adult literacy rate of 87.8% (UNICEF 2013).
4.3.1.6 Item 6 and 7: Employment status and profession (Job type)

Seventy (40%) of the respondents were in employment at the time of the study. Fifty eight (58) (33.5%) respondents had not had a job in the past year, and about 17 (10%) were minors. The highest proportion of the respondents, 52 (30.2%), were in the unskilled manual category and 34 (19.6%) had a professional managerial/clerical job. Respondents employed in the mining sector or working as machine operators constituted eight (4.6%) of the study sample. Only one (0.6%) respondent was from the music/sound industry. Nineteen respondents did not indicate profession. See the details in Table 4.2
Table 4.2: Employment status and profession of the respondents

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sub categories</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employment</td>
<td>Currently employed</td>
<td>70</td>
<td>40.5%</td>
</tr>
<tr>
<td></td>
<td>Not employed within the last 12 months</td>
<td>58</td>
<td>33.5%</td>
</tr>
<tr>
<td></td>
<td>Not employed for more than 12 months</td>
<td>25</td>
<td>14.5%</td>
</tr>
<tr>
<td></td>
<td>Minor</td>
<td>17</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>No answer</td>
<td>3</td>
<td>1.8%</td>
</tr>
<tr>
<td>Profession/ Job type</td>
<td>Professional/technical Managerial</td>
<td>34</td>
<td>19.7%</td>
</tr>
<tr>
<td></td>
<td>Clerical</td>
<td>12</td>
<td>6.9%</td>
</tr>
<tr>
<td></td>
<td>Sales and Service</td>
<td>20</td>
<td>11.6%</td>
</tr>
<tr>
<td></td>
<td>Skilled Manual</td>
<td>15</td>
<td>8.6%</td>
</tr>
<tr>
<td></td>
<td>Unskilled Manual</td>
<td>52</td>
<td>30.1%</td>
</tr>
<tr>
<td></td>
<td>Mining/Machine operators</td>
<td>8</td>
<td>4.6%</td>
</tr>
<tr>
<td></td>
<td>Sound technicians/ Music</td>
<td>01</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td>Agriculture</td>
<td>01</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td>Scholars</td>
<td>06</td>
<td>3.5%</td>
</tr>
<tr>
<td></td>
<td>No answer</td>
<td>19</td>
<td>10.4%</td>
</tr>
</tbody>
</table>

4.3.1.7 Item 8: Marital Status

The married respondents plus respondents living together constituted about 85 (50%) of the sample. However, there was almost equal numbers of the married and never married among the respondents, 79 (46%) and 76 (44%) respectively as shown in Figure 4.6.
The Zionist religion constituted the largest religious affiliation among the respondents 39 (22.5%) followed by the Charismatic Christians, 36 (20.8%) and the Pentecostals, 30 (17.3%) with 9 (5.2%) who had no religious affiliation as shown in Table 4.3.
4.3.2 Clinical characteristics and history of treatment among the respondents

4.3.2.1 Item 10: History of TB disease and comorbidity

In response to the question on history of TB disease and comorbidity, of the 173 respondents, 44 males and 51 females (55%) had a previous history of TB treatment.
4.3.2.2 History of Streptomycin use for TB treatment

A total number of 7 males and 11 females (18%) were treated with streptomycin for a previous episode of tuberculosis as reflected in Figure 4.7 and Table 4.5.
Table 4.4: Clinical Characteristics (history of TB disease and exposure to TB treatment) (N=173)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sub category</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous TB treatment</td>
<td>No History</td>
<td>76</td>
<td>43.93%</td>
</tr>
<tr>
<td></td>
<td>History present</td>
<td>95</td>
<td>54.9%</td>
</tr>
<tr>
<td></td>
<td>History Unknown</td>
<td>02</td>
<td>1.16%</td>
</tr>
<tr>
<td>Previous TB episode</td>
<td>Drug Susceptible</td>
<td>59</td>
<td>40.1%</td>
</tr>
<tr>
<td>(n=146)</td>
<td>Retreatment (D-S)</td>
<td>86</td>
<td>58.90%</td>
</tr>
<tr>
<td></td>
<td>DR-TB case</td>
<td>01</td>
<td>0.68%</td>
</tr>
<tr>
<td>Previous Streptomycin</td>
<td>No history</td>
<td>149</td>
<td>89.2%</td>
</tr>
<tr>
<td>DR-TB at enrolment</td>
<td>Previous treatment</td>
<td>18</td>
<td>10.8%</td>
</tr>
<tr>
<td></td>
<td>Presumed</td>
<td>21</td>
<td>12.21%</td>
</tr>
<tr>
<td></td>
<td>Confirmed</td>
<td>148</td>
<td>86.05%</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>3</td>
<td>1.73%</td>
</tr>
</tbody>
</table>

4.3.2.3 Item 11: HIV status of respondents

The majority 136 (79%) of the study patients were HIV positive and 37(21%) HIV negative. One hundred and thirty-four 134(98.5%) were aware of their HIV status at the time of enrolment and 133 (97.8) were taking HIV treatment (see Figure 4.8 and 4.9).

Figure 4.8: HIV sero-status of the respondents (frequency and percentage)
Female respondents were more likely to be HIV positive than male respondents were (p value = 0.044). Age group was significantly associated with HIV status (p value = 0.000). The prevalence of HIV was highest age group 40-44 years, followed by 30-34 years age group and 35-39 years age group.

![HIV status by gender](image)

**Figure 4.9: HIV sero-status of the respondents by gender**

**4.3.2.4 Item 12: Comorbid conditions (other than HIV)**

Five (3%) respondents had high blood pressure and all were female but only one was on medication for hypertension. There were four (2.3%) respondents with diabetes mellitus and they were all male but only two (2) were on anti-diabetic treatment. Four (2.3%) patients had known renal disease (2 males, 2 females). Please see table 4.6 for details.
<table>
<thead>
<tr>
<th>Table 4.5: Clinical Characteristics (concurrent comorbidities)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variables</strong></td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td><strong>HIV status (n=173)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>On ART (HIV Pos) (n=134)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Diabetes Mellitus (n=173)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Comorbid with Renal Disease (n=173)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular disorder (n=173)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Hypertension 9173)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>CD4 Count (n=173)</strong></td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>

### 4.3.2.5 Item 13: Clinical symptoms and concurrent medications

The five commonest presenting symptoms and signs of MDR-TB reported by the respondents at baseline assessment as shown in Table 4.7 were:

1. Weakness and/or fatigue (95%);
2. Night sweats (92%);
3. Chest pain (91%);
4. Loss of appetite (86%); and
5. Weight loss (85%)
### Table 4.6: Clinical symptoms at the diagnosis of MDR-TB reported by the respondents

<table>
<thead>
<tr>
<th>Symptoms at diagnosis</th>
<th>Subcategory</th>
<th>Frequency</th>
<th>Percent (%)</th>
<th>Symptoms at diagnosis</th>
<th>Subcategory</th>
<th>Frequency</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High grade fever</td>
<td>No</td>
<td>135</td>
<td>78.3%</td>
<td>Loss of appetite</td>
<td>No</td>
<td>24</td>
<td>13.7%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>38</td>
<td>21.97%</td>
<td></td>
<td>Yes</td>
<td>149</td>
<td>86.3%</td>
</tr>
<tr>
<td>Low grade fever</td>
<td>No</td>
<td>85</td>
<td>49.13%</td>
<td>Nausea/Vomiting (n=173)</td>
<td>No</td>
<td>146</td>
<td>84.3%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>88</td>
<td>50.87%</td>
<td></td>
<td>Yes</td>
<td>27</td>
<td>15.6%</td>
</tr>
<tr>
<td>Night Sweats</td>
<td>No</td>
<td>14</td>
<td>8.09%</td>
<td>Visual problems (n=173)</td>
<td>No</td>
<td>165</td>
<td>95.38%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>159</td>
<td>91.91%</td>
<td></td>
<td>Yes</td>
<td>08</td>
<td>4.62%</td>
</tr>
<tr>
<td>Unproductive Cough</td>
<td>No</td>
<td>72</td>
<td>41.62%</td>
<td>Dyspnea (n=173)</td>
<td>No</td>
<td>131</td>
<td>75.72%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>101</td>
<td>58.38%</td>
<td></td>
<td>Yes</td>
<td>42</td>
<td>24.28%</td>
</tr>
<tr>
<td>Productive Cough</td>
<td>No</td>
<td>103</td>
<td>59.54%</td>
<td>Headache v</td>
<td>No</td>
<td>77</td>
<td>44.51%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>70</td>
<td>40.4%</td>
<td></td>
<td>Yes</td>
<td>96</td>
<td>55.49%</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>No</td>
<td>149</td>
<td>86.13%</td>
<td>Hearing loss (n=173)</td>
<td>No</td>
<td>173</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>24</td>
<td>13.87%</td>
<td></td>
<td>Yes</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Chest pain (n=173)</td>
<td>No</td>
<td>15</td>
<td>8.7%</td>
<td>Weight loss (n=173)</td>
<td>No</td>
<td>27</td>
<td>15.61%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>158</td>
<td>91.33%</td>
<td></td>
<td>Yes</td>
<td>146</td>
<td>84.39%</td>
</tr>
<tr>
<td>Weakness/Fatigue (n=173)</td>
<td>No</td>
<td>08</td>
<td>4.62%</td>
<td>Thirsty (n=171)</td>
<td>No</td>
<td>132</td>
<td>75.78%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>165</td>
<td>95.3%</td>
<td></td>
<td>Yes</td>
<td>39</td>
<td>24.22%</td>
</tr>
<tr>
<td>Diarrhea (n=173)</td>
<td>No</td>
<td>164</td>
<td>94.8%</td>
<td>Loss of appetite (n=173)</td>
<td>No</td>
<td>24</td>
<td>13.7%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>09</td>
<td>5.2%</td>
<td></td>
<td>Yes</td>
<td>149</td>
<td>86.3%</td>
</tr>
<tr>
<td>Nausea/Vomiting (n=173)</td>
<td>No</td>
<td>146</td>
<td>84.3%</td>
<td></td>
<td>Yes</td>
<td>27</td>
<td>15.6%</td>
</tr>
</tbody>
</table>

### 4.3.2.6 Item 14: Medications used by the respondents

One hundred and seventy two (99.4%) respondents were on treatment using the national standard regimen for MDR-TB during the intensive phase of treatment is 8 Km-Lfv-Cs/Tr-Ethio-PZA-PAS. One (0.6%) patient received amikacin instead of kanamycin. One hundred and thirty three (76.9) HIV positive respondents also received ART. In addition, however, five (2.8%) respondents were on paracetamol as depicted in Table 4.8.
### 4.3.2.7 Item 15: ARV medications used by respondents

Respondents who were HIV positive also received antiretroviral medicines for treatment of HIV in addition to the medications for MDR-TB. The majority of the HIV positive respondents were on a Tenofovir based regimen 101 (59%), followed by the Zidovudine based regimen 19 (11%), Abacavir based regimens 4 (6%) and the Stavudine based regimens 4 (1.3%). One hundred and twenty (70.2%) HIV patients were on Efavirenz and only 10 (5.6%) on Nevirapine.

<table>
<thead>
<tr>
<th>Name of Medication</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDR-TB regimen at enrolment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>No</td>
<td>03</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>170</td>
</tr>
<tr>
<td>Amikacin</td>
<td>No</td>
<td>172</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>01</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>No</td>
<td>03</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>170</td>
</tr>
<tr>
<td>Para Aminosalicylic Acid</td>
<td>No</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>97</td>
</tr>
<tr>
<td>Pyranazinamide</td>
<td>No</td>
<td>06</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>167</td>
</tr>
<tr>
<td>Terizidone</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>173</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>No</td>
<td>03</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>170</td>
</tr>
<tr>
<td><strong>HIV Treatment regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>None</td>
<td>154</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>19</td>
</tr>
<tr>
<td>Tenovir</td>
<td>None</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>101</td>
</tr>
<tr>
<td>3TC</td>
<td>None</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>131</td>
</tr>
<tr>
<td>Stavudine</td>
<td>None</td>
<td>169</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>04</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>None</td>
<td>163</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>10</td>
</tr>
<tr>
<td>Abacavir</td>
<td>None</td>
<td>167</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>06</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>None</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>122</td>
</tr>
<tr>
<td><strong>Other medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent Paracetamol</td>
<td>None</td>
<td>168</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>05</td>
</tr>
</tbody>
</table>
SECTION C

4.3.3 Life style and physical characteristics

4.3.3.1 History of smoking among respondents

While the 155 (89.6%) respondents did not smoke, three (2%) were current smokers and 12 (7%) were previous smokers. Current smoking was referred to as currently smoking or stopped smoking less than 6 months while previous smokers were defined as those who had not smoked for at least 6 months after quitting smoking. See table 4.10 for further details.

Figure 4.10: History of smoking among the respondents
4.3.3.2 Drinking Alcohol

The majority of the respondents, 135 (78%) reported no history of drinking alcohol. Three respondents, all males, were current drinkers. Twenty-six (26) males and six females (18.5%) were previous drinkers. See Figure 4.11.

Figure 4.11: History of drinking alcohol among the respondents (frequency and percentage)

4.3.3.3 History of exercise

Only 17 (9.8%) of the study respondents reported involvement in regular exercise prior to their illness (at least once or twice a week). Women were not likely to engage in any form of exercise or exercise less than once a month (p value = 0.010). See table .4.12
4.3.3.4 Ear health (History of ear infections and conductive hearing loss)

The baseline assessment of hearing health showed that 28(16.2%) of the respondents had a history of ear infection.

Table 4.8: Ear Health (history of ear infections and conductive hearing loss)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History Ear Infection</td>
<td>None</td>
<td>137</td>
</tr>
<tr>
<td>Childhood</td>
<td>09</td>
<td>5.20%</td>
</tr>
<tr>
<td>Adult</td>
<td>19</td>
<td>10.89%</td>
</tr>
<tr>
<td>unknown</td>
<td>08</td>
<td>4.62%</td>
</tr>
<tr>
<td>Baseline conductive hearing loss</td>
<td>Normal</td>
<td>168</td>
</tr>
<tr>
<td>Conductive</td>
<td>5</td>
<td>3%</td>
</tr>
</tbody>
</table>
4.3.3.5 Fluid consumption among the respondents

Men were more likely to consume more fluids than women (p value 0.040) were overall, 80(46.2%) of the study respondents reported that they consumed at least 1-2 litres of fluids per day.

4.3.3.6 Hydration status of the respondents

The majority 114(66%) of the patients were dehydrated at the time they were enrolled into MDR-TB management (see Figure 4.13)

Figure 4.13: Hydration status of respondents at baseline

At least 21(12%) of the respondents were exposed to noise at the work place and 58(33%) during leisure. Men were more likely to be exposed to noise at the work place and during leisure than women were (p value = 0.002).
Figure 4.14: Exposure to noise by respondents at baseline

4.3.3.7: Baseline body temperature of the respondents

Figure 4.15: Body temperatures of the respondents at baseline
4.3.3.8 Baseline weight

The modal weight band of the respondents was 50-59k kg while the baseline average weight was 51.7kg (95% CI: 49.16-54.40). See table 4.10 and Figure 4.16.

Table 4.9 Baseline weight bands of the respondents (N=161)

<table>
<thead>
<tr>
<th>Weight bands</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline weight</td>
<td>35-49</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>50-59</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>60-69</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>70-79</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>80-96</td>
<td>5</td>
</tr>
</tbody>
</table>

Figure 4.16: Boxplots for the baseline weight of respondents in kilograms
1=Male and 2= Female
4.3.4 Incidence of hearing loss

In this cohort study, the research aimed to determine incidence of hearing loss and if an association exits between the exposure to HIV infection (as well as other risk factors) and hearing loss incidence. Hearing loss was analysed as a categorical outcome (hearing loss; no hearing loss). However, incidence rates calculated as continuous variable. The Table 4.11 shows the incidence rates of high frequency hearing loss.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Sub category</th>
<th>High frequency 4 and 8 kilohertz</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rate per 1000 person days Confidence Intervals</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>3.3</td>
</tr>
<tr>
<td>Age Group</td>
<td>15-29</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>30-49</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>50-69</td>
<td>7.0</td>
</tr>
<tr>
<td>Profession/</td>
<td>Agriculture/ other</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Manual Workers (skilled and unskilled)</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>Office (Managers and Clerical)</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>Machine operators, Miners and drivers</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td>Scholars and pupils</td>
<td>2.4</td>
</tr>
<tr>
<td>Dyspnoea present</td>
<td>No</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>7.4</td>
</tr>
<tr>
<td>Noise exposure</td>
<td>Not sure</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>At work</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>During leisure</td>
<td>2.8</td>
</tr>
<tr>
<td>BMI</td>
<td>Normal</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Under weight</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>0</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>11+</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>08-11</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>&lt;08</td>
<td>12.3</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Normal</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>2.5</td>
</tr>
</tbody>
</table>
### 4.3.5 Associations of high frequency hearing loss

#### Table 4.11: Bivariate Analysis (Associations with high frequency hearing loss)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Counts</th>
<th>No Hearing Loss</th>
<th>Hearing Loss</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (n=159)</td>
<td>Male</td>
<td>23</td>
<td>51</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>42</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Age (n=159)</td>
<td>15-29</td>
<td>29</td>
<td>25</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>30-49</td>
<td>33</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50-69</td>
<td>03</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Job type (n=159)</td>
<td>Miner/Machine operator/ Sound or music Operator</td>
<td>0</td>
<td>9</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Office based (Manager/clerical)</td>
<td>21</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Manual (skilled/unskilled)</td>
<td>25</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Agriculture/Other</td>
<td>12</td>
<td>05</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea of admission (n=159)</td>
<td>Dyspnoea absent at initiation of treatment</td>
<td>56</td>
<td>69</td>
<td>0.054</td>
</tr>
<tr>
<td></td>
<td>Dyspnoea present at initiation of treatment</td>
<td>09</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Noise Exposure (n=159)</td>
<td>Not sure</td>
<td>31</td>
<td>56</td>
<td>0.078</td>
</tr>
<tr>
<td></td>
<td>At work</td>
<td>05</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>During Leisure</td>
<td>29</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Rifampicin Resistant (n=144)</td>
<td>No Rifampicin Mono-Resistance at initiation of treatment</td>
<td>16</td>
<td>16</td>
<td>0.278</td>
</tr>
<tr>
<td></td>
<td>Rifampicin Mono-Resistance at initiation of treatment</td>
<td>44</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Pre-treatment hydration status (n=102)</td>
<td>Not hydrated</td>
<td>25</td>
<td>40</td>
<td>0.145</td>
</tr>
<tr>
<td></td>
<td>Dehydrated</td>
<td>33</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>11+</td>
<td>33</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>08-11</td>
<td>9</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;08</td>
<td>01</td>
<td>07</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>Normal</td>
<td>40</td>
<td>60</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>2</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>Normal</td>
<td>27</td>
<td>42</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Underweight</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Over weight</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Temporal associations of hearing loss and several independent variables were explored (see table 4.12)

4.3.6 Risk factors for hearing loss

4.3.6.1 Univariate Analysis of risk factors for high frequency hearing loss

On univariate regression analysis, the following were risk factors for DR TB treatment related sensorineural hearing loss (see Table 4.13):

- being of male gender (p value =0.033),
- poor baseline hydration status at the start of MDR-TB treatment (p value =0.012),
- use of Abacavir as backbone in the ART regimen in MDR-TB (p value =0.017) and
- low of <8 g/dl baseline HB (p value <0.001), low BMI (p value =0.003), presence of dyspnoea at the start of treatment (p value < 0.001 ) were found to be risk factors for high frequency hearing loss.

4.3.6.2 Multivariate Analysis of risk factors for high frequency hearing loss

On the Cox regression model, the following variables were dropped: education, religion, noise, body-mass index, regimen for HIV, religion, and CD4 count. Variables retained in the model with statistically significant relationship with high frequency hearing loss were as follows and Table 4.13 contains the details:

- Compared to agriculture as a day-to-day employment, the hazard ratio of high frequency hearing loss was 4.2 times in the Miners/machine Operators and Sound Industry (HR: 5.4, CI 1.2-24.03, p value =0.024)
- Patients who had dyspnoea at initiation of MDR-TB treatment were 3.4 times likely to develop high frequency hearing loss (HR: 3.4, CI 1.8-6.3, p value =0.000).
Low baseline haemoglobin was a risk factor for hearing loss (p value<0.01). Patients with HB 8-11 g/dl and those with HB less than 8g/dl were 2 times and 8.5 times respectively more likely to develop hearing loss compared to those with HB above 11g/dl (p value <0.01). See table 4.13.

Table 4.12: Non HIV related Risk measurements for high frequency hearing loss continued

<table>
<thead>
<tr>
<th>Variable (Ref group)</th>
<th>Univariate Analysis</th>
<th>P-value</th>
<th>Multivariate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude HR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender: Male</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>0.23</td>
</tr>
<tr>
<td>Female</td>
<td>0.64 (0.42- 0.96)</td>
<td>0.033</td>
<td>0.69 (0.37-1.2)</td>
<td></td>
</tr>
<tr>
<td>Baseline Hydration:</td>
<td>1.00</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.87 (1.14- 3.003)</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dehydrated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Job type: Agric/other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office based (Manager/clerical)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miner/Machine operator/ Sound or music Operator</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual (skilled/unskilled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scholar</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night sweats: No</td>
<td>1.00</td>
<td>--</td>
<td></td>
<td>0.112</td>
</tr>
<tr>
<td>Yes</td>
<td>0.57 (0.29-1.14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydration:</td>
<td>1.00</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.35 (0.87-2.10)</td>
<td>0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dehydrated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline BMI: Normal</td>
<td>1.00</td>
<td>--</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Underweight</td>
<td>2.14 (1.29- 3.35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea. Absent</td>
<td>1.00</td>
<td>--</td>
<td>1.00</td>
<td>0.000</td>
</tr>
<tr>
<td>Present</td>
<td>3.4 (1.8-6.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline creatinine:</td>
<td>1.00</td>
<td>--</td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Normal</td>
<td>1.81 (0.84-3.90)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Hb level:</td>
<td>1.00</td>
<td>--</td>
<td>1.00</td>
<td>0.02</td>
</tr>
<tr>
<td>11+</td>
<td>1.78 (0.96- 3.17)</td>
<td>0.07</td>
<td>1.98 (1.11-3.55)</td>
<td></td>
</tr>
<tr>
<td>8-11</td>
<td>5.02 (2.17- 11.64)</td>
<td>&lt;0.01</td>
<td>3.8 (3.33-21.64)</td>
<td>0.000</td>
</tr>
<tr>
<td>&lt;8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.4 HIV and Hearing loss

4.4.5 HIV and hearing loss

4.4.5.1 Association of HIV and Hearing loss

Of the three HIV related parameters measured in the current study, only ARV regimen was associated with MDR-TB treatment related hearing loss (p value =0.017), compared to HIV status and HIV treatment (Figure 4.14).

Table 4.13: Association of HIV parameters and hearing loss

<table>
<thead>
<tr>
<th>variable</th>
<th>Sub categories</th>
<th>Number with no hearing loss</th>
<th>Number with hearing loss</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV status (n=159)</td>
<td>Negative</td>
<td>16</td>
<td>20</td>
<td>Fischer’s exact 0.62</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>49</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>HIV treatment (n=163)</td>
<td>Yes [(HIV +)]</td>
<td>44</td>
<td>84</td>
<td>0.491</td>
</tr>
<tr>
<td></td>
<td>No [HIV (-)]</td>
<td>15</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>ARV regimen (n=125)</td>
<td>TDF Based</td>
<td>40</td>
<td>52</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>AZT Based</td>
<td>4</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D4T based</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABC based</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

4.4.5.2 Risk measurements by HIV

Males are worse off than females and there is no distinct difference by HIV status. The incidence rate among the HIV positive patients was 4.2/1 000 person days (CI: 3.4-5.3) and for HIV negative patients, 3.6/1 000 person days (CI: 2.4-5.7). ART regimen containing Abacavir (ABC) backbone has survival distributions that were statistically different (see Table 4.14).
Table 4.14: Risk measurements for High frequency hearing loss and HIV

<table>
<thead>
<tr>
<th>Variable (Ref group)</th>
<th>Incidence ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender: Male</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>0.58 (0.39- 0.89)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>HIV: negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>NRTI backbone: TDF based</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZT/d4T based</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.12 (0.60- 2.07)</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>3.53 (1.37- 9.09)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>CD4 count: &lt;200</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200-500</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.76 (0.64-4.82)</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>2.90 (0.91- 9.30)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>NRTI backbone: TDF based</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZT</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.37 (0.76- 2.49)</td>
<td>0.294</td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.29 (1.28- 8.40)</td>
<td>0.013</td>
</tr>
</tbody>
</table>
4.5 SURVIVAL DISTRIBUTION AND TIME TO HEARING LOSS

4.5.1 Time to hearing loss by socio demographic characteristics

4.5.1.1 Gender and Age: Survival analysis and time-to-hearing loss

Males had worst survival distribution compared females and age group 50-69 years and also had poorer survival when compared to the younger age groups as shown in Figure 4.17 and 4.18. The median failure time among males was 94 days and 80 days among females (see table 4.15)

![Survival distribution by gender](image)

Figure 4.17: Hearing loss distribution by gender
4.5.1.2 Time to hearing loss by Job type

Figure 4.18: Hearing loss distribution by age group (right)

Figure 4.19: Hearing loss survival and job type
4.5.2 Time to hearing loss by HIV variables

4.5.2.1 HIV status

No distinct difference by HIV status was observed in survival distribution (p value = 0.59). See Figure 4.21. The time to hearing loss was 84 days in both HIV positive and HIV negative respondents (Table 4.15).
4.5.2.2 Time to hearing loss by status of ARV treatment

However, when survival by ART regimen were compared using NRTI backbone, there was statistical significance among the regimens. Patients on Abacavir had a higher failure rate when compared to TDF based regimen as shown in Figure 4.22. The median time to hearing loss in respondents 104 days on ABC, 100 days for those on AZT and 83 days for those on TDF (see Table 4.15 for details)
4.5.3 Time to hearing loss by clinical parameters

4.5.3.1 Time-to-hearing loss between Body mass index and Haemoglobin

Underweight patients and patients with low haemoglobin level failed at faster rates than normal patients with normal BMI did (p value=0.01) and haemoglobin level above 11 g/dl (p value <0.01). See Figure 4.23 and 4.24.
Respondents with HB less than 8g/dl had the mean time hearing loss of 142 days compared to respondents with HB between 8 and 11g/dl of 98 days and HB more than 11g/dl of 160 days. See Table 4.24
4.5.3.2  **Time to hearing loss and dyspnoea**

Presence of dyspnoea is associated with higher rates of failure when compared with absence of dyspnoea at the start of treatment (p value <0.01) – see Figure 4.25.

![Figure 4.25: Hearing loss distribution by dyspnoea](image)

4.5.3.3  **Time to hearing loss and hydration status**

![Figure 4.26: Hearing loss survival distribution by hydration status](image)
Table 4.15: Median and mean times to hearing loss

Median time to failure: 84 days (IQR: 54.5-147); Mean: 103.9 (sd: 67.2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of events</th>
<th>Median (IQR)</th>
<th>Mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Male</td>
<td>53</td>
<td>94 (49-160)</td>
<td>108.5 (72.3)</td>
</tr>
<tr>
<td>Female</td>
<td>47</td>
<td>80 (57-126)</td>
<td>98.7 (61.3)</td>
</tr>
<tr>
<td>Night sweats: No</td>
<td>12</td>
<td>83 (54.5-149)</td>
<td>105.3 (72.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>88</td>
<td>84 (54.5-147)</td>
<td>103.7 (66.9)</td>
</tr>
<tr>
<td>Baseline Hb: &gt;11</td>
<td>17</td>
<td>147 (83-213)</td>
<td>144.1 (71.2)</td>
</tr>
<tr>
<td>8-11</td>
<td>8</td>
<td>86.5 (55-144.5)</td>
<td>103 (70.0)</td>
</tr>
<tr>
<td>&lt;8</td>
<td>5</td>
<td>44 (34-56)</td>
<td>51.2 (27.4)</td>
</tr>
<tr>
<td>Bas.hydration: Normal</td>
<td>41</td>
<td>97 (72-174)</td>
<td>114.8 (63.5)</td>
</tr>
<tr>
<td>Dehydrated</td>
<td>44</td>
<td>66 (39.5-112.5)</td>
<td>87.1 (63.7)</td>
</tr>
<tr>
<td>CD4 count: &lt;200</td>
<td>90</td>
<td>83.5 (51-151)</td>
<td>104.7 (68.7)</td>
</tr>
<tr>
<td>200-500</td>
<td>4</td>
<td>79 (44-109)</td>
<td>76.5 (38.6)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>2</td>
<td>164.5 (97-232)</td>
<td>164.5 (95.5)</td>
</tr>
<tr>
<td>NRTI backbone: TDF</td>
<td>60</td>
<td>83 (56-151.5)</td>
<td>106.9 (71.3)</td>
</tr>
<tr>
<td>AZT</td>
<td>13</td>
<td>100 (59-160)</td>
<td>118.5 (65.4)</td>
</tr>
<tr>
<td>D4T</td>
<td>0</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>ABC</td>
<td>4</td>
<td>104.5 (59-125)</td>
<td>92 (47.1)</td>
</tr>
<tr>
<td>Weight category: &lt;50</td>
<td>31</td>
<td>83 (58-117)</td>
<td>100.2 (63.9)</td>
</tr>
<tr>
<td>50-&lt;60</td>
<td>40</td>
<td>81 (47.5-147)</td>
<td>101.2 (68.8)</td>
</tr>
<tr>
<td>60-&lt;70</td>
<td>19</td>
<td>94 (43-170)</td>
<td>105.1 (66.9)</td>
</tr>
<tr>
<td>70+</td>
<td>8</td>
<td>109 (76-146.5)</td>
<td>113.1 (60.5)</td>
</tr>
<tr>
<td>Productive cough: No</td>
<td>61</td>
<td>104 (58-177)</td>
<td>119.4 (71.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>68 (42-98)</td>
<td>79.7 (51.7)</td>
</tr>
<tr>
<td>HIV test result: Neg</td>
<td>21</td>
<td>84 (35-151)</td>
<td>97.8 (67.8)</td>
</tr>
<tr>
<td>Pos</td>
<td>79</td>
<td>84 (56-147)</td>
<td>105.5 (67.4)</td>
</tr>
</tbody>
</table>
CHAPTER 5

DISCUSSION OF RESULTS

5.1 INTRODUCTION

The previous chapter presented the findings of the empirical study. Chapter 5 discusses the results based on the analysis of data. Chapter 5 discusses the descriptive statistics such as age, gender, region of origin, education, profession, occupation marital status, and religious affiliation, and the inferential statistics.

5.2 DISCUSSION OF THE DESCRIPTIVE STATISTICS

5.2.1 Socio-demographic characteristics of the respondents

5.2.1.1 Gender

The findings of this study indicate that there were more female respondents 95 (55%) than the males 78(45%) reflecting a sex ratio of male: female of 0.82. This is similar to the results from the Swaziland Demographic and Health Survey (SDHS) of 2007 that showed that there were 53 females to every 43 male citizens in Swaziland, giving a sex ratio of 1:1.14, that is 88 men to 100 women (Central Statistics Office (CSO) [Swaziland] and Macro Inc, 2008:9). The statistics also reflect the health seeking behaviour for TB services. For instance, the 2009 National Tuberculosis Control Programme annual report indicates that 55% of clients receiving HIV testing were females and 45% males (NTCP 2009:28).

5.2.1.2 Age

According to the results, the age of the respondents ranged from 15 years to 68 years. The mean age was 33.9 years. Fifty two percent of the sample was 34 years or younger. This is in line with Swaziland’s demographic and health survey of 2007 which found that Swaziland’s population was young, with 44 percent of the total
population under 15 years of age, and less than 4 percent is 65 years or older (Central Statistics Office (CSO) [Swaziland] and Macro Inc, 2008:9).

5.2.1.3 Respondent's Region of origin and nationality

The respondents from Manzini region constituted 41% the study respondents. Respondents for Lubombo region constituted 30% of the respondents and Hhohho 25%. Respondents from Shiselweni region constituted the least proportion of (4%). There were fewer respondents from Shiselweni because there is an MDR-TB treatment facility serving catchment area that covers most of the region (Swaziland Ministry of Health 2010:28). According to the results, there were more female respondents than males in each of the regions with the exception of Hhohho region. The reason for this finding is not clear. In addition, the majority of the respondents, 97.6% (169) were black Swazis, while the white Swazis constituted 1.68% (02) and black Africans of other nationalities, 1.68% (02). This picture reflects the hospitality of Swaziland where the country is multi-cultural, with almost 4% are white Swazis or black Africans from other African countries.

5.2.1.4 Respondent's highest educational attainment

This study revealed that educational levels of respondents ranged from no formal education to tertiary education. Fifty-nine respondents (34%) had completed secondary education, 40 (23.1%) completed tertiary education, and 39 (22%) had some secondary education. Only 2 respondents (1%) had no formal education. The findings from the study compare well with the country’s adult literacy rate estimated at 87.8% (UNICEF 2013). Education is a key determinant of the lifestyle and status an individual enjoys in a society. Studies have consistently shown that educational attainment has a positive effect on health behaviours and attitudes.

From the data, a regional pattern of the educational attainment shows that respondents from either Hhohho or Manzini were more likely to be more educated than respondents from either Lubombo or Shiselweni (p value = 0.014). These findings are consistent with the results of the SDHS of 2008. According to the SDHS, across the regions, men and women in Manzini are better educated than those in other regions, and likewise men and women in Lubombo are the least educated.
The SDHS also showed that educational attainment is positively related to the wealth status of the household and Manzini and Hhohho are the most endowed regions in the country, and among the four regions, households in Manzini and Hhohho are more likely to fall in the highest wealth quintile than those living in the other regions (Central Statistics Office (CSO) [Swaziland] and Macro Inc, 2008:23). In addition, the male respondents were more likely to be more educated than female counterparts were (p value = 0.014). Although the results from the general population showed slight differentials between sexes in the levels of education attained, with men generally having higher educational levels (Central Statistics Office (CSO) [Swaziland] and Macro Inc, 2008:11).

5.2.1.5 Employment status and profession (Job type)

Only 40% of the respondents were in employment at the time of the study. About half of the respondents had not had a job in the past year. These results mirror the population level findings of the SDHS of 2008 (Central Statistics Office (CSO) [Swaziland] and Macro Inc, 2008:23) where 40% (versus 40% in this study) of the population had current employed and 50% did not have employment in the preceding 12 months (versus 48.0% in this study). In this study, about 10% were minors. According to the results, the highest proportion of the respondents, 30%, were in the unskilled manual category and 19% had a professional managerial/clerical job. Respondents employed in the mining sector or working as machine operators constituted 4.6% of the study sample and those in the sound/music industry constituted 1%. In comparison to the findings of the SDHS, with six occupational categories under which those currently employed: professional, technical, and managerial; clerical; sales and services; skilled manual; unskilled manual; and agricultural, the results are contrary. In the SDHS, the majority of currently employed women worked in sales and services (56 percent) and for the men were evenly employed in sales and services and as skilled manual labourers (29 percent and 32 percent, respectively). Some professions expose the population to excessive noise, and unless noise levels are controlled or the workers wear protective gear, such employees will be at risk of noise induced hearing loss that can potentiate ototoxic hearing loss.
5.2.1.6 Marital Status and religious affiliations.

According to the findings of this study, the combination of the marrieds and those living together constituted about 50% of the respondents in the sample, reflecting an almost even distribution with the never married among the respondents, 79 (46%) and 76 (44%) respectively. The Zionist religion constituted the largest religious affiliation among the respondents at 22.5% (39) followed by the Charismatic Christians, 20.8% (36) and the Pentecostals, 17.3% (30). The SDHS also found that the Zionist religion was the largest religious affiliation in Swaziland at 37% (Central Statistics Office (CSO) [Swaziland] and Macro Inc, 2008:28).

5.2.2 Clinical parameters of the respondents

5.2.2.1 HIV status and comorbid conditions among respondents

One hundred and thirty six (78%) of the study patients were HIV positive and 37 (22%) HIV negative. One hundred and thirty-four (99%) respondents were aware of their HIV status at the time of enrolment and 133 (98%) respondents were taking HIV treatment. The very high number of HIV positive respondents was expected given that Swaziland has the highest HIV prevalence in the world, at 26% in the age group 15-49 years (Central Statistics Office (CSO) [Swaziland] and Macro Inc, 2008). Tuberculosis is also often associated with HIV. The finding that 78% of the respondents were HIV positive confirms the impact of HIV on tuberculosis incidence (Lawn, Bekker, Middelkoop, Myer & Wood 2006:1040; Wells, Cegielski, Nelson, Laserson, Holtz, Finlay, Castro & Weyer 2007:S86). Routine MOH statistics show that the prevalence of HIV among TB patients is 80% (Swaziland Ministry of Health 2010:23). Female respondents were more likely to be HIV positive than male respondents with (p value = 0.044). The results reflect the national picture. A recent population-based study where measures of HIV prevalence were produced and compared against similarly measured HIV prevalence estimates from the 2006-7 SDHS showed an HIV prevalence of 39% among females aged 18-49 years and 24% among males of the same aged group (Bicego et al 2013).
Multiple morbidities (MM) are common in patients with MDR-TB increasing complexity and the impact on health services, providers and patients, and opportunities for chronic diseases screening in a population linked to care. In one study, 22.6% of the patients in a high HIV/TB setting presented with MM (Oni, Youngblood, Boulle, McGrath, Wilkinson & Levitt 2015:1). In this study, MM were found as follows: i) five respondents (3%) had high blood pressure and all were female but only one was on medication for hypertension; ii) four respondents (2%) had diabetes mellitus and they were all male but only two were on anti-diabetic treatment; and iii) four patients (2%) had known renal disease (2 males, 2 females).

Diabetes Mellitus is one of the commonest co-morbidity in patients with tuberculosis. (Kang, Kim, Jo, Kim, Park, Kim, Kim, Lee, Lee, Park, Koh, Kim & Shim 2013:472). Other respiratory conditions may also exist although this study did not find any, and the functional status may require additional rehabilitation (Godoy, Mello, Lopes, Costa, Guimaraes, Pacheco Castanho & Menezes 2012:1949).

Because of the MM, respondents who were HIV positive also received antiretroviral medicines for treatment of HIV in addition to the medications for MDR-TB. The majority of the HIV positive respondents were on a Tenofovir based regimen (59%), followed by the Zidovudine based regimen (11%), Abacavir based regimens (06%) and the Stavudine based regimens (04%). One hundred and twenty (122) HIV patients were on Efavirenz and only 10 on Nevirapine. Current WHO guidelines recommend that patients on rifampicin should not receive Nevirapine because of the drug-to-drug interaction and bioavailability of Nevirapine when co-administered with anti-TB medicines (World Health Organization 2014a). The reduction of nevirapine concentrations with concomitant rifampicin is greater than with Efavirenz, particularly during the lead-in dose period when subtherapeutic concentrations occur in the majority of TB patients (Maartens, Decloedt & Cohen 2009). The number of respondents on Nevirapine was lower than anticipated because MDR-TB regimen does not contain rifampicin as efavirenz is preferred to Nevirapine (Bonora & Di Perri 2008:306).
5.2.2.2 Life style characteristics: smoking and drinking

The majority of the respondents 155 (89.6%) did not smoke, three were current smokers and 12 were previous smokers. Current smoking was defined as currently smoking or stopped smoking less than 6 months while previous smokers were defined as those who had not smoked for at least 6 months after quitting smoking. Smoking impacts treatment outcomes like bacteriological conversion during treatment (Magee, Kempker, Kipiani, Tukavadze, Howards, Narayan & Blumberg 2014:1) and some studies suggest that second smoke could be associated with hearing loss (Fabry, Davila, Arheart, Serdar, Dietz, Bandiera & Lee 2011:82-5; Lalwani, Liu & Weitzman 2011b:655). Strict prevention of children exposure to second-hand smoke should be encouraged by every means because of its impact on hearing which could be augmented when ototoxic drugs are administered (Talaat, Metwaly, Khafagy & Abdelraouf 2014:46-9).

The majority of respondents, 135 (78%) reported no history of drinking alcohol. Three respondents, all males, were current drinkers. Twenty-six (26) males and six females were previous drinkers (18.5%). This finding raises concern as all patients on medication are advised not to take alcohol. Moreover, an association of drinking and hearing loss has been reported in students (Li, Zhang, Li & Guo 2014:1499).

5.2.2.3 Exposure to noise among respondents

In this regard, the results show that at least 46% of the respondents had noise exposure at the work place or during leisure. This is likely to impact on the incidence of hearing loss given that noise is a well-known risk factor for noise induced hearing loss. Noise potentiates aminoglycoside induced hearing loss (Li &Steyger 2009b:26-32). Men were more likely to be exposed to noise at the work place and during leisure than women were (p value = 0.002). The possible explanation is that men are likely work with machines, in the mines or sound industry that exposes them to excessive noise.
5.2.2.4 **Weight of respondents**

The modal weight band of the respondents was 50-59k kg while the baseline average weight was 51.7kg (95% CI: 49.16-54.40).

5.2.2.5 **History of Exercise among respondents**

Only 10% of the study respondents reported involvement in regular exercise prior to their illness (at least once or twice a week). Women were not likely to engage in any form of exercise or exercise less than once a month.

5.3 **DISCUSSION OF INFERENTIAL STATISTICS**

5.3.1 **Incidence of hearing loss**

The first objective of the study was to establish the incidence of hearing loss among MDR-TB patients in Swaziland. According to the study results, the majority of the patients developed hearing loss as follows: overall 94 respondents out of 159 (60%); 74 out the 123 (60.1%) of the HIV positive respondents and 23 out of 37 (55.6%) the HIV negative respondents respectively developed hearing loss during the injectable phase of DR-TB phase. The incidence of hearing loss among male was higher than females (p value=0.03), among those exposed to noise at work than the exposed during leisure (p value=0.02), and in those with job type of a miner, a machine operator or driver.

The incidence of hearing loss in this study is similar to what falls within the range of other studies within the southern Africa region. Van der Walt et al (2013) report a hearing loss of 38.9% in South Africa. On the other hand, two studies in South Africa have reported slightly different incidences. Ramma and Ibekwe respectively (2012) reported an incidence rate of 47% in South African patients in Cape Town, while Harris et al (2012) reported incidences of 40% among HIV negative patients and 70% among HIV positive patients in Mpumalanga. In Botswana, Modongo (2014:1)
found hearing loss incidence of 62% among study respondents on MDR-TB in a retrospective study.

While other studies in the literature do not provide for incidence rates, this study results indicate a general crude incidence rate for high frequency hearing loss (HFHL) of 4.1/1 000 person days of observation (CI 3.3-5.0/1 000). The incidence rate among the HIV positive patients was 4.2/1 000 person days (CI: 3.4-5.3) and for HIV negative patients, 3.6/1 000 person days (CI: 2.4-5.7).

Incidence of hearing loss was a result of direct measurement of hearing sensitivity, and incident cases defined the comparisons between the baseline and follow-up audiometry based on criteria for defining cases found in section 3.3.2.7. It is important to note that usually it is the frequencies of 250-8 000 Hz that are used in hearing sensitivity testing because that is the range representing most of the speech spectrum, although the human ear can detect frequencies from 20-20 000 Hz.

Studies show that early ototoxicity corresponds with damage to hair cells in the basal region of the cochlea, where higher frequency sounds are processed. Animal studies have also shown that ototoxic damage progresses from high to low frequencies. Testing for high frequency hearing sensitivity was prioritised because it tests the highest audible frequencies within the speech range; allows for early detection of ototoxic changes and the detection of hearing changes before the lower frequencies necessary for understanding speech are affected (Audiology 2009; Fausti, Henry, Schaffer, Olson, RH. and WJ., 1992:1026-32; Fausti et al 2005:52).

This paragraph puts the discussion in the preceding paragraph in context. High frequency hearing loss affects a person’s ability to hear the consonant sounds of F, S, T, and Z, differentiating words that sound alike, especially words that contain S, F, SH, CH, H, TH, T, K or soft C sounds, and higher octaves, like a woman’s or a child’s voice, or a bird chirping. Therefore, loss of hearing in those frequencies makes the sounds harder to discern although they can hear vowels well (Berke 2014:[Sa], Crawford, 2012:[Sa]). On the other hand, low frequency hearing loss makes it difficult for the individual to hear sounds in frequencies 2 000 Hz and below although they may still hear sounds in the higher frequencies (Berke 2014:[Sa]).
to that, people with low frequency hearing loss can still understand human speech well. Audiograms were used to record hearing sensitivity of the respondents in this study and provide a good indication of the degree of hearing loss with pure tones. However, they do not provide details on the person’s ability to understand speech. An innovative technique; “the speech banana", superimposes the audiograms over a mapped conversational speech on an audiogram (the "speech banana"), and provides more information to interpret the results (Figure 5.1). Figure 5.1 shows that vowels fall in the "louder" ranges, and they lie lower on the chart. On the other hand consonants are higher-pitched than vowels, and they lie more to the right on the chart, higher on the chart and in the lower decibel ranges (Constantine 2011). Furthermore, Figure 5.1 portrays a normal sloping to profound hearing loss in the left ear and moderate to severe hearing loss in the right ear. In this regard, the patient can hear no conversation in the right ear. The left ear, however, hears all but the soft, upper frequency consonants.

![Figure 5.1: Speech banana superimposed on an audiogram showing different hearing losses in the left and right ears](image)

Figure 5.1: Speech banana superimposed on an audiogram showing different hearing losses in the left and right ears
On the contrary, Figure 5.2 shows bilateral mild sloping to profound hearing loss in a child. With only a few consonant and vowels sounds audible, this child would miss most of the distinguishing speech features.

![Audiogram](image)

**Figure 5.2**: Speech banana superimposed on an audiogram showing similar bilateral hearing losses in the left and right ears

### 5.3.2 Risk factors for high frequency hearing loss

As part of explanatory analysis of this study, statistical methods utilised temporal associations to establish the risk factors and determinants for hearing loss among the cases. According to WHO:

“A risk factor is any attribute, characteristic, or exposure of an individual that increases the likelihood of developing a disease or injury”

-(World Health Organization, [Sa]-b)

Risk factors are variables with a lower likelihood of a positive outcome and higher likelihood of undesirable outcomes. In order to establish whether an association exists or not between hearing loss and the independent variable, Chi square statistics as the measure of association. High frequency hearing loss was the dependent variable and the independent variables were characteristics in the socio-demographic, clinical or lifestyle profiles of the respondents.
According to the results of the study, on bivariate analysis, Age group (p value=0.02), gender (p value =0.2), job type (p value =0.003), ARV regimen (p value =0.004), Haemoglobin level (0.039) and body mass index (0.018) were significantly associated with hearing loss.

The association between age and hearing loss is documented. Patients who developed auditory toxicity were significantly older (p value =0.01) in a randomised trial (Gatell, Ferran, Araujo, Bonet, Soriano, Traserra & SanMiguel 1987:1383). It appears that damage is more significant in the elderly who may have fewer hair cells at the beginning of treatment or lower endogenous protective mechanisms than other individuals with compromised auditory function (Rybak 2007:364, Rybak & Whitworth 2005:1313). On the contrary, a study in Cape Town on cochlea-vestibular clinical and audiometric findings among XDR and MDR-TB patients did not find an association with age and sex (Ramma & Ibekwe 2012).

The association between gender and hearing loss as been documented. A study in Iran found the hearing loss among men was higher than among women (Javadi et al., 2011:905). In this study, all the diabetic patients developed hearing loss, all of whom where female respondents. It appears that the development of hearing loss was more associated with the existence of diabetes mellitus (DM). No statistically significant association between hearing loss and DM was found because of the small sample. Suboptimal glycemic control was also associated with a nearly threefold increased risk of high-frequency hearing impairment (Akinpelu et al 2014:767; Bainbridge & Cowie 2009; Oh et al 2014; Sogebi 2013:244). It is postulated that some of the mechanisms by which hearing is affected in diabetic patients include thickened vessels of the stria vascularis and the internal auditory artery, as well as demyelination of the eighth cranial nerve (Carrasco et al 1990:411; de Moraes Marchiori et al 2006:533).

While there was an association between hearing loss and dyspnoea and noise exposure, the association was not statistically significant for either, (p value =0.054) for dyspnoea on admission and (p value =0.078) for noise exposure respectively. The implications of this finding although not statistically significant, that whenever
hazardous noise exists in the workplace, patients on MDR-TB treatment are vulnerable to the additive effect of the aminoglycosides. To this end, measures are required to reduce noise levels as much as possible to protect exposed workers. Measures are also required to monitor the effectiveness of hearing loss prevention programmes at the workplace because noisy environments potentiate susceptibility to noise induced cochlear damage (Fausti et al 2005).

The mechanism for noise induced hearing loss and/or potentiation of aminoglycoside SNHL is that excessive sound (unprotected exposure above 95dBA) damages the hair cells and the blood supply in the cochlea, (Dobie, 2008:565, 2005a:630; Rabinowtz 2012:14; Thurston 2013:367). The damage may directly result from the noise, or indirectly from very high levels of continuous sound, that causes vasoconstriction of the vessels of the stria vascularis in the cochlea blood supply. This renders the hair cells relatively anoxic and thus secondarily damaged. The amount and type of direct hair cell damage depends on the intensity of the sound and level of damage due to aminoglycosides and noise exposure will increase hearing thresholds, resulting in threshold shifts toward higher values (poorer hearing) (Li & Steyger 2009a:26-32).

The results of the study show that occupation/job type are associated with SNHL. The explanation for such association of job type and hearing loss is not very clear. One study in the gold mines found that patients had a higher occurrence of hearing loss than the controls from non-gold mines. However, patients with multiple treatments for TB were at even a higher risk (Brits, Strauss, Eloff, Becker & Swanepoel 2011). A study in US marines and other trades suggests that excessive noise exposure and lack of hearing protection and the major risk factors to hearing loss difference across occupations (Abel 2005:1128). Hence, these statistically significant results could point to men’s risk behaviour of exposure to unprotected noise at work in mining, undocumented genetic predisposition or other risk factors that are associated with the male gender. These are collaborated by findings in a 16 year cohort study that documented changes to hearing acuity that exceeded 15 dB at high frequencies in 42.8% of men and 27.7% of women (Marlenga, Berg, Linneman, Wood, Kirkhorn & Pickett 2012:479). Analyses of risk factors for NIHL showed that risks increased in association with higher levels of the most common
recreational and occupational noise sources, as well as chemical exposures with ototoxic potential. Use of hearing protection and other safety measures, appeared to offer some protection hearing conservation programmes should focus on a broader range of exposures, whether in occupational or non-occupational settings, and some priority exposures could include gunshots, chainsaws, power tools, smoking and potentially some chemical exposures (Marlenga et al 2012).

Reasons for low haemoglobin being associated with hearing loss are not clear. The possibility of anoxia to the hair cells in the cochlea. In a study to investigate effect of blood parameters in patients on Cisplatin (an anti-cancer ototoxic medicine) found that decreased serum albumin level, haemoglobin level, red blood cell count, and haematocrit were associated with an increased likelihood of significant hearing loss during chemotherapy (Blakley, Gupta, Myers & Schwan 1994:541).

5.3.3 Univariate regression analysis for risk factors for high frequency hearing loss

In addition to bivariate analysis, the results of the univariate regression analysis indicated that the following were risk factors for DR TB treatment related sensorineural hearing loss.

- being of male gender (p value =0.033),
- poor baseline hydration status at the start of MDR-TB treatment (p value =0.012),
- use of Abacavir as backbone in the ART regimen in MDR-TB (p value =0.017), and
- low of <8 g/dl baseline HB (p value <0.001), low BMI (p value =0.003), presence of dyspnoea at the start of treatment (p value < 0.001 ) were found to be risk factors for high frequency hearing loss.
5.3.4 Multivariate analysis for risk factors for high frequency hearing loss

The Cox regression model was used to control for confounders. According to the study results, the following variables were dropped: education, religion, noise, body-mass index, regimen for HIV, religion, and CD4 count. Variables retained in the model with statistically significant relationship with high frequency hearing loss were as follows:

- Compared to agriculture as a day-to-day employment, the hazard ratio of high frequency hearing loss was 4.2 times in the Miners/machine Operators and Sound Industry (HR: 5.4, CI 1.2-24.03, p value =0.024)
- Patients who had dyspnoea at initiation of MDR-TB treatment were 3.4 times likely to develop high frequency hearing loss (HR: 3.4, CI 1.8-6.3, p value =0.000).
- Low baseline haemoglobin was a risk factor for hearing loss (p value<0.01). Patients with HB 8-11 g/dl and those with HB less than 8g/dl were 2 times and 8.5 times respectively more likely to develop hearing loss compared to those with HB above 11g/dl (p value <0.01).

5.3.5 Salient features of the results

In this study, 172 respondents were on Kanamycin as the injectable aminoglycoside and only one respondent on Amikacin, hence unable to compare types of drugs as risk factor for hearing loss. However, it appears that studies where amikacin was the predominant drug, incidence of SNHL was higher as reported in Javadi et al, 2011; Modongo et al, 2014 Sturdy et al (2011). This study found bacteriological status of confirmed Rifampicin resistance on GeneXpert was associated with MDR-TB hearing loss (p value= 0.078) but not a statistically significant risk factor. In children, bacteriological confirmation was a risk factor for hearing loss (Seddon et al 2013:320).

This study further revealed that no respondents had a family history of hearing loss. However, genetic predisposition and family history of ototoxicity has been implicated
in predisposing certain individuals to future ototoxicity (Jing et al 2014). Sickle-cell disease also predisposes to a significant incidence of sensorineural hearing loss (SNHL) in SCD patients (36.95%), although the patients maybe clinically asymptomatic (Al Okbi et al 2011:392). The mechanism for this seems to be linked to ischaemia (Przewonzy, Gasecki, Narozy & Nyka 2008:745). Przewonzy et al (2008:745) found that the highest risk for hearing loss in a group of patients experiencing the early stage of ischemic stroke were age above 60 years, male gender, bilateral ischaemic focuses and arterial hypertension.

5.3.6 HIV and High frequency hearing loss

5.3.6.1 Incidence of Hearing loss and HIV serostatus, ART treatment and level of immunosuppression.

In this study, while the general incidence in the sample was 94 out of 159 (60%). The incidence of SNHL among the HIV positive patients was 60.1%, while it was 55.6% among the HIV negative patients. The incidence rate was 4.2/1 000 person days (CI: 3.4-5.3) among the HIV positive respondents and for HIV negative respondents, it was 3.6/1 000 person days (CI: 2.4-5.7). While there was preponderance by HIV positive respondents for SNHL, there was no statistical difference in the hazard rates (p value =0.59). In South Africa, 70% of the HIV positive patients MDR-TB patients developed SNHL compared 40% HIV negative MDR-TB patients (Harris et al 2012:363). In Botswana, while bivariate analysis of data indicated an association between HIV infection and SNHL, among MDR-TB association disappeared after adjusting for confounders (Modongo et al 2014).

Studies suggesting the association between hearing loss and the HIV status, level of immune suppression and ARV have been inconclusive. While one study to detect differential HIV effects for Low-frequency pure-tone average (LPTA) at 250, 500, 1000, and 2000 Hz and high-frequency PTA (HPTA) at 3000, 4000, 6000, and 8000 Hz found poorer low frequency and high frequency hearing in HIV positives than HIV negative adults (Torre, Hoffman, Springer, Cox, Young, Margolick & Plankey 2014a). On the contrary, another study on distortion product acoustic emissions, found that poorer cochlear function was not associated with HIV status (Torre, Hoffman,
Springer, Cox, Young, Margolick & Plankey 2014). This has led some scientists to postulate that the changes that HIV/AIDS patients might have in the conventional audiological assessment and high frequency audiometry may suggest involvement of both the peripheral and central auditory pathways (Assuiti et al 2013:248-255).

According to the results of this study, ARV regimen was associated incidence with MDR-TB treatment related hearing loss (p value =0.017).

ART regimen containing abacavir (ABC) back bone, has survival distributions that were statistically significant.

There are some postulations that ARVs could be ototoxic; and if used in combination with aminoglycoside antibiotics used in the treatment of MDR-TB, the possibility of additive ototoxic is high. This study investigated the association between the co-administration of ART and MDR-TB treatment and hearing loss in order to determine the additive ototoxicity between aminoglycoside and ARV and abacavir containing regimens were shown to be associated with hearing loss. Khoza-Shangase (2011:145-53) shows statistically and clinically significant association was obtained for distortion product otoacoustic emissions (DPOAEs) among patients on HAART, particularly at high frequencies suggesting subclinical hearing loss on DPOAEs although they had normal pure tone function after six months of follow up. Van de Walt et al (2013) found that HIV-infected per se, did not predispose a patient to experience severe adverse drug reactions (SADRs) including sensorineural hearing loss for patients on MDR-TB treatment. Their study confirms that the rate and range of SADRs amongst HIV-infected ART naive and uninfected patients are similar. In fact, HIV-uninfected cases experienced slightly more, (1.35) serious adverse drug reactions on average, compared to the 1.25 in HIV-infected cases (Van der Walt et al 2013). Schouten found no association between NRTI with hearing in a prospective study (Schouten et al 2006).

The study investigated the impact of CD4 on MDR-TB treatment related hearing loss (MDR-TB-TR-HL). Because number of cases were CD4 taken during this period was very low, the study did not analyse those data during the development of this report, and hence we cannot ascertain whether there is/no association. A study by Van der
Westhuizen, Swanepoel de, Heinze and Hofmeyer (2013) on audiological and ontological manifestations in adults with HIV, found a general increase in SNHL that becomes statistically significant towards the advanced stages of HIV disease progression when compared to the HIV negative. Thus, it is plausible that the HIV infection by itself does not lead to a higher risk of developing hearing loss but is likely associated with other factors that, by themselves or in combination increase the patient’s risk of AG-induced hearing loss.

5.4 SURVIVAL ANALYSIS AND TIME TO HEARING LOSS

In 1964, Gerald Caplan introduced the trilogy dealing with prevention and control of mental disorders. He introduced the concepts of primary, secondary and tertiary prevention whereby primary, secondary and tertiary prevention programmes focus on different aspects of the natural history of disease, while program planning, staffing and staff training are discussed from a standpoint of prevention (Caplan 1964). In its application to the subject of interest in this study, primary prevention aims at inhibiting the development of hearing loss before it occurs, ideally, either through preventing MDR-TB or avoidance of ototoxic medications in the management of MDR-TB. Time to hearing loss is an important variable in secondary prevention that aims to identify and detect hearing loss in its earliest stages before it is noticeable, when it is possible to prevent progression or minimise complications. Screening for the earliest signs of decrease in hearing sensitivity achieves secondary prevention and the time to hearing loss is useful in determining optimum intervals for screening for ototoxicity. The results were presented using survival distribution in Chapter 4 and are discussed in this section. Where it is not possible to prevent or ameliorate hearing loss, the purpose of tertiary prevention is to improve the quality of life for people by rehabilitation (therapy to restore functionality and self-sufficiency) among people already affected by a disease in order to mitigate catastrophic outcomes (Caplan 1964)
5.4.1 Survival analysis and time-to-hearing loss

The life table, survival distribution, and Kaplan-Meier survival function estimation are all descriptive methods for estimating the distribution of survival times from a sample. Survival analysis offers regression models for estimating the relationship of (multiple) continuous variables to survival times. In this study, we used the cumulative proportion surviving (survival function). This is the cumulative proportion of cases surviving hearing loss up to the respective interval. Since the probabilities of survival are assumed independent across the intervals, the probability is computed by multiplying out the probabilities of survival across all previous intervals (Rich, Neely, Paniello, Voelker, Nussenbaum & Wang 2010:4). The resulting function is also called the survivorship or survival function. The researcher started by calculating the median survival time. This is the survival time at which the cumulative survival function is equal to 0.5 (50th percentile). The 50th percentile (median) for the cumulative survival function is usually not the same as the point in time up to which 50% of the sample survived, given that censoring, is observations prior to this time. In general, the median time to high frequency hearing loss (high-tone average 4 and 8kHz) was 84 days (IQR=55-157 days) for middle frequency hearing loss frequency (the pure-tone middle-tone average; 0.5, 1, 2 and 4 kHz) the median time was 98 days (60-158 days). No studies were found in literature to have investigated this construct.

Typically, survival analysis is linked to the hazard rate defined as the probability per time unit that a case that has survived to the beginning of the respective interval will fail in that interval. Specifically, it is computed as the number of failures per time units in the respective interval, divided by the average number of surviving cases at the mid-point of the interval.

In this study we used Kaplan-Meier Product-Limit Estimator to estimate the survival function directly from the continuous survival or failure times (Rich et al 2010:331-6). Multiplying out the survival probabilities across the "intervals" (i.e., for each single observation) gives us the survival function:
\[ S(t) = \prod_{j=1}^{t} \frac{(n-j)}{(n-j+1)} \delta(j) \]

Where:

- \( S(t) \) is the estimated survival function,
- \( n \) is the total number of cases, and,
- \( \prod \) denotes the multiplication (geometric sum) across all cases less than or equal to \( t \);
- \( \delta(j) \) is a constant that is either 1 if the \( j \)th case is uncensored (complete), and 0 if it is censored.

- (Kaplan & Meier 1958)

### 5.4.1.1 Gender: Survival analysis and time-to-hearing loss

The results from the analysis of the study showed that males have a high hazard rate for SNHL than the females and hence worse off survival for high frequency hearing loss while on MDR-TB treatment than females (\( p \) value=0.03). There are no previous studies from the literature to explain the observed difference.

### 5.4.1.2 Age: Survival analysis and time-to-hearing loss

The results also indicated that the age group 50-69 years had poorer survival when compared to the younger age groups (\( p \) value =0.02). While some of the literature collaborates this finding, the finding has not been consistent across all studies. Presbycusis is proposed as one of the mechanisms (Langer et al 2013:458; Mudd 2012)

### 5.4.1.3 Survival analysis and the Clinical parameters

Survival analysis for key clinical parameters mirrors the findings discussed in Section 5.3.2. No distinct difference by HIV status was observed in survival distribution (\( p \) value =0.59). However, when survival by ART regimen were compared using NRTI
backbone, there was statistical significance among the regimens. Patients on Abacavir had a higher failure rate when compared to TDF based regimen.

Underweight patients and patients with low haemoglobin level fail at faster rates than normal patients with normal BMI (p value=0.01) and haemoglobin level above 11 g/dl (p value <0.01). The explanation is provided in section 5.3.2.

Presence of dyspnoea is associated with higher rates of failure when compared with absence of dyspnoea at the start of treatment (p value <0.01)

5.4.2 Time to event analysis and optimal frequency for audiology

The diagnosis of hearing loss occurred at a median time of 84 days (IQR, 54.5-120 days) in those confirmed by audiogram. This is the first prospective study to date to examine meticulously the time it takes for persons on MDR-TB treatment to develop hearing loss.

5.5 HYPOTHESES TESTING

5.5.1 Interpreting the Hypothesis

<table>
<thead>
<tr>
<th>P-value</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>P &lt; 0.01</td>
<td>Very strong evidence against H0</td>
</tr>
<tr>
<td>P &lt; 0.05</td>
<td>Moderate evidence against H0</td>
</tr>
</tbody>
</table>
**Study hypothesis 1:**

The incidence ratio of sensorineural hearing loss during the intensive phase of MDR-TB treatment increases proportionally with the duration of treatment.

If incidence ratio of sensorineural hearing loss is stated as \(a/b\) and the duration of treatment is stated as \(d\)

The study hypothesis can be stated as \(a/b \propto d\)

**Null hypothesis 1:**

“There is no relationship between the incidence of hearing loss among MDR-TB patients on MDR-TB treatment and the length of treatment during the intensive phase of MDR-TB treatment”

Likewise, the null hypothesis can be stated as \(a/b \not\propto d\)

**Study hypothesis 2**

MDR-TB patients living with HIV infection have a higher incidence ratio of sensorineural hearing loss than HIV negative MDR-TB patients during the intensive phase of MDR-TB treatment.

- If the Incidence ratio of SNHL in HIV positive MDR-TB patients = \(\lambda_1\)
- And If the Incidence ratio of SNHL in HIV negative MDR-TB patients =\(\lambda_2\)
- Then study hypothesis can be restated as \(\lambda_1 > \lambda_2\)

The results show that other factors influenced incidence of MDR-TB related hearing loss than the length on MDR-TB treatment.

Conclusion: the results of the study fail to reject the null hypothesis 1.
Null hypothesis 2:

“There is no difference in the incidence ratio of sensorineural hearing loss in MDR-TB patients living with HIV and MDR-TB patients who are HIV free during the intensive phase of MDR-TB treatment.

- If the Incidence ratio of SNHL in HIV positive MDR-TB patients = $\lambda_1$
- And If the Incidence ratio of SNHL in HIV negative MDR-TB patients = $\lambda_2$
- Likewise the null hypothesis can be restated as.........................$\lambda_1 = \lambda_2$

Based on Figure 5.1 Incidence ratio of hearing loss among the HIV positive MDR-TB patients is not statistically significant from the incidence ratio of SNHL among the HIV negative respondents. P value =0.59

Conclusion: the results of the study fail to reject the null hypothesis 2.

5.6 SUMMARY AND CONCLUSION

This study reveals that the MDR-TB treatment-related high frequency hearing loss in Swaziland is one of the highest in the region. Of 159 respondents, 94 developed high frequency hearing loss. Total observation time was 22,032-person. The findings are in consonance with the findings in other parts Southern Africa. In Botswana, Madongo et al (2014) reports an incidence of 62%, while in South Africa, Harris and others (2012) report a hearing loss incidence of 57%. Risk factors for development of hearing loss were male gender, occupation as a miner, low haemoglobin level, HIV treatment with Abacavir regimen and presentation with dyspnoea. The median time for development of hearing loss ranged from 54.5 days to 147 days.
CHAPTER 6

DEVELOPMENT OF BEST PRACTICE GUIDELINES TO MONITOR AND PREVENT HEARING LOSS RELATED TO DRUG RESISTANT TUBERCULOSIS TREATMENT

6.1 INTRODUCTION

Guidelines are “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances” - (Shekelle, Woolf, Grimshaw, Schunemann & Eccles 2012).

Good guidelines serve as a quality improving strategy but barriers to implementation must be removed for guidelines to be successful (Wallen, Mitchell, Melnyk, Fineout-Overholt, Miller-Davis, Yates & Hastings 2010). The previous chapter discussed the findings and conclusions drawn from the analysis of the empirical study. In this chapter, best practice guidelines to monitor and prevent hearing loss related to DR-TB are developed. The chapter starts with the background and the theoretical framework underpinning this study. Subsequently, the justification for the development of the best practice guidelines and the development of the best practice guidelines in order prevent permanent hearing loss through raised awareness, monitoring, and prevention of ototoxicity.

In chapters 4 and 5, the study results revealed that patients on MDR-TB treatment in Swaziland are at risk of developing permanent sensorineural hearing loss. In chapters 1 and 2 this study also revealed that there are no clear best practice guidelines available to the various cadres of health care workers involved in the management of MDR-TB patients, hospital managers involved in the allocation of resources and the affected patients and their families. In South Africa, a recent study revealed that 80-100% of the health care workers managing TB did not inquire about family history of hearing impairment and that 74% of the health care workers lacked awareness about ototoxicity and hearing loss associated with MDR-TB.
treatment (Khoza-Shangase 2013:2140). Yet loss of hearing can be one of the most catastrophic adverse drug reaction experienced by patients. Hearing loss refers to any reduction of, or difficulties with hearing. Hearing loss is caused by dysfunctions anywhere along the auditory pathway. There are three general categorisations of hearing loss: based on where in the ear the impairment is located (the type of hearing loss), the severity of the impairment that affects a person’s hearing sensitivity (the degree of hearing loss), and which ears are affected (the configuration or laterality of the hearing loss). In South Africa, the finding in the study referred to earlier that only 9% of the health care workers provided information on ototoxicity monitoring to their patients and lack of awareness on their role or that of the audiologist in monitoring ototoxicity was partly due to lack of guidelines and protocols.

The situation in Swaziland concerning ototoxicity monitoring is not much different from that in South Africa. This current study found lack of guidance at the MDR-TB treatment sites on how to assess patients for hearing loss and what to do to minimise hearing loss in their patients. The proposed best practice guidelines are for various cadres of health care workers involved in the management of MDR-TB patients and hospital managers. The best practice guidelines will service as a road map to guide nurses, doctors, audiologists, hospital managers, pharmacists and policy makers in determining the appropriate course of action when faced with the need to address conserve hearing loss in patients on MDR-TB.

6.2 BACKGROUND OF THE STUDY

The development of the best practice guidelines addresses the fifth objective of the research study that investigated the incidence of MDR-TB treatment related hearing loss in Swaziland and best practices to monitor and prevent hearing loss related to DR-TB treatment. Best practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care (Shekelle et al 2012). Good guidelines serve as a quality improvement strategy (Wallen et al 2010:2761).
Tuberculosis (TB) is a major threat to public health, with a global incidence of approximately nine million, and a mortality rate of over one million per year (WHO 2013). In 2012, some 3.6% of newly diagnosed TB cases and 20% of those previously treated for TB had MDR-TB, translating to a global burden of 450,000 cases of MDR-TB. With increased use of molecular diagnostic tools (Al-Ateah, Al-Dowaidi & El-Khizzi 2012; Bodmer & Strohle 2012; Cauda 2014; Feasey, Banada, Howson, Sloan, Mdolo, Boehme, Chipungu, Allain, Heyderman, Corbett & Alland 2013) and availability of second line TB medicines, a larger proportion of MDR-TB patients are being treated (World Health Organization 2011c).

The injectable aminoglycoside and polypeptide antibiotics used in the treatment of MDR-TB can cause ototoxicity and irreversible sensorineural hearing loss (SNHL) in some patients which may even progress after treatment has been completed (de Jager & van Altena 2002; Seddon et al 2013).

Adult onset of SNHL is associated with disability and psychosocial effects, as well as reduced productivity and quality of life (Shield 2006). For example, affected individuals may have difficulty participating in social activities, enjoying music, speech discrimination and localizing sounds (Gates Mills 2005). Increased emotional dysfunction, depression, and social isolation have also been reported for all age groups (Boi, Racca, Cavallero, Carpaneto, Racca, Dall' Acqua, Ricchetti, Santelli & Odetti 2012; Skrbic, Milankov, Veselinovic & Todorovic 2013; Southall, Gagne & Jennings 2010; Southall, Jennings & Gagne 2011). Figure 6.1 presents a schematic on consequences of hearing loss on the victims.
The World Health Assembly resolutions of 1985 and 1995 called on member countries to develop strategies for prevention of hearing loss. According to the World Health Report of 2003, adult onset hearing loss was the second leading global cause of Years Lived with Disability (YLDs) in 2000 (Mathers et al 2010). Early detection and rehabilitation may prevent hearing loss and reduce YLDs. This study found easily modifiable risk factors of MDR-TB treatment-related hearing loss and these provide the basis of the best practice for use by clinicians and health care staff in resource-limited settings.

### 6.3 THEORETICAL UNDERPINNING OF THE GUIDELINES

The theories underpinning this study are discussed briefly here as they have been dealt with in Chapters 1 and 2. Refer to Figure 6.2 and 6.3.
Figure 6.2: The Neuman Systems model

Source: (Freese & Lawson 2010)
Figure 6.3 Enhanced ADR monitoring framework

Briefly, the study framework by Neuman’s System model of nursing (NSM) provides a useful best practice model for monitoring and prevention of sensorineural hearing loss (SNHL) in MDR-TB patients in the following manner (Geib, 2010, Neuman, 2002).

- First, according to the model, medical and nursing goals are guided by the development of comprehensive diagnoses, determination of appropriate interventions, evaluation of outcomes, and mitigating possible harm. The patients and caregivers form a partnership relationship to negotiate desired outcome goals of optimal health retention, restoration and maintenance.

- Second, multiple factors in the medical, work, family, and developmental history of the patient, as well as the pathophysiology and sociocultural realm influence the incidence of SNHL. From a hearing preservation perspective, the model suggests that clinical and nursing interventions occur through three prevention modalities based on Caplan’s concept of level of prevention (Caplan, 1964). Caplan described three levels of prevention for mental disorders but these are now widely applied to other disease conditions as well.
and these are primary, secondary, and tertiary prevention. WHO guidelines for ototoxicity prevention outline some of the actions for primary, secondary and tertiary prevention as illustrated in Figure 6.1 (Olusanya et al 2014b; World Health Organization 2006).

- Three, the clinical care of MDR-TB starts with assessment of the patient's physiological, psychological, developmental, socio-cultural and spiritual background, in order to conceptualise and analyse the patient's system, and to apply appropriate diagnosis, treatment goals and interventions. When SNHL is inevitable, mobilisation of external resources for assisted hearing, family and community support, and understanding may promote rehabilitation and function, as well as physiological and psychological health.

Table 6.1: WHO framework for hearing loss primary, secondary, and tertiary prevention

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
<th>Tertiary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ototoxicity</td>
<td>Avoidance of ototoxic drugs or only rational and prescribed use, use of antioxidants</td>
<td>Early detection and prompt management</td>
</tr>
<tr>
<td>Exposure to excessive and/or prolonged noise</td>
<td>Education, hearing conservation, enforceable regulations</td>
<td>Fitting of hearing devices (hearing aids, cochlear implants, etc.), hearing rehabilitation, training in sign language and special or inclusive education.</td>
</tr>
</tbody>
</table>

In this study, NSM in nursing practice is complemented by the Enhanced Monitoring Framework (EMF) for monitoring adverse drug reactions proposed by (Steinman et al 2011:1513-20). According to Steinman et al (2011:1513-20), team-based approaches for patient management are emphasised, integrating monitoring ADRs in clinical practice, use of health information technology and systems redesign (Figure
6.3). Key activities include tracking of laboratory tests, timely notification of physician of critical results, use of risk assessment tools and enhanced patient participation (Steinman et al 2011).

According to the enhanced monitoring framework, instead of the patient presenting with signs and symptoms and/or a disease diagnosis and the physician consulting evidence and guidelines in the prescribing process as in traditional method, the physician should consider medication prescribing is viewed as an ongoing process that begins rather than ends at the initial prescribing decision. Care quality is judged in part on the quality of monitoring for drug side effects, effectiveness, adherence, and therapeutic necessity, and whether the clinician makes appropriate changes to address any problems that are detected (Steinman et al 2011). In the context of hearing preservation, the framework puts teamwork, baseline assessments and continued monitoring, and documentation at the centre of prevention efforts for the permanent SNHL.

### 6.4 RATIONALE FOR THE BEST PRACTICE GUIDELINES

#### 6.4.1 Monitoring ototoxicity and prevention of hearing loss

Audiologic monitoring for ototoxicity may be performed for two purposes according to the (American Academy of Audiology 2009):

- early detection of changes to hearing status attributable to enable changes to be made to the drug regimen, and
- audiologic intervention when hearing impairment has occurred.

Health care practitioners must be aware of their roles and responsibilities in hearing preservation. Early intervention then becomes the responsibility of all health care practitioners through the implementation of primary, secondary and tertiary prevention. It is important to standardise the assessment of hearing for patients being treated for MDR-TB in the country. Such an approach improves clinical case
management. Standardisation includes the schedule and duration of testing as well as the testing methodology.

6.4.2 Enabling patients to report hearing loss

Health care practitioners must assist patients and their families to maintain effective communication where hearing loss occurs, particularly when speech frequencies are lost. Khoza-Shangase (2013: 2140-43) found that only 9% of health care practitioners inquired or provided information on ototoxicity and hearing loss.

6.4.3 Planning resources and ensuring availability of tools and resources for hearing screening and screening strategies

Audiometry is the preferred method for hearing assessment in adults and older children (Seddon et al 2012:1277). Testing is conducted in a sound-proof room or booth with headphones placed over the patient's ears. Frequencies tested are in the range of 125 to 8 000 Hz. Audiometry requires patient co-operation and concentration and is therefore appropriate for adults and children over 5 years of age with normal development. For those unable to co-operate with testing, it may be necessary to assess the patency of the neuronal auditory circuit and that involves measuring otoacoustic emissions (OAEs), which are small sounds continuously produced by a functioning cochlea.

In low resource settings, other available screening techniques for testing hearing sensitivity include physical diagnostic tests, such as the whispered voice, finger rub, and watch-tick tests (bearing in mind that many modern watches no longer audibly tick); single-question screening or longer patient questionnaires; and handheld audiometers.
6.4.4 Standardizing the categorisation of Hearing Loss

The World Health Organisation (WHO) defines disabling hearing impairment in adults as a permanent unaided hearing threshold level (average for frequencies 0.5, 1, 2, 4 kHz) for the better ear of 41 dB or greater (WHO 2001). In children under 15 years of age, disabling hearing impairment is defined as permanent unaided hearing threshold level (average for frequencies 0.5, 1, 2, 4 kHz) for the better ear of 31 dB or greater. However, many other standards are different.

The WHO also classifies hearing impairment into five grades in better ear and provides qualitative description (Olusanya 2008; Olusanya et al 2014b).

- Grade 0 is No impairment; 25 dB or better refers to no or very slight hearing problems.
- Grade 1 refers to slight impairment, and 26 - 40 dB the person is able to hear and repeat words spoken in normal voice at 1 metre. Counselling and hearing aids may be needed.
- Grade 2 is moderate impairment with a 41 - 60 dB range, and the person is able to hear and repeat words using a raised voice at 1 metre and hearing aids are usually recommended.
- Grade 3 is severe impairment with a threshold of 61 - 80 dB, and the person is able to hear some words when shouted into the better ear and certainly, hearing aids are needed. If not available, lip-reading and signing should be taught.
- Grade 4 is profound impairment including deafness and a threshold of 81 dB or greater. The person is unable to hear and understand even a shouted voice. Hearing aids may help understanding words but additional rehabilitation is needed, lip-reading, and sometimes signing may be essential.
6.4 PROCESS OF DEVELOPING THE GUIDELINES

This section discusses the steps followed in the development of the best practice guidelines to monitor and prevent hearing loss related to MDR-TB treatment. In Step 1, the researcher drew evidence for the formulation of the guidelines from the summary and conclusions of this study finding. In Step 2, the researcher also consulted key stakeholders through meetings during which findings from the literature review were presented.

Two models influenced the process of developing guidelines, namely: “A guideline on guideline development” (Ansari & Rashidian 2012) and a model developed in Eccles et al (2012) for developing clinical practice guidelines. This process is outlined below:

1. Defining the purpose and scope of the best practice guidelines;
2. Review of the findings of the empirical study;
3. Review of the literature;
4. Development of the first draft of the guidelines;
5. Establishment of the guidelines development group (GDG);
6. GDG review, discuss, reach consensus on first draft of guidelines and provide inputs. Revised guidelines produced;
7. Seek inputs from the reference group;
8. Present to stakeholders and validate the guidelines.

The details of the application of the process for the development of best practice guidelines are discussed in this section (see 6.5.1-6.5.8)

6.5.1 Defining the purpose and scope of the best practice guidelines

The purpose was established and scope developed by the researcher. Details are found in section 6.6.1
6.5.2 Review of the findings of the empirical study

The findings of this study are compiled and details are found in Section 6.6.2 of this thesis.

6.5.3 Review of the literature

Appraisal of the existing literature was conducted on an ongoing basis and details are found in Section 6.6.3 of this thesis.

6.5.4 Development of the first draft of the guidelines

The first draft of the guidelines was developed and shared with the guidelines development group for inputs. Details are outlined in Section 6.6.4 of this thesis.

6.5.5 Establishment of the guidelines development group (GDG)

The GDG worked on the draft guidelines over a couple of months, consulting widely and providing input into the best practice guidelines. The GDG consisted of ENT surgeon, audiologist, and audiology technician clinicians and clinical Advisors.

6.5.6 GDG review, discuss, reach consensus on first draft of guidelines and provide inputs. Revised guidelines produced

Consensus was achieved on the key guidelines before they were shared with the guidelines reference group.

6.5.7 Seek inputs from the reference group

The Reference group consisted of persons familiar with the subject matter and external to the GDG. Feedback from the GDG was incorporated into the draft prior to sharing with the stakeholder. However, the process of feedback remained open until the finalisation of the best practice guidelines.
6.5.8 Present to stakeholders and validate the guidelines

The draft of best practice guidelines were presented to 50 stakeholders on the 23 April 2015. Input was received and incorporated.

6.5 THE APPLICATION OF THE PROCESS FOR THE DEVELOPMENT OF BEST PRACTICE GUIDELINES

6.6.1 Defining the purpose and scope of the best practice guidelines for the monitoring and prevention of hearing loss associated with MDR-TB treatment

6.6.1.2 Explanation of best practice guidelines and the purpose

As defined in 6.1; best practice guidelines assist practitioner and patient decisions about appropriate health care for specific clinical circumstances” (Shekelle et al 2012). A best practice is a method or technique that has consistently shown results superior to those achieved with other means, and used as a benchmark. In addition, a "best" practice can evolve to become better as improvements are discovered. Best practices are used to maintain quality as an alternative to mandatory legislated standards and can be based on self-assessment or benchmarking (Bogan & English 1994). However, in clinical practice, a best practice guideline can be referred to as a clinical practice guideline, which is a document with the aim of guiding decisions and criteria regarding diagnosis, management, and treatment in specific areas of healthcare. Best practice guidelines are based on an examination of current evidence within the paradigm of evidence-based medicine (Medicine 2011; The Agree Collaboration 2003; Wikidepia). Guidelines are viewed as useful tools for making care more consistent and efficient and for closing the gap between what clinicians do and what scientific evidence supports (Burgers et al 2003).
6.6.1.3 **Scope of the best practice guidelines**

The main purpose of the best practice guidelines is to present a solution-focused effective and efficient approach towards early detection, management, and prevention of hearing loss among TB patients on MDR-TB treatment.

6.6.1.4 **Potential users of the guidelines**

The best practice guidelines have been primarily developed for health care personnel who are involved in managing TB patients such as the nurses, clinicians, doctors, and audiologists. The secondary target will be the managers of the health facilities, policy and decision makers that develop strategic interventions and policies; mobilise resources and are actively involved in monitoring and quality assurance of TB programs as well as improved access to quality patient care. Lastly, the guidelines will target patients who access TB treatment services to create awareness and information that will foster measures and positive behaviours for hearing preservation.

6.6.1.5 **Objectives of the best practice guidelines**

The overall objective of the best practice guidelines was to raise awareness of the adverse effects of ototoxic MDR-TB drugs to enable early detection and prevention of SNHL. The use of guidelines will assist making of better decisions for clinical management of patients and improvement in the evidence used for policy planning and the data for the advancement science.

The best practice guidelines will:

- Strengthen institutional capacity towards preventing deafness and hearing loss among TB patients
- Provide focused practice guidelines for early identification, diagnosis and treatment of causes of hearing loss and deafness among TB patients on MDR-TB treatment by health care practitioners.
• Create awareness on the magnitude of ototoxicity caused by MDR-TB drugs in order catalyse early detection and prevention of hearing loss among health care practitioners.

6.6.1.6 **Expected Benefits**

Effective utilisation of these best practice guidelines is intended to generate the following benefits:

• Availability of various high quality services for prevention, early identification, treatment, referral, rehabilitation for hearing impairment and deafness among TB patients right from community based health care facilities to national referral hospitals.

• Awareness creation among the health practitioners on the early detection, management, and prevention of hearing loss among TB patients.

• Increased capacity building of health workers to ensure better care regarding early detection, management, and prevention of hearing loss among TB patients.

6.6.2 **Review of the findings of the empirical study**

According to this study, the generation of current evidence on ototoxicity and best practices provides a framework for contextualised best practice guidelines. In Chapters 4 and 5, very high incidence of MDR-TB treatment-related SNHL became evident. In a study of 159 patients treated for MDR-TB observed for 22,032 person days, 94 (60%) developed high frequency hearing loss. The incidence rate in the full cohort was 4.1/1 000 person days of observation. Among the HIV positive patients the incidence was 4.2/1 000 person days (CI: 3.4-5.3) and for HIV negative patients, 3.6/1 000 person days (CI: 2.4-5.7). Time-to-hearing loss analysis results were presented in Chapters 4 and 5, providing a basis for recommendation of audiometric
testing frequency. As stated in Sections 4.3.5 and 4.3.6 hearing loss was associated with male gender, age group, Abacavir containing ARV regimen, job type of a miner/machine operator or taxi driver, low haemoglobin level, and low body-mass index (0.018). While there was an association of dyspnoea on admission and noise exposure, the associations were not statistically significant, their pointers for modifiable risk factors. Table 6.4 presents the summary of the best practice guidelines and the basis for the recommendation from the study and from the theoretical frameworks.
### 6.6.3 Summary of best practice guidelines and application of the evidence

#### 6.6.3.1 Best practice guidelines for prevention, treatment and management of hearing loss

<table>
<thead>
<tr>
<th>Best Practice Guidelines</th>
<th>Study Findings</th>
<th>Elements of NSM and EMF</th>
</tr>
</thead>
</table>
| **Guideline 1:** Drug Resistant Tuberculosis (DR-TB) treatment sites should establish an ototoxicity-monitoring programme. Where audiology services cannot be provided on site, there should be a functional referral system in place. | - High incidence of SNHL among study respondents (60% of respondents developed SNHL)  
- Lack of ototoxic monitoring programs at MDR-TB treatment centres.  
- Data collection for the study at sites without audiology services was through outreach programs | NSM: Six phases of the Nursing process are required for holistic care: assessment, diagnosis, identification of outcomes, planning, implementation, evaluation  
EMF: All HCW should be involved in monitoring ADRs |
| **Guideline 2:** All health care workers, administrators, and managers have delineated roles and responsibilities for implementing programmes focused on prevention, treatment, and management of hearing loss among DR-TB patients. | The pilot study revealed that there was a lack of awareness about audiological monitoring of treatment as part of quality care. Guidelines for roles and responsibilities were non-existent. HCWs were lacking in awareness of the role of the audiologist as part of the team providing care. Acceptance of routine monitoring audiology at the hospital was a quality improvement project | 1. Nursing processes: Planning and evaluation  
Nursing goals |
| **Guideline 3:** All patients with DR-TB should have a thorough assessment of risk factors for hearing loss prior to exposure to second-line anti-TB medications. | Baseline assessments showed that some respondents have pre-existing hearing losses. Conductive hearing loss due to wax impaction and due to middle ear infection was alleviated promptly through pre-treatment assessment. Family risk factors for hearing loss can also be assessed | Nursing diagnosis |
Guideline 4: Each DR-TB treatment site, and dependent ‘baby’ facilities, should have a system for monitoring ototoxicity through pharmacovigilance protocols and tools. Pharmacovigilance monitoring should be used as a basis for informed medical decision-making, especially where there is observed change in hearing thresholds.

A high burden of incident hearing loss was revealed by the study. Health facilities were lacking tools and protocols for hearing loss referrals between the main treatment centre and the feeder health facilities and yet timely assessment is of essence if interventions are going to have an impact on hearing conservation.

Lack of tools to capture modifiable risk factors

6.6.3.2 Best practice guidelines for procedures conducted by health care providers

<table>
<thead>
<tr>
<th>Best Practice Guidelines</th>
<th>Study Findings</th>
<th>Elements of NSM and EMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline 5: All DR-TB patients enrolled into care should have a pre-treatment assessment and baseline audiometry conducted prior to initiating treatment, or within 72 hours of the first dose of an aminoglycoside or polypeptide antibiotic. For facilities without audiology services, patients should be referred to an audiologist at an audiometry center within two days.</td>
<td>It is a best practice to establish a baseline for hearing sensitivity for future reference and comparison. MDR-TB treatment is associated with threshold shifts and significant threshold shifts require changes in the dosing and/or drug regimen in order to preserve hearing. Timing of hearing loss ranges from anywhere within the first month to post treatment. The median range of time to hearing loss ranged from 54.5 days to 147 days.</td>
<td>Nursing assessment and diagnosis</td>
</tr>
<tr>
<td>Guideline 6: At initiation of MDR-TB treatment, all modifiable risk factors for hearing</td>
<td>This study found that the following modifiable factors need to be addressed with a possibility</td>
<td>Nursing assessment and diagnosis</td>
</tr>
</tbody>
</table>
impairment (dehydration, renal insufficiency, dyspnoea and fever) should be addressed prior to administration of aminoglycosides or polypeptide antibiotics.

| Guideline 7: All DR-TB patients should receive regular scheduled two-weekly audiometry during the first 60 days of treatment and, thereafter, monthly assessment throughout the injectable phase of treatment. Urgent evaluation should be arranged whenever a patient reports decreased hearing sensitivity. | More than 25% of respondents who developed hearing loss did so within the first 2 months. The median time to hearing loss ranges from 54.5 days to 147 days (median is 84 days). More frequent testing improves the chances of early intervention soon after detection of ototoxicity. | Nursing assessment and diagnosis |
| Guideline 8: Audiometry should be conducted at least once within six months after completion of injectable MDR-TB treatment. | Hearing loss is progressive. Patients hearing loss grades worsening during follow up in the study | Nursing goals and outcomes |

| of reducing the incidence of hearing loss |
| - Improving hydration status |
| - attending to dyspnoea |
| - attending to low haemoglobin level |
| - excluding and attending to pre-existing conductive hearing loss |
| - attending to pre-existing diabetes |
### 6.6.3.3  Best practice guidelines for documentation and record keeping

<table>
<thead>
<tr>
<th>Best Practice Guidelines</th>
<th>Study Findings</th>
<th>Elements of NSM and EMF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guideline 9:</strong> All health care workers should be trained in documentation and record keeping of adverse drug reactions. Proactive targeted observation (and recording), analysis and action are central to the hearing loss prevention programme.</td>
<td>Incident cases were identified through thorough record keeping. Early and proactive interventions for Secondary and tertiary prevention depend on targeted observation and analysis of records recording.</td>
<td>Nursing evaluation</td>
</tr>
</tbody>
</table>

### 6.6.3.4  Best practice guidelines for public health actions

<table>
<thead>
<tr>
<th>Best Practice Guidelines</th>
<th>Study Findings</th>
<th>Elements of NSM and EMF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guideline 10:</strong> The public should be provided with appropriate evidence based documentation and clear guidelines for early detection of hearing loss among DR-TB patients, including risks arising from abuse or improper use of ototoxic drugs.</td>
<td>High incidence of hearing loss among MDR-TB patients.</td>
<td>Nurse-client relationship</td>
</tr>
<tr>
<td><strong>Guideline 12:</strong> Information and educational materials should be used to provide correct and</td>
<td>Some respondents declined enrolment into the study because of fear of hearing loss. Some</td>
<td>Nurse-client relationship and nursing goals and outcomes.</td>
</tr>
</tbody>
</table>

221
accurate information on ototoxicity in a simple and engaging way.

defaulted their medication based on the fear for SNHL

Client system extends to family and community

<table>
<thead>
<tr>
<th><strong>Guideline 13:</strong> Regulation and legislation should be implemented to ensure that only appropriate health care workers conduct prescription and administration of ototoxic medication.</th>
<th>Aminoglycosides used in MDR-TB management are ototoxic and should be used judiciously. Previous exposure increases risk for SNHL during MDR-TB treatment</th>
<th>Nurse-client relationship and nursing goals and outcomes. Client system extends to family and community</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guideline 14:</strong> Wherever possible, DR-TB patients with hearing impairment should be provided with or referred for hearing aids early enough to prevent deterioration of hearing.</td>
<td>Hearing aids reduce progression of hearing loss. Health care workers need to discuss potential hearing loss with patients so that patients are clear on what to do should they start experiencing hearing loss</td>
<td></td>
</tr>
</tbody>
</table>
6.6.4 Review of existing literature

The WHO estimates that around 360 million people suffer from disabling hearing loss worldwide. In 1995, the World Health Assembly developed guidelines to address this burden. These guidelines may be applied to address MDR-TB-related hearing loss, where increasing use of MDR-TB treatment is likely to increase the prevalence of hearing loss (Olusanya et al., 2014a). The high incidence of hearing loss associated with MDR-TB treatment was also in Botswana (62%), Iran (71%) and South Africa (40% and 57%) (Harris et al., 2012, Modongo et al., 2014, Seddon et al., 2013, Van der Walt et al., 2013). Lower incidence has been reported in the United Kingdom (18%), and in the Netherlands (18%) (de Jager & van Altena, 2002, Sturdy et al., 2011).

6.5.1.1 Interpretation of Evidence in the development of best practice guidelines

This study utilised the US Preventive services task force (2014) Guide to clinical preventive services framework (US Preventive services task force, 2014 #842) for describing the quality of the evidence. The USPSTF is an independent panel of experts in prevention and primary care that evaluates available evidence and makes recommendations about clinical preventive services, including screenings, counseling, and preventive medications. The Task Force determines whether or not the evidence supports providing a clinical preventive service in primary care settings to people without symptoms. For a service to be recommended, the evidence must show that the potential benefits of providing that service outweigh the potential harms. The grade linked to each recommendation reflects both the magnitude of net benefit and the strength and certainty of the evidence supporting the provision of a specific preventive service. These grades translate to practice guidance for clinicians: high priority, medium and low.
<table>
<thead>
<tr>
<th>Level of Certainty</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.</td>
</tr>
</tbody>
</table>
| **Moderate**      | The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as:  
  - The number, size, or quality of individual studies.  
  - Inconsistency of findings across individual studies.  
  - Limited generalizability of findings to routine primary care practice.  
  - Lack of coherence in the chain of evidence.  
  As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion. |
| **Low**           | The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of:  
  - The limited number or size of studies.  
  - Important flaws in study design or methods.  
  - Inconsistency of findings across individual studies.  
  - Gaps in the chain of evidence.  
  - Findings not generalizable to routine primary care practice.  
  - Lack of information on important health outcomes.  
  More information may allow estimation of effects on health outcomes. |

Source: (USPSTF 2014:99)
### 6.6.5 Recommendations and summary of evidence

**Table 6.3: Guidelines, summary of the evidence and recommendations for implementation of prevention and monitoring strategy for hearing loss associated with MDR-TB.**

<table>
<thead>
<tr>
<th>GUIDELINE</th>
<th>SUMMARY OF EVIDENCE FROM THE REVIEW OF LITERATURE AND THE STUDY FINDINGS ON WHICH THE BEST PRACTICE GUIDELINES ARE BASED</th>
<th>RECOMMENDATIONS FOR IMPLEMENTATION</th>
</tr>
</thead>
</table>
| 1. Drug Resistant Tuberculosis (DR-TB) treatment sites should establish an ototoxicity-monitoring programme. Where audiology services cannot be provided on site, there should be a functional referral system in place. **Strong recommendation, high quality evidence** | Situation: Hearing loss is an important public health concern with substantial economic and societal costs. The incidence of hearing loss associated with MDR-TB treatment in Swaziland is high and there are no monitoring and prevention systems in place. Solution:  
- Audiometric monitoring for ototoxicity is primarily performed for early detection of changes to hearing status when it is possible to institute interventions to prevent further deterioration of hearing.  
- The current preferred method for testing hearing is audiometry for adults and older children (those able to cooperate with testing). The responsibility for hearing loss monitoring and its prevention is currently undefined.  
- Early intervention is the responsibility of all health care workers through implementation of primary, secondary | The Drug Resistant Tuberculosis (DR-TB) treatment sites should:  
- Plan resources to ensure availability and utility of audiology equipment, forms of requesting for audiology services and human resources for hearing screening.  
- Establish ototoxicity monitoring and prevention services to: identify ototoxicity; enable timely identification of at-risk patients; provide pre-treatment counselling regarding potential ototoxic effects; take valid baseline measures (pre-treatment or early in treatment); conduct monitoring evaluations at sufficient intervals to document progression of hearing loss or fluctuation in sensitivity; and conducts follow-up evaluations to determine post-treatment effects. |
and tertiary prevention. Health care workers and authorities are unclear about appropriate interventions for patients presenting with deteriorating or loss of hearing.

- Early detection enables audiology intervention when hearing impairment has occurred.

(Audiology, 2009, Seddon et al., 2012).

- Establish a referral system for every patient to receive baseline audiometry where audiometry services cannot be provided on site.

- Establish supportive hearing programmes to assist patients with communication in the event of loss of speech frequencies.

2. All health care workers, administrators and managers have delineated roles and responsibilities for implementing programmes focused on prevention, treatment and management of hearing loss among MDR-TB patients.

**Strong recommendation, Low quality evidence**

Interdisciplinary collaboration may lead to improvements in health care access, outcomes of health care, and satisfaction of health care workers and their patients. Interdisciplinary collaboration may also improve recruitment and retention of health care workers and communication. Clear definitions of providers’ roles and expectations with regard to shared care are essential in order to reduce the possibility of ambiguity and misunderstanding regarding protocols, procedures, responsibility and authority (Paquette-Warren et al 2004). In an ototoxicity monitoring and prevention programme:

- Audiologists should be responsible for establishing the testing protocol, patient testing, interpretation and management of data derived from monitoring and prevention programmes. They should also be responsible for follow-up management when hearing loss is clinically significant.

- Pharmacists should be responsible for storing and dispensing DR-TB treatment sites should:

- Establish a multi-disciplinary approach to monitoring and prevention of hearing loss among patients on MDR-TB treatment. The physician, audiologist and occupational therapist should provide leadership in championing the balance between pursuing cure and ensuring quality of life is maintained.

- Develop a chart showing the roles and responsibilities of all health worker cadres in the prevention, detection, and management of ototoxicity among MDR-TB patients. Delineated responsibility and improvement of communication among the health care workers will ensure that each cadre fulfils a defined role in primary, secondary and tertiary prevention.
MDR-TB drugs, providing non-prescription drugs, health care aids and devices, and providing patients and health care workers with information related to drug use. Together with audiologists and doctors, pharmacists’ should develop risk assessment tools and monitor implementation of pharmacovigilance tools.

- Doctors should be responsible for the assessment of the physical and mental health of patients, including establishing a diagnosis, initiating treatment and preventing disease or disability where possible. More generally, doctors should be responsible for overall patient wellbeing, and for managing the implementation and running of the ototoxicity programme.

- The laboratory staff should be responsible for interpreting tests, including critical values of certain risk factors, and for notifying doctors where an abnormality is detected in order to prevent or mitigate further hearing loss.

- Nurses should be responsible for health promotion, and for assessing the adequacy of patient care. They should be involved in the provision of supportive, preventive, therapeutic, palliative and rehabilitative care, in order to optimise patient function. Nurses should also conduct pre-treatment assessments, be involved in the management of modifiable risk factors and support patients with communication difficulties.

- Engage health care administrators and managers in ototoxicity monitoring and prevention interventions in order to improve patient quality of life and outcomes increase advocacy and the provision of resources, and promote an enabling environment.
| 3. All patients with MDR-TB should have a thorough assessment of risk factors for hearing loss prior to exposure to second-line anti-TB medications. | While aminoglycoside antibiotic administration is the most important risk factor for the development of MDR-TB treatment related hearing loss, several factors may potentiate this risk. These factors are modifiable and non-modifiable, and may be cumulative.  
- Documented risk factors include: familial and genetic predisposition of the patient, especially in patients with genetic mutations of genes coding mitochondrial 12S RNA, such as A1555G and T1095C and so on, exposure to noise during aminoglycoside treatment, cumulative dosage of aminoglycosides, previous exposure to aminoglycosides, age of the patient (especially extreme ages), existence of renal dysfunction and chronic renal disease, and the presence of hypertension and other systemic disorders.  
- Concurrent exposure to other ototoxic drugs, such as loop diuretics, platinum-based antineoplastic drugs, salicylates and NSAIDs, anti-malarial drugs (especially quinine), is also associated with increased risk of hearing loss.  
- In Swaziland, additional risk factors include dyspnoea, use of abacavir for treatment of HIV in MDR-TB patients and job type. | DR-TB treatment sites should:  
- Conduct a thorough assessment of risk factors for hearing loss prior to exposure to second-line anti-TB medications. Assessments should include: family history of hearing impairment; occupational and recreational exposure to noise; use of other ototoxic medications; previous recurring inner ear infections; familial predisposition and genetic factors; and systemic diseases (for example, diabetes)  
- Implement appropriate monitoring of patient hearing on the basis of their risk assessment  

**Strong recommendation, High quality evidence**
4. Each DR-TB treatment site, and its ‘baby’ facilities, should have a system for monitoring ototoxicity through pharmacovigilance protocols and tools. Pharmacovigilance monitoring should be used a basis for informed medical decision-making, especially where there is observed change in hearing thresholds.

Strong recommendation, High quality evidence

Health care workers and health facilities do not adequately report adverse drug reactions.
- Early detection and monitoring of ototoxicity can reduce the impact of hearing loss.
- In the event of deterioration in hearing sensitivity during MDR-TB treatment, treatment modification can prevent further hearing loss.
- If hearing sensitivity is not impaired during treatment, no changes are required, though monitoring for delayed changes in hearing sensitivity should continue.
- Monitoring provides an opportunity for counselling and rehabilitation during and after treatment.
- Monitoring provides the basis for informed medical decision-making.


- Establish a reporting system to enable documentation of hearing loss frequency and magnitude, as well as the impact of adverse events.
- Early detection of hearing loss should be linked to risk reduction strategies for adverse drug reactions. WHO grades for hearing impairment should be incorporated in the pharmacovigilance tool.

<table>
<thead>
<tr>
<th>Grade of Impairment</th>
<th>Audiometric ISO value (average of 500, 1000, 2000, 4000 Hz)</th>
<th>Impairment description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (no impairment)</td>
<td>25 dBHL or less (better ear)</td>
<td>No or very slight hearing problems. Able to hear whispers</td>
</tr>
<tr>
<td>1 (Slight impairment)</td>
<td>21-40 dBHL (better ear)</td>
<td>Able to hear and repeat words spoken in normal voice at 1 metre</td>
</tr>
<tr>
<td>2 (Moderate impairment)</td>
<td>41-50 dBHL (better ear)</td>
<td>Able to hear and repeat words using raised voice at 1 metre</td>
</tr>
<tr>
<td>3 (Severe impairment)</td>
<td>51-60 dBHL (better ear)</td>
<td>Able to hear some words when shouted into better ear</td>
</tr>
<tr>
<td>4 (Profound impairment including deafness)</td>
<td>61 dBHL or greater (better ear)</td>
<td>Unable to hear and understand even a shouted voice</td>
</tr>
</tbody>
</table>

5. All DR-TB patients enrolled

Baseline testing establishes whether patients have any pre-

DR-TB treatment sites should ensure that:
into care should have a pre-treatment assessment and baseline audiometry conducted prior to initiating treatment, or within 72 hours of the first dose of an aminoglycoside or polypeptide antibiotic. For facilities without audiology services, patients should be referred within two days.

**Strong recommendation, High quality evidence**

existing hearing impairment and enables comparison with subsequent tests during DR-TB treatment.  
- Audiologic monitoring for ototoxicity is performed for early detection of existing impairment and changes to hearing sensitivity, enabling audiologic intervention when hearing impairment occurs. Thresholds for acceptable versus unacceptable hearing loss should be defined and used to prompt intervention. The thresholds are: 26-40 dB Mild hearing loss; 41-60 dB Moderate hearing loss; 61-80 dB severe hearing loss; 81+ dB Profound hearing loss.  
- Significant threshold shift criteria for a case of hearing with follow up compared with baseline measurements and ototoxicity defined as any of: i) a 20 dB decrease at any one frequency, ii) a 10 dB decrease at any two adjacent frequencies (American Speech-Language-Hearing Association., 1994; Audiology, 2009).

| 6. At initiation of MDR-TB treatment, all modifiable risk factors for hearing impairment (dehydration, renal) | Aminoglycosides and polypeptide antibiotics are ototoxic, affecting both vestibular and cochlear function of the inner ear through damage to the sensory neuroepithelium of the inner ear. The risk of ototoxicity is increased in the presence of modifiable risk factors. | DR-TB treatment sites should:  
- Ensure risk factors for hearing impairment are addressed prior to administration of aminoglycosides or at the earliest opportunity. |

- All DR-TB patients enrolled into care should undergo pre-treatment assessment and baseline audiometry prior to initiating treatment, or within 72 hours of the first dose of an aminoglycoside or polypeptide antibiotic.  
- For facilities without audiology services, ensure referral to appropriate facilities within 2 days.
<table>
<thead>
<tr>
<th>Insufficiency, dyspnoea and fever should be addressed prior to administration of aminoglycosides or polypeptide antibiotics.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factors</strong> such as transient renal dysfunction, dehydration, smoking, job type and exposure to noise. (Gopinath et al 2010; Harris et al 2012).</td>
</tr>
<tr>
<td><strong>Strong recommendation, High quality evidence</strong></td>
</tr>
<tr>
<td><strong>Ensure patients</strong> are hydrated and do not have any other conditions that have been known to accelerate ototoxicity among MDR patients.</td>
</tr>
<tr>
<td><strong>Ensure patients</strong> are apyrexic. Pyrexic patients need stabilisation prior to MDR-TB treatment.</td>
</tr>
<tr>
<td><strong>Use patient history, weight and age to inform anti-TB drug regimen.</strong></td>
</tr>
<tr>
<td><strong>Provide patient counselling</strong> about drug adherence, and how to cope with MDR-TB treatment, as well as information on the benefits and side effects of relevant drugs.</td>
</tr>
<tr>
<td><strong>Ensure audiometry</strong> is conducted at the beginning of treatment and is repeated at regular two-weekly or monthly intervals.</td>
</tr>
<tr>
<td><strong>Audiometry tests</strong> should be conducted every two weeks during the first 60 days of treatment and monthly throughout the injectable phase of treatment.</td>
</tr>
</tbody>
</table>

**7. All MDR-TB patients** should receive regular scheduled two-weekly audiometry during the first 60 days of treatment, and thereafter monthly assessment throughout the injectable phase of treatment. Urgent evaluation should be arranged whenever a patient reports decreased hearing.

Most MDR-TB-associated hearing loss observed in Swaziland occurs within 60 days of receiving ototoxic drugs. More frequent assessments of hearing during this period is therefore critical.

- When audiologic monitoring detects hearing impairment or changes to hearing status, medical and audiologic interventions and rehabilitation may prevent disabling hearing impairment and disability (Duggal & Sarkar 2007; Seddon et al 2012).

All MDR-TB patients receiving aminoglycosides or polypeptide antibiotics should have regular scheduled audiometry. DR-TB treatment sites should:

- Ensure audiometry is conducted at the beginning of treatment and is repeated at regular two-weekly or monthly intervals.
- Audiometry tests should be conducted every two weeks during the first 60 days of treatment and monthly throughout the injectable phase of treatment.
hearing sensitivity or symptoms such as tinnitus or vertigo.

Strong recommendation, High quality evidence

treatment. Urgent evaluation should be arranged whenever a patient reports decreased hearing sensitivity (see Guideline 4).

- Audiometry results should be compared with baseline results in order to determine whether there has been a significant threshold shift/change.

- If high-frequency hearing loss is detected, the offending drug should be stopped or dose reduced. It may be possible to stop the drug before hearing loss involves frequencies required for speech, without impairing successful treatment. However, where hearing loss has been reported, the health practitioner should consider the following:
  - Reducing the frequency of the drug administration to 5 times or even 3 times per week from daily dosing.
  - Lowering the drug dosage if this does not compromise the regimen.
  - Discontinuing the drug if this will not compromise the regimen.
  - Prescribing an alternative treatment regimen with less ototoxic medications when early SNHL is detected.
8. Audiometry should be conducted at least once within six months after completion of injectable MDR-TB treatment

**Strong recommendation, High quality evidence**

- The degree of hair cell damage in the organ of Corti\(^1\) and hearing loss is directly proportional to drug dosage.
- Association of hearing loss with treatment duration and total aminoglycoside dosage has been reported. Aminoglycosides may persist in the inner ear tissues for more than six months, therefore patients may continue to be susceptible to ototoxicity long after completion of treatment.
- Continuation of monitoring beyond the duration of drug treatment is therefore required.
- Among adults and children, hearing impairment associated with aminoglycosides can develop after the aminoglycoside has been stopped ((de Jager & van Altena 2002; Seddon et al 2012).

9. All health care workers should be trained in documentation and record keeping of adverse drug reactions. Proactive targeted observation (and recording), analysis and action are central to the hearing loss prevention

Among the public and health care professionals there is limited awareness about the effects of anti MDR-TB antibiotics, loop diuretics and some NSAIDs on hearing.

- Health care workers who are aware about ototoxicity may not be familiar with the fact that each phase of the ototoxicity programme generates its own form of records, and the information from the various records must be considered in order to evaluate the effectiveness of the hearing loss prevention programme.

All DR-TB treatment sites and non DR-TB sites should ensure that:

- There is a system for recording and reporting ototoxicity, and that health care workers receive appropriate training in order to use it. Training should specifically enable healthcare workers to use records that the system generates. For an ototoxicity prevention programme, all health care workers should be trained in the documentation and record keeping of adverse drug reactions.

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1 The organ of Corti comprises both outer and inner hair cells. There are approximately between 15,000 and 16,000 of these hair cells in one ear (Plewes 2006). Inner hair cells are the mechanoreceptors for hearing: they transduce the vibration of sound into electrical activity in nerve fibres, which is transmitted to the brain and perceived as hearing.
| programme. Strong recommendation, High quality evidence | prevention programme.  
- Some of these records may be occupationally relevant. Not all health care workers will be familiar with the requirements for ototoxicity monitoring.  
- Health care workers may not be aware of the tools used to detect and monitor hearing loss among MDR-TB patients, nor of the relevant protocols where hearing loss is detected. There is therefore a need for training.  
(Coleman, Fernery & Evans 2011:371-7). | workers should be trained in documentation and record-keeping of adverse drug reactions, including ototoxicity.  
- Records should be examined and analysed on a regular basis.  
- The recording system for monitoring adverse drug reactions should define the variable being monitored, the system to be used to monitor, and reliability of recording, continuity and threshold for actions.

| 10. The public should be provided with appropriate evidence-based documentation and clear guidelines for early detection of hearing loss among MDR-TB patients, including risks arising from the abuse or improper use of ototoxic drugs Strong recommendation, High quality evidence | The general public are largely unaware that medications, such as anti MDR-TB antibiotics, loop diuretics and some NSAIDs, can cause transient or permanent hearing loss.  
- Occupational noise and social noise can potentiate hearing impairment in patients receiving MDR-TB treatment. Protective equipment, where available, is not always available or acceptable to the workforce or the public. It is therefore recommended that noise should be reduced and/or avoided.  
- Public awareness campaigns reduced ototoxicity in studies conducted in China and South Africa. | The Ministry of Health through the national TB programme should:  
- Sensitize the health care providers to increase awareness of the risks associated with abuse or improper use of ototoxic drugs, drug dosage and duration of drug treatment  
- Create public awareness materials on hearing loss and prevention strategies.  
- Address the problem of work place and social noise including provision of protectors, and reducing noise and noise exposure where possible. |
### 11. Professional education and training should be tailored to the needs of all categories of health care worker, taking into account roles and responsibilities

**Strong recommendation, Low quality evidence**

- Lack of trained personnel to carry out audiometric testing is a significant challenge to the development of hearing conservation programmes during MDR-TB treatment.

- Several cadres of health care worker have a role in monitoring and prevention of ototoxicity. Professional education and training therefore needs to be tailored to the needs of each cadre, based on their roles and responsibilities.

  (Seddon et al 2012).

### 12. Information and educational materials should be used to provide correct and accurate information on ototoxicity in a simple and engaging way.

**Strong recommendation, high quality evidence**

Although a significant proportion of hearing loss among patients with MDR-TB is associated with anti-TB drugs, environmental chemicals such as organic solvents, asphyxiating gases, pesticides, and heavy metals may also play a role. The public may not be aware of these ototoxic agents, nor of their role in protecting themselves and their family members from them. Evaluation of individuals who have had environmental ototoxic exposures and noise-induced hearing loss can help in making

- General practitioners, clinicians, nurses, audiologists, pharmacists and community health care workers should be informed about the potential for particular drugs to cause ototoxicity, possible interactions of these drugs, and ototoxicity prevention and early detection strategies.

- Beyond training, sensitization of health care workers should be conducted through information brochures and campaigns.

- Experienced and qualified personnel should conduct in-service training and experiential learning on ototoxicity in order to increase awareness of health care workers about ototoxicity.

- Appropriate information dissemination material should be made available in health care centres, hospitals, schools, colleges and other public places concerning risk factors for ototoxic hearing loss.
decisions regarding the potential ototoxicity of exposure to an unknown chemical agent or preceding noise-induced hearing loss.

| 13. Regulation and legislation should be implemented to ensure that prescription and administration of ototoxic medications are conducted only by appropriate health care workers | • Local data is lacking to increase awareness of the decision makers on the impact of hearing loss.  
• Our study on the incidence of MDR-TB related hearing loss in Swaziland provides data that can be used to develop measures for prevention and to mobilise funds for further research towards better MDR-TB treatment, as well as rehabilitation of those with hearing loss.  
• Various studies have revealed that in most developing countries there are no restrictions concerning access to ototoxic drugs. In Swaziland, a recent study conducted among pharmacists by the pharmacist at the TB hospital and Management Science of Health (MSH) revealed that it is possible to obtain prescription drugs, including aminoglycosides, without a prescription.  
(Olusanya 2013; Smith 2005). | • There should a deliberate effort to raise awareness about ototoxic hearing loss among of decision makers through sharing of evidence and best practices.  
• Decision makers should be lobbying health facility managers for funding to provide hearing aids, and for decentralisation of audiology services. |

| 14. Wherever possible, MDR-TB patients with hearing impairment should be provided with or referred for hearing aids | • Audiologic rehabilitation, that is, the process of providing training and treatment to improve hearing, is necessary for those who develop hearing impairment.  
• Hearing rehabilitation services focus on adjusting to hearing |

To mitigate the social and economic impact of MDR-TB hearing loss, wherever possible, persons with drug induced hearing impairment should be provided with aids early enough to prevent deterioration of hearing.
early enough to prevent deterioration of hearing

Strong recommendation, High quality evidence

According to the WHO, the grade of hearing impairment is as shown but disabling HL starts at grade 2

- 0 – No impairment: 25 dB or better (better ear)
- 1 – Slight impairment: 25 dB or better (better ear)
- 2 – Moderate impairment: 41-60 dB (better ear)
- 3 – Severe impairment: 61-80 dB (better ear)
- 4 – Profound impairment including deafness: 81 dB or greater (better ear).

(Olusanya et al 2014b)

- For Grade 2 hearing loss, counseling and potential interventions including hearing aids may be required by the patient.
- For Grade 3 hearing loss, hearing aids are usually recommended.
- For Grade 4 hearing loss, hearing aids are required, however if these are not available, lip-reading and signing should be taught.
- For profound hearing loss, hearing aids may help the patient to decipher speech. Additional rehabilitation may be needed, and supporting the patient to develop lip-reading and signing skills is essential.
### Roles and Responsibilities of health Care workers

Table 6.4: Stakeholder roles and responsibilities for prevention, treatment, and management of hearing loss

<table>
<thead>
<tr>
<th>STAKEHOLDER</th>
<th>ROLES AND RESPONSIBILITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy makers</td>
<td>• Carry out advocacy, communication and social mobilisation (ACSM) to bring about policy reforms and the development of institutional structures to support hearing loss programmes for MDR-TB patients.</td>
</tr>
<tr>
<td></td>
<td>• Create a policy environment &amp; mobilise resources for the implementation of effective TB programmes to reduce the number of MDR-TB cases.</td>
</tr>
<tr>
<td></td>
<td>• Support the implementation of surveillance programmes to manage ototoxicity among MDR-TB patients.</td>
</tr>
<tr>
<td></td>
<td>• Provide guidance concerning the improvement of hospital facilities and services to meet the needs of TB patients with hearing loss.</td>
</tr>
<tr>
<td>Hospital administrator/ senior medical officers and matrons</td>
<td>• Provide resources to strengthen the implementation of programmes to prevent, treat and manage hearing loss among MDR-TB patients.</td>
</tr>
<tr>
<td></td>
<td>• Implement on-site surveillance to ensure health care facilities are adequately detecting and managing hearing loss among MDR-TB patients. Health care facilities should conduct initial and ongoing evaluations for each patient regarding the reduction risks of ototoxicity among MDR-TB patients.</td>
</tr>
<tr>
<td></td>
<td>• Develop a facility-specific plan for the reduction of hearing loss among MDR-TB patients, informed by surveillance data findings. This plan should include standard operating procedures for staff to implement in the event of hearing loss.</td>
</tr>
<tr>
<td></td>
<td>• Ensure sufficient funding is allocated from the annual facility budgets to support MDR-TB hearing loss programmes.</td>
</tr>
<tr>
<td></td>
<td>• Purchase appropriate drugs, commodities and supplies.</td>
</tr>
<tr>
<td></td>
<td>• Establish a patient records management system.</td>
</tr>
<tr>
<td></td>
<td>• Ensure sufficient and appropriately trained health care workers are employed to run high quality services.</td>
</tr>
<tr>
<td></td>
<td>• Establish health care facility networks and a referral system.</td>
</tr>
<tr>
<td>Health practitioners (doctors, clinicians and other specialists)</td>
<td>• Carry out diagnostic tests and examine patients for symptoms.</td>
</tr>
<tr>
<td></td>
<td>• Identify co-morbidities and medical, pathophysiological, psychological and sociocultural risk factors for hearing loss.</td>
</tr>
<tr>
<td></td>
<td>• Monitor treatment adherence and audiometric testing.</td>
</tr>
<tr>
<td></td>
<td>• Refer patients for hearing screening and audiometry.</td>
</tr>
<tr>
<td></td>
<td>• Prescribe appropriate drugs and inform patients of adverse drug effects</td>
</tr>
<tr>
<td></td>
<td>• Educate the community on early detection of hearing loss and the availability of treatment and rehabilitation for hearing impairment among MDR-TB patients.</td>
</tr>
<tr>
<td></td>
<td>• Refer patients with hearing loss to Ear, Nose and Throat doctors and audiologists for appropriate treatment, including hearing aid provision and fitting, cochlea implant surgery and rehabilitation.</td>
</tr>
<tr>
<td></td>
<td>• Complete patient records.</td>
</tr>
<tr>
<td>Nurses</td>
<td>• Educate patients and the community on early detection of hearing loss and the availability of treatment and rehabilitation for hearing impairment, through health education talks and community awareness campaigns.</td>
</tr>
<tr>
<td></td>
<td>• Participate in the diagnosis and management of patients with MDR-TB.</td>
</tr>
</tbody>
</table>
- Identify cases of hearing loss and refer patient for further assessment.
- Provide treatment for common ear conditions, including cerumen impaction and acute suppurative otitis media, with guidance from doctors.
- Distribute ear-drops and other medications as instructed by doctors.
- Provide counselling to patients on the side effects of drugs, and how to cope with hearing loss.
- Complete appropriate registers and clinical records for TB patients.

**Audiologists**

- Establish and in collaboration with doctors and administrators manage MDR-TB hearing loss programmes, including in-service education and interpretation of hearing test results.
- Advocate for and supervise hearing loss programmes.
- Design, implement and coordinate occupational and community hearing loss prevention programmes, which should include: assessment of individual exposure to ototoxic agents; identification and reduction of exposure to noise; education for employers and employees; screening for hearing loss; recommendations for treatment; and counselling for use of hearing protection.
- Train and supervise non-audiologists involved in monitoring audiometry in the health care setting.
- Conduct screening, diagnostic tests and follow up audiometry, using baseline audiometry results to identify significant threshold shifts.
- Provide preventive, promotive, curative, medical and social rehabilitative services.
- Make recommendations to prescribing doctors concerning patient treatment.
- Conduct surveillance and maintain patient records.
- Manage hearing loss that is not medically treatable by and prescribing amplification and/or assistive listening devices, and supporting the patient and their family in accessing counselling and developing communication strategies.
- Provide information to patients regarding treatment and rehabilitation in the event of hearing loss.

**Pharmacy**

- Lead the pharmacovigilance teams, monitor adverse drug reactions and develop risk assessment tools.
- Dispense medication and check drug doses are correct.
- Identify potential drug interactions and prevent adverse effects.

**Laboratory staff**

- Conduct tests to identify patient risk factors for ototoxicity, including renal function tests, blood glucose tests.
- Manage lab tracking systems for tests are early notification of critical abnormal results for example, creatinine clearance values.

**Patients**

- Monitor hearing and present early to an appropriate facility if hearing deteriorates.
- Voice their concerns and questions about the hearing loss prevention programme and MDR-TB treatment more generally.
- Comply with guidelines on how to prevent hearing loss.
- Communicate information about MDR-TB treatment related hearing loss to other patients and the community at large, and help to inform and train their colleagues in the use of occupational hearing protection.
- Approach programme facilitators (health care workers) and their employers to report any health and safety concerns.
- Adhere to treatment advice on prevention of further damage.
Community based workers and family members

- Educate patients and the community on early detection of MDR-TB-related hearing loss, as well as available treatments, through health education talks and community awareness campaigns.
- Support and counsel patients on MDR-TB treatment to ensure risks are managed.
- Support patient with hearing loss to accept their disability and maintain communication through the use of lip reading and sign language.
- Identify hearing loss in the elderly and enable them to access suitable management or rehabilitation.

Table 6.5: Procedures for health care workers during pre-treatment assessment

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
<th>Description</th>
<th>Responsibility</th>
</tr>
</thead>
</table>
| 1    | Assessing patient risk of hearing loss prior to initiation on MDR-TB treatment | The health practitioner is expected to:  
- Take the patient's history of exposure to loud noises or ototoxic agents, including: occupational exposures; previous recurring middle ear infections; familial predisposition and genetic factors; and certain systemic diseases, such as diabetes, hypertension, chronic kidney disease and sickle cell disease.  
- Most at risk people are those that work in noisy places for prolonged periods (more than 8 hours at noise levels >85dB or for more than 1 hour at noise levels >95dB (Audiology, 2009)).  
- High risk occupations include machine operators, industrial workers and those working in the music industry (for example, disco jockeys).  
- Assess patients' previous exposure to aminoglycosides.  
- Counsel patients with pre-existing vestibulo-cochlear impairment on the potential risks of MDR-TB treatment, and gain informed consent prior to drug treatment.  
- Conduct tests to assess and document patients’ physical state, including hydration status, temperature, and presence of absence of dyspnoea.  
- Optimise and stabilise patient physical state before initiating aminoglycosides | Nurse                  |
| 2    | Ear examination, hearing screening and diagnostic audiometry for hearing sensitivity | Conduct a pre-treatment audiometry at initiation of MDR TB treatment to assess baseline hearing sensitivity and the need for further hearing tests.                                                                 | Audiologist            |
| 3    | Recommendations for MDR-TB treatment                                    | Recommendations should be informed by the pre-treatment assessment results, including patient fit and readiness to commence MDR-TB treatment.                                                             | Doctor or audiologist  |
### Table 6.6: Procedures for health care workers at initiation of the patient on MDR-TB treatment

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1    | Preparation for treatment | - Ensure the patient is well hydrated and does not have any conditions known to accelerate ototoxicity  
- Ensure patients are apyrexic and observations are stable prior to drug administration. |
| 2    | Determination of the regimen | - Determine an appropriate regimen based on the patient’s history, weight and age. |
| 3    | Patient counselling on adherence | - Provide patient counselling on drug adherence, and how to cope with the drug treatment, including its benefits and likely side effects. |

### Table 6.7: Procedures for health care workers for monitoring patients on MDR-TB treatment

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1    | Patient review and monitoring as recommended by the guidelines | - Review patients progress on the MDR-TB treatment.  
- If decreased hearing sensitivity is reported patients should be referred for audiometry.  
- Compare results from follow-up audiometry with the baseline results. |
| 2    | Monitor hearing loss | - Diagnose hearing loss when one of the following criteria are met: (i) ≥20 dB decrease at any one test frequency, (ii) ≥10 dB decrease at any two adjacent frequencies, or (iii) loss of response at three consecutive frequencies where responses were previously obtained. Apparent changes should be compared to baseline measurements, and confirmed by repeat testing, generally within 24 hours.  
- Communicate results of audiology monitoring to patients and other health care workers.  
- Ensure that the drug dosage administered is appropriate for weight and age, as toxicity increases with both. |
| 3    | If ototoxicity and/or hearing loss is detected | Consider: (i) reducing the frequency of drug administration to three to five times per week; (ii) lowering the dose of the suspected agent if this can be done without compromising the regimen; or (iii) stopping the drug before hearing loss progresses to the frequencies needed for speech communication.  
**Caution:**  
- Hearing loss is generally not reversible  
- The risk of further hearing loss should be weighed against the risk of stopping the drug  
- Monitoring serum drug concentrations is essential |
If there is significant irreversible hearing loss • Refer patient for rehabilitation and counselling.

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Post treatment evaluation</td>
<td>Given that aminoglycosides remain in the cochlea long after cessation of treatment, patients should be monitored for hearing loss every six months in the first year after completion of MDR-TB treatment.</td>
</tr>
<tr>
<td>2</td>
<td>If new onset hearing loss is detected</td>
<td>Refer to specialist services such as hearing aid fitting as appropriate.</td>
</tr>
</tbody>
</table>

**Table 6.8: Procedures for health care workers post-MDR-TB treatment**

### 6.7 SUMMARY AND CONCLUSIONS

The World Health Organization defines disabling hearing impairment in adults as permanent hearing threshold level of 41 decibels or greater. At this level of impairment, most people can only distinguish words spoken at one metre if they are spoken in a raised voice. Hearing impairment/loss and deafness due to ototoxicity is associated with MDR-TB treatment and is generally irreversible but avoidable in some instances within the health care system. In the management of MDR-TB, injectable aminoglycosides are the cause of hearing impairment from ototoxic damage. Health workers need to be aware of modifiable determinants of ototoxicity, which can be derived from the family and medical history including family susceptibility to hearing loss, socio-demographic characteristics such as patient age and general health, current and previous drug exposure characteristics such as daily drug dosage, duration and route of ototoxic drug administration; length of exposure to ototoxic drugs. Awareness about MDR-TB related hearing loss is low, and there are no global guidelines for monitoring and prevention of ototoxicity to assist countries with largest burden of MDR-TB and burgeoning MDR-TB treatment programs to prevent this type hearing loss. The “Best practice guidelines for preventing hearing loss in patients on treatment for drug resistant tuberculosis in Swaziland provides a comprehensive guide to setting up an ototoxicity monitoring program, key outputs of the program and outlines how monitoring and prevention activities should be conducted. It includes guidelines for assessing patient risks and major determinants of ototoxicity, prior to initiation on TB drugs, as well as surveillance during and after treatment.

The next chapter provides a conclusions, limitations, and recommendations from the study to develop the best practice guidelines.
CHAPTER 7
SUMMARY, CONCLUSIONS, LIMITATIONS AND RECOMMENDATIONS OF THE STUDY

7.1 INTRODUCTION

This chapter presents the major conclusions of the study, discusses the limitations, and suggests recommendations for practice and further research. The World Health Organization defines disabling hearing impairment in adults as a permanent hearing threshold level of 41 decibels or greater. At this level of impairment, most people can only distinguish words spoken at one metre if spoken in a raised voice. Hearing impairment and deafness due to ototoxicity are important and common side effects of DR-TB treatment. Hearing loss due to ototoxicity is generally irreversible but avoidable in some instances, through prevention and rational use of the ototoxic drugs within the health care system. Injectable aminoglycosides are the most common cause of hearing impairment from ototoxic damage amongst TB patients. Health workers need to be aware of modifiable determinants of ototoxicity, which can be derived from the family and medical history including family susceptibility to hearing loss, socio-demographic characteristics such as patient age and general health, current and previous drug exposure characteristics such daily drug dosage, duration and route of ototoxic drug administration; length of exposure to ototoxic drugs. There are no global guidelines for monitoring and prevention of ototoxicity to assist countries with the largest burdens of DR-TB and burgeoning DR-TB treatment programmes. Existing guidelines are largely inadequate and lack explicit clinical guidance.

The conclusions are presented according to the aim and objectives of the study. The purpose of the study was to improve monitoring and prevention of hearing loss in MDR-TB patients in Swaziland and thereby develop best practice guidelines for monitoring and prevention of hearing loss associated with MDR-TB treatment in Swaziland. The best practice guidelines would contribute to strengthening institutional capacity towards preventing hearing loss among MDR-TB patients by enabling early identification,
diagnosis, and mitigation interventions. The overall aim of the study was to explore and determine the incidence of hearing loss, calculate the incidence ratios, determine the extent to which HIV influences the incidence of hearing loss, determine the risk factors and analyse the time to hearing loss related to MDR-TB treatment. To do this, the following primary research questions emerged:

- What is the incidence of hearing loss among drug resistant TB patients receiving DR-TB treatment in Swaziland?
- What are the risk factors for hearing loss associated with DR-TB treatment?
- How does HIV/AIDS influence the incidence for hearing loss among patients receiving DR-TB treatment in Swaziland?
- What is the mean of hearing loss free survival time and what is the optimal frequency for audiology testing for monitoring of patients on DR-TB treatment in Swaziland to enable early prompt detection of ototoxicity?
- How can best practices for monitoring and prevention of MDR-TB treatment related hearing loss be developed?

To support exploration of the research questions, this study had five objectives addressed as follows. The first objective focused on establishing the incidence of hearing loss among drug resistant TB patients receiving DR-TB treatment in Swaziland. Chapters 4 and 5 presented and discussed the results in detail. The risk factors for hearing loss associated with DR-TB treatment in Swaziland were analysed and results presented in Chapters 4 and 5 in response to objective 2 of the study. Results for objective three, whose focus was to determine the extent to which HIV/AIDS influenced the incidence of SNHL and objective 4 which sought to determine the time-to-hearing loss were also presented in chapters 4 and 5. The last objective focused on developing best practice guidelines for monitoring and prevention of hearing loss associated with MDR-TB treatment in Swaziland and the best practice guidelines are presented in Chapter 6.

Additionally, however, the study also tested two study hypotheses:
**Study hypothesis 1:**

The incidence ratio of sensorineural hearing loss during the intensive phase of MDR-TB treatment increases proportionally with the duration of treatment.

**Study hypothesis 2**

MDR-TB patients living with HIV infection have a higher incidence ratio of sensorineural hearing loss than HIV negative MDR-TB patients during the intensive phase of MDR-TB treatment.

The results of the hypothesis testing are presented in Chapter 5.

### 7.2 RESEARCH DESIGN AND METHODS

This was a quantitative observational correlational prospective cohort study with a nested case-cohort study. The results of the empirical study were used to develop draft best practice guidelines, which were presented to key informants, guidelines development committee and to stakeholders for validation.

The empirical study was conducted between November 2012 and October 2014 and the findings used to answer the research questions posed at the beginning of the study. By answering the research questions, the researcher was able to build a local evidence base to inform the best practice guidelines the empirical study was conducted in a high HIV and TB prevalence setting and the study population consisted of MDR-TB patients attending MDR-TB treatment sites for their treatment initiation and monthly treatment follow up. The researcher enrolled a cohort of 173 respondents who were followed up until when they hearing loss developed, completed 8 months of the intensive phase of DR-TB treatment, or were lost to follow up. Data was collected using longitudinal data collection method for the monthly measurement of hearing sensitivity using pure tune audiometry and laboratory
parameters, analysis and interpretation statistical measures by exposure to HIV and other risk factors and characteristics using STATA statistical software. Results were presented using tables, graphs (see Chapter 4), and discussed in chapter 5. The Cohort design allowed for the determination of incidence; accurate relative risk (risk ratio) estimation; inference to the temporal relationship; time-to-event analysis for development of hearing impairment; and quantification of risk factor’s effect on hearing loss and optimised information bias through unambiguous identification of study population.

While some existing international guidelines provided recommendations to conduct audiometry to monitor hearing loss, no clear guides were provided on the “how” and the “who”. Key evidence for the formulation of the guidelines arose from the summary of the literature review and findings of an empirical study conducted by the researcher (2012-2014). Stakeholder involvement comprised many separate meetings and platforms to present the findings from critical appraisal of the literature and the empirical study and enrich the draft.

7.3 THEORETICAL MODEL

The study is based on the application of Neuman’s Systems model. The model provides a comprehensive flexible holistic and system based perspective for nursing and health care for patients being treated for MDR-TB. Developed by Betty Neuman, the Neuman's System model is a nursing theory based on following key concepts:

- the client system (which maybe an individual, family group or community);
- interacting variables of the client system which are the physiological, psychological, spiritual, developmental and sociocultural;
- client’s response to actual or potential environmental stressors (internal, external and created environments), the reaction to it, and reconstitution factors that are dynamic in nature (Freese & Lawson 2010; Geib 2010:237).
• emphasis on prevention, as intervention for retention, attainment, and maintenance of optimal client system wellness; and
• The purpose of the nurse is to retain of the client system's stability through the three levels of prevention.

Primary prevention to protect the normal line and strengthen the flexible line of defence. Primary prevention relates to good clinical practice that is applied in client assessment and intervention, in identification and reduction of possible or actual risk factors. Secondary prevention to strengthen internal lines of resistance, reducing the reaction, and increasing resistance factors. Secondary prevention also relates to symptomatology following a reaction to stressor, appropriate ranking of intervention priorities and treatment to reduce their noxious effects. Tertiary prevention to readapt and stabilise and protect reconstitution or return to wellness following treatment. Tertiary prevention also relates to adjusted processes taking place as reconstitution begins.

Betty Neuman Systems model provides a comprehensive, flexible, holistic, and system-based perspective for medical practice including monitoring and prevention of hearing loss for patients on MDR-TB treatment. It also provides a structure for critical thinking (an active process that guides action). It also guides a framework for the development of comprehensive diagnoses, determination of appropriate interventions and evaluation of outcomes as part of the nursing diagnosis, treatment goals, and Outcomes. The review of the literature revealed the four paradigms of Neumann Systems model.

i) The person is viewed the human being as well as a total person, as a client system, and the person is a layered multidimensional being physiological (physicochemical structure and function of the body); psychological (has mental processes and emotions); has relationships and social/cultural expectations and activities; has spiritual beliefs and undergoes processes related to development over the lifespan.

ii) The environment: the model considers the environment with the totality of the internal and external forces (intrapersonal, interpersonal, and extra-personal stressors) which surround a person and with which they interact at any given time).
iii) Health, whereby the model equates health to wellness where the condition in which all parts and subparts (variables) are in harmony with the whole of the client and the client system moves toward illness and death when more energy is needed than is available;

iv) Medical practice/nursing- giving a unique profession that is concerned with all of the variables, which influence the response a person might have to a stressor, a person is seen as a whole, and it is the task of nursing to address the whole person. The expected actions are those that will assist individuals, families and groups to maintain a maximum level of wellness, and the primary aim is stability of the patient/client system, through nursing interventions to reduce stressors by the use of primary, secondary, and tertiary interventions.

### 7.4 SUMMARY AND INTERPRETATION OF RESEARCH FINDINGS

The findings of the study from the two phases are summarised and presented according to the study objectives.

#### 7.4.1 Establish the incidence of hearing loss among drug resistant TB patients receiving DR-TB treatment in Swaziland

The study revealed that sixty-percent of the patients developed high frequency hearing loss. The incidence rate among the HIV positive patients was 4.2/1 000 person days (CI: 3.4-5.3) and for HIV negative patients, 3.6/1 000 person days (CI: 2.4-5.7). The incidence is similar to Botswana (62%) and South Africa (47%).

#### 7.4.2 Determine the risk factors for hearing loss associated with DR-TB treatment

The study validated findings by Wu and others who have also shown that HIV prevalence, and length of treatment were not significant factors for hearing loss (Wu et al 2013).
7.4.3 Determine the extent to which HIV/AIDS influenced the incidence of hearing loss related to MDR-TB treatment in Swaziland

The study found that HIV infection was not an independent risk factor for hearing loss in MDR-TB patients. However, use of certain ARVs especially Abacavir containing regimens predisposed an individual to a higher odd of hearing loss.

7.4.4 Determine the optimal frequency for audiology testing for monitoring of patients on DR-TB treatment in Swaziland

This is the first prospective study to date to examine meticulously the time it takes for persons on MDR-TB treatment to develop hearing loss. We found that the median time to high frequency hearing loss was 84 days with a range from 54.5 days to 147 days. The respondents were followed up at 22,032 person days.

7.4.5 Develop best practice guidelines for the monitoring and prevention of hearing loss related to MDR-TB treatment

These best practice guidelines are expected to assist in decision-making during clinical management of patients, and policy planning and key objectives of the best practice guideline are to:

1. To raise awareness of the adverse effects of ototoxic MDR-TB drugs to enable early detection and prevention of SNHL;
2. To facilitate early identification, diagnosis and treatment of hearing loss and deafness among TB patients as a result of ototoxicity;
3. To strengthen institutional capacity towards preventing SNHL deafness and hearing loss among MDR-TB patients;
4. To provide guidelines for rehabilitation and psychosocial support to affected patients;
The best practice guidelines were grouped into three thematic areas:

- Guidelines for prevention, treatment, and management of hearing loss comprising establishing an ototoxicity-monitoring programme. Involving all health care workers, health care administrators with clear and delineated roles assessing risk factors to hearing loss prior to exposure to second-line anti-TB medications. And a system for monitoring of ototoxicity through pharmacovigilance protocols and tools.

- Guidelines for procedures to be conducted by health care providers encompassing baseline audiometry conducted prior to initiating treatment, or within 72 hours of the first dose of an aminoglycoside or polypeptide antibiotic, addressing all modifiable risk factors for hearing impairment (dehydration, renal insufficiency, dyspnöea, and fever) their correction prior to administration of aminoglycosides or polypeptide antibiotics, scheduling audiometry.

- Guidelines for Documentation and Record Keeping encompasses guidelines for training in documentation and record keeping of adverse drug reactions.

- Guidelines for Public Health Actions which encompasses Guidelines for communication strategy and public education for the public, professional education and training health care workers as well as engagement of policy makers for appropriate regulatory and legislation framework.

Hypothesis testing

The study failed to reject both hypothesis stated at the beginning of study.
7.5 CONCLUSIONS

The study found a very high incidence of hearing loss associated with MDR-TB treatment. It also highlighted modifiable and non-modifiable risk factors for DR TB treatment related sensorineural hearing loss, as follows on univariate and bivariate analysis.

- being of male gender (p value =0.033),
- poor baseline hydration status at the start of MDR-TB treatment (p value =0.012),
- use of Abacavir as backbone in the ART regimen in MDR-TB (p value =0.017), and
- low of <8 g/dl baseline HB (p value <0.001), low BMI (p value =0.003), presence of dyspnoea at the start of treatment (p value < 0.001 ) were found to be risk factors for high frequency hearing loss.

On multivariate analysis, and after controlling for confounders the following variables showed a very high hazard rates:

i) compared to agriculture as a day-to-day employment, the hazard ratio of high frequency hearing loss was 4.2 times in the Miners/machine Operators and Sound Industry (HR: 5.4, CI 1.2-24.03, p value =0.024);

ii) Patients who had dyspnoea at initiation of MDR-TB treatment were 3.4 times likely to develop high frequency hearing loss (HR: 3.4, CI 1.8-6.3, p value =0.000) and

iii) Low baseline haemoglobin was a risk factor for hearing loss (p value<0.01). Patients with HB 8-11 g/dl and those with HB less than 8g/dl were 2 times and 8.5 times respectively more likely to develop hearing loss compared to those with HB above 11g/dl (p value <0.01).

iv) The median time to hearing loss was 84 days (IQR 54.5 -147)
7.6 RECOMMENDATIONS

Based on the results of the study, the following recommendations are presented:

- There is a need for the establishment of stringent pharmacovigilance systems to document and quantify all drug induced adverse events. The MDR-TB best practice guidelines therefore recommend careful and systematic monitoring of patients to help prevention as much possible hearing loss as a result of ototoxicity. Monitoring should include comprehensive patient assessment of risks and major determinants of ototoxicity, before they are initiated on the drugs, surveillance of proper dosage and duration, as well as assessment of symptoms. Wherever possible, audiometry should be carried out periodically for high risk TB patients.

- Adoption and effective utilisation of the best practice guidelines in Swaziland, which then is expected to generate the following benefits:

  1. Availability of local community-based and national centralized services for prevention, early identification, treatment, referral and rehabilitation for MDR-TB treatment-related SNHL and deafness
  2. Reduction in the incidence, severity and extent of MDR-TB-related hearing impairment.
  3. Improved service network and referral system
  4. Increased awareness of ototoxic MDR-TB drug side effects among health workers, including how to detect, manage and prevent them
  5. Increased capacity of health workers to improve the quality of care for affected patients.

- Training and capacity building of health workers on the rational use of ototoxic drugs among TB patients remains critical to prevent the inappropriate and discriminatory use of these drug by health workers managing TB patients. This
training should be given continuously as part of their continued professional development.

- The public should be made aware of the adverse effects and potential damage some TB drugs may have on their hearing to help them report any effects that could be noticed among TB patients. Production of education materials with a clear message would go a long way in acquainting the public on the hazards of ototoxic drugs among TB patients.

- Investments in need technology for alleviating loss is urgent. Exciting possibilities have been report in Nature through the use of stem cell and gene therapy and the possibility that auditory function can be restored or at least maintained reveals the need for more research in this area (Muller & Barr-Gillespie 2015).

- New drugs that are safe and of a shorter duration are also urgently required. However in the meantime, national governments should strongly consider the use of new and repurposed drugs that have less impact on hearing to be utilised for patients with risk factors that cannot be modified. The notion of use of the repurposed drugs may provide hope for the multitudes in dare need of MDR-TB treatment but without its ADRs such as irreversible hearing loss.

- Given the inadequate accessibility to audiometry screening in low resource settings, mobile devices such as smart phones can be used for initial screening of hearing loss prior to referral to hearing sensitivity testing centres.

Further research is required into the following areas:

- Linkage between ototoxicity and vestibulotoxicity;
- Impact of an ototoxicity programme on the reduction in the incidence of hearing loss;
- Experiences and needs of patients experiencing hearing loss;
- Effectiveness of an assisted hearing programme for MDR-TB patients;
Perceptions of family members on hearing loss in family members experiencing hearing loss and their role as hearing relatives in promoting communication;

Impact of newer drugs with less ototoxic effects and the repurposed drugs on hearing loss.

### 7.7 CONTRIBUTIONS OF THE STUDY

The key contributions of the study can be summarised as: generation of local evidence, sensitisation of clinicians, policy makers and managers about hearing loss, development of best practice guidelines that have been adopted from the MOH, policy advocacy and identification of areas for further research.

This study was conducted at a time when the rate of MDR-TB is increasing in Swaziland, and globally, at alarming rates and the threat of further resistance projected unless several interventions to control the epidemic were put in place, including development of new and safer drugs. The rapid scale-up of current treatments is associated hearing loss related to MDR-TB and the increasing interest in the area reveals that hearing loss is more widespread than previously thought. Moreover, while tuberculosis itself is a cause, sometimes it has catastrophic financial consequences to individuals and families. Patients and families need protection against the additional potential catastrophic psychosocioeconomic impact of adult onset hearing loss through better monitoring and prevention strategies, and assisted hearing technologies as part of the MDR-TB treatment package. Raising awareness about this required generation of local evidence. It must be pointed out that the study generated new data to fill specific knowledge on hearing loss associated with MDR-TB treatment. Beyond raising awareness and sensitisation of health cares for engagement, the knowledge generated has many other potential applications such advocacy for enabling policies and resources, exposing need gaps in knowledge and hence the identification of further areas of research and the development of guidelines, protocols and job aides for health care workers. The findings can also be used as a motivation tool for health care workers’ engagement in the monitoring of patients for hearing loss and in the provision of timely intervention to avert the potential psychological,
physical, social and economic consequences of hearing loss. Loss of hearing is a silent, destructive condition that contributes to immense human suffering and globally is a huge contributor to years lived with disability.

The possible implications of the study include the following:

- **Improving Clinical Practice, Patient care and Quality of life.** According to the Institute of Medicine, clinical practice guidelines are defined as “…statements that include recommendations, intended to optimise patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options”. Accordingly, guidelines have two parts: i) a systematic review of the existing evidence from studies, in response to a clinical question in mind, considering the strength of the evidence on which clinical decision-making for that condition is based as the basis of the guideline. And ii), a set of recommendations, involving both the evidence and value judgments regarding benefits and harms of alternative care options, addressing how patients with that condition should be managed, everything else being equal (Consensus report, institute of medicine. Clinical practice guidelines we can trust. March 23, 2011, 2011). This study contributes to the call made by Sturdy and others, who have studied hearing loss and anti-MDR-TB treatments, for better clinical data to inform guidelines for monitoring hearing loss related to MDR-TB treatment (Sturdy et al 2011). The study also translates the evidence into practice guidelines in line with what Davies et al (2008:29), Dulko (2007:29), Herdeiro, Polonia et al (2004:483-9), Ploeg, Davies, et al (2007:2010-9) and Tanenbaum (2005:163-73) have posited that the goal of research evidence is to change the practitioners’ behaviour by bridging the distance from research to practice and securing a central place for research in the consulting room. The results of the study demonstrate a high burden of hearing loss among MDR-TB patients is Swaziland. While there is no difference in the incidence of hearing loss between HIV negative and HIV positive patients, the study time-to-event analysis shows that HIV positive patients develop hearing loss sooner than the negative counter parts. There is need for more aggressive monitoring in
people living with HIV for hearing sensitivity, but this needs to be preceded with otologic and tympanometric examinations to rule out other middle ear conditions that are associated with HIV. Given a lack of guidelines, this leads to unregulated practice and missed opportunities for better patient care. As a product of the study, best practices have been developed, and thus provide a basis for implementing standardised monitoring practices to improve quality of patient care and minimise variations in service delivery.

- Raising awareness on the need for pharmacovigilance system for all adverse drug reactions: The study provides evidence of the big problem facing patients on MDR-TB treatment in Swaziland and the need to urgently institute measures for pharmacovigilance. WHO has recommended implementation of pharmacovigilance by all countries but this has lagged behind in Swaziland (World Health Organization 2011c). The results of the study were used to sensitise stakeholders on hearing loss monitoring and need for pharmacovigilance. Renewal of interest in pharmacovigilance is a critical contribution of the study and the potential result is envisaged as imparting positive attitude of managers towards availing of resources and tools for monitoring all the ADRs related to MDR-TB treatment.

- Awareness of the need to provide Counselling and support to patients and families: The study corroborates the findings by Groce and others that the deaf in Swaziland face communication problems with health care workers and are more likely to be misinformed about HIV prevention measures. Therefore, for families of the people with hearing loss, sign language and communication skills for patients and significant others needs to be taught. Collaboration with sign language organisations to train staff at the MDR-TB treatment sites becomes an essential package of the community linkages component of MDR-TB care.

- Guidance to Policy makers and health planners: This research documents the quantifiable outcomes of a standardised intervention and enables evidence based planning and a basis for construction of a hearing health policy for MDR-TB patients. Policy makers and health planners will be able to use the evidence to create an enabling environment for early intervention and data for planning
procurement hearing aid services/ assisted listening devices, rehabilitation and reintegration of cases of hearing impairment and family counselling and education.

7.8 STUDY LIMITATIONS

Data in a longitudinal study is more likely to be incomplete and of poorer quality because of the frequency of loss to follow up and missing data. In this study, although it was the doctors and patients made decisions on the next appointment, appoint schedules were tracked by the study team. Sometimes the treatment follow-up appointment dates and the audiology follow-up appointment conflicted. To avert any potential threat to the validity of the study strategies to ensure adequate follow up for audiometry appointments were devised. Follow up was done telephonically through short text messages (sms) or voice reminders and transport re-imbursements were made follow up reminders.

The findings in this study are representative of incidence of hearing loss for the 8 months when patients were on the intensive phase of treatment during which, aminoglycoside antibiotics are a key medicine. Some studies shown evidence of progressive ototoxic effects even after the stoppage of the offending drug (Seddon, Thee, Jacobs, Ebrahim, Hesseling & Schaaf, 2013a). The eight months follow up period however, represents the current WHO recommended duration for injectable aminoglycosides. The findings from this study, therefore, cannot, be extrapolated for the entire MDR-TB treatment period of 24 months.

In order to determine the incidence of hearing loss, repeated audiometry testing of respondents over time was conducted. Repeated measures can also lead to confounding due to learning effects. The audiology team was aware of this and hence exercise extra caution. Where indicated, non-behavioural testing methods using of ABR studies were conducted to negate this effect.

One of the main weaknesses for observational studies is confounding and measures were undertaken to minimise consequences of confounding. Given that the researcher does
not allocate exposure there is always a possibility that known and unknown potential confounders that influence outcome and hence lead to bias. Therefore, in this study, a priori identification of potential confounders was done and unknown confounders dealt with immediately they were discovered, during the data collection or analysis. Techniques such as restriction of participation in the study and stratified analysis within strata of the confounding variables (for example age) were used..

Despite the limitations, the findings from the study are reliable and valid

### 7.9 CONCLUDING REMARKS

According to the WHO, multidrug resistant tuberculosis MDR-TB is a global health security risk and carries grave consequences for those affected and WHO therefore called for MDR-TB to be addressed as a public health crisis in 2013. Prevention of MDR-TB is the first priority, while scaling up rapid testing, detection of all MDR-TB cases and prompt access to appropriate MDR-TB care and preventing transmission of MDR-TB through appropriate infection control are the next priorities. Currently use of ototoxic medications in the treatment regimens adversely affects quality of life of patients during treatment and in the post treatment period and associated mortality due to poor adherence to MDR-TB treatment.

Hearing loss remains an invisible and unrecognised public health issue with grave social, psychological, and economic consequences. Currently, guidelines for early detection and management to halt further deterioration of hearing sensitivity for patients on MDR-TB treatment in the low and middle-income countries that bear the greatest brunt of MDR-TB to deal are lacking. Existing guidelines are largely inadequate and clinicians do not give adequate guidance on what to do when and how. While the best practice guidelines developed in this study will go a long way in assisting health care workers in Swaziland improve practice in dealing with hearing health of MDR-TB patients, the ultimate goal should be replacing the aminoglycosides in the MDR-TB regimen. In the meantime,
advocacy should be stepped up for the use new and repurposed drugs like Bedaquiline and Delaminad for treating patients at high risk for MDR-TB treatment related hearing loss.
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ANNEXURES
ANNEXURE A: Supporting letters
A1 High degrees Committee approval
FROM: The Chairman  
Scientific and Ethics Committee  
P. O. Box 5  
Mbabane

TO: Dr Haumba  
Principal Investigator

DATE: 30th March 2012

REF: MH/599C

RE: Best Practice Guidelines to monitor and prevent Drug Resistant T.B. Treatment Related Hearing Impairment

The committee thanks you for your submission to the committee on the above mentioned title. After reviewing your protocol the committee requests that you attach a budget as this seems to be a complicated and well involved study. The study title is okay and the facts are well documented, your objectives are justified and well presented. The design is very detailed but too scientific, it could have been simplified. The study is in accordance with ethical and scientific standards, the committee therefore grants you authority to conduct the study. You are requested to adhere to the specific topic and inform the committee through the chairperson of any changes that might occur in the duration of the study which are not in this present arrangement.

The committee wishes you the best and is eagerly awaiting findings of the study to inform proper planning and programming to use for analysis

Yours Sincerely,

[Signature]

Dr S.M. Zwane  
Chairperson Scientific and Ethics Committee  
cc: See Members
ANNEXURE A3: Application for approval by Management of the TB Hospital

The Senior Medical Officer,
National TB hospital
Ministry Of Health,
Manzini, Swaziland,
Dear Sir,

RE: BEST PRACTICE GUIDELINES TO MONITOR AND PREVENT DRUG RESISTANT TUBERCULOSIS TREATMENT RELATED TO HEARING IMPAIRMENT - DOCTOR OF LITERATURE ET PHILOSOPHY (Health Studies) RESEARCH PROPOSAL

I submit my application to request permission for the above mentioned research to be conducted at your health facility in Swaziland as a partial fulfillment for my doctoral study. I declare that the researcher is competent and accountable and will strive to achieve the highest possible level of excellence, integrity and scientific quality in the research. The research will benefit society and contribute to knowledge on the subject of multi-drug resistant TB induced hearing impairment. All efforts will be made to ensure that information on the research undertaken, as well as the results and implications of the completed research are appropriately disseminated and contribute to the development of guidelines to monitor and prevent drug resistant tuberculosis treatment related hearing impairment.

In case of additional information, the applicant can be contacted on +26876026400 or +26824047154. Consideration for the application will highly be appreciated.

Yours sincerely,
Dr Samson Mlwita Haumba, MPH, MB (Int Med), MD
Researcher/ Doctoral Student
ANNEXURE B

ANNEXURE B1: QUESTIONNAIRE 1: GENERAL QUESTIONNAIRE

BEST PRACTICE GUIDELINES TO MONITOR AND PREVENT DRUG RESISTANT TUBERCULOSIS TREATMENT RELATED HEARING IMPAIRMENT

Respondent’s Number…………………….. Date…………………….. Treatment facility………………..

Office Use

SECTION A: RESPONDENT’S DEMOGRAPHIC CHARACTERISTICS

Please indicate the appropriate option in the shaded box adjacent to the option

<table>
<thead>
<tr>
<th>1. Age (at last birthday)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>15-19 years</td>
<td>1</td>
</tr>
<tr>
<td>20-24 years</td>
<td>2</td>
</tr>
<tr>
<td>25-29 years</td>
<td>3</td>
</tr>
<tr>
<td>30-34 years</td>
<td>4</td>
</tr>
<tr>
<td>35-39 years</td>
<td>5</td>
</tr>
<tr>
<td>40-44 years</td>
<td>6</td>
</tr>
<tr>
<td>45-49 years</td>
<td>7</td>
</tr>
<tr>
<td>50-54 years</td>
<td>8</td>
</tr>
<tr>
<td>55-59 years</td>
<td>9</td>
</tr>
<tr>
<td>60-64 years</td>
<td>10</td>
</tr>
<tr>
<td>65+</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Gender</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male=1</td>
<td>Female=2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Nationality and Race</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Swazi: Black of African</td>
<td>1</td>
</tr>
<tr>
<td>Swazi: Caucasian/White</td>
<td>2</td>
</tr>
<tr>
<td>Other Nationality: Black of African</td>
<td>3</td>
</tr>
<tr>
<td>Other nationality: Caucasian/White</td>
<td>4</td>
</tr>
<tr>
<td>Other Nationality: other race than any of above</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Region</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Hhohho</td>
<td>1</td>
</tr>
<tr>
<td>Manzini</td>
<td>2</td>
</tr>
<tr>
<td>Lubombo</td>
<td>3</td>
</tr>
<tr>
<td>Shiselweni</td>
<td>4</td>
</tr>
<tr>
<td>Does not know</td>
<td>5</td>
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</tbody>
</table>

Respondent’s Number……………….. Treatment facility………………..
### 5. Highest level of education

<table>
<thead>
<tr>
<th>Education Level</th>
<th>Code</th>
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</thead>
<tbody>
<tr>
<td>No Education</td>
<td>1</td>
</tr>
<tr>
<td>Completed Primary school (7th Grade)</td>
<td>3</td>
</tr>
<tr>
<td>Completed secondary school (5th Grade)</td>
<td>5</td>
</tr>
<tr>
<td>Tertiary education</td>
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</tr>
<tr>
<td>Do not know/ missing</td>
<td>99</td>
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</table>

### 6. Employment Status

<table>
<thead>
<tr>
<th>Employment Status</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currently employed (did work in past 1 month: includes those on leave, sickness, regularly employed)</td>
<td>1</td>
</tr>
<tr>
<td>Not employed in the last 12 months</td>
<td>2</td>
</tr>
<tr>
<td>Not employed for more than 12 months</td>
<td>3</td>
</tr>
<tr>
<td>Minor (Child)</td>
<td>4</td>
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<tr>
<td>Does not know</td>
<td>99</td>
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</table>

### 7. Profession

<table>
<thead>
<tr>
<th>Profession</th>
<th>Code</th>
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</thead>
<tbody>
<tr>
<td>Professional/Technical/Managerial</td>
<td>1</td>
</tr>
<tr>
<td>Clerical</td>
<td>2</td>
</tr>
<tr>
<td>Sales and services</td>
<td>3</td>
</tr>
<tr>
<td>Skilled Manual</td>
<td>4</td>
</tr>
<tr>
<td>Unskilled manual</td>
<td>5</td>
</tr>
<tr>
<td>Mining/ machine operator</td>
<td>6</td>
</tr>
<tr>
<td>Sound technician/music industry</td>
<td>7</td>
</tr>
<tr>
<td>Agriculture</td>
<td>8</td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
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</tbody>
</table>

### 8. Marital Status

<table>
<thead>
<tr>
<th>Marital Status</th>
<th>Code</th>
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<tbody>
<tr>
<td>Never married</td>
<td>1</td>
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<tr>
<td>Married</td>
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</tr>
<tr>
<td>Living together</td>
<td>3</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>4</td>
</tr>
<tr>
<td>Widowed</td>
<td>9</td>
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</tbody>
</table>

### 9. Religious affiliation

<table>
<thead>
<tr>
<th>Religious Affiliation</th>
<th>Code</th>
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</thead>
<tbody>
<tr>
<td>Protestant/Anglican</td>
<td>1</td>
</tr>
<tr>
<td>Roman Catholic</td>
<td>2</td>
</tr>
<tr>
<td>Charismatic</td>
<td>3</td>
</tr>
<tr>
<td>Pentecostal</td>
<td>4</td>
</tr>
<tr>
<td>Apostolic</td>
<td>5</td>
</tr>
<tr>
<td>Methodist</td>
<td>6</td>
</tr>
<tr>
<td>Seventh Adventian</td>
<td>7</td>
</tr>
<tr>
<td>Zionist church</td>
<td>8</td>
</tr>
<tr>
<td>None</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
</tr>
</tbody>
</table>
SECTION B: Treatment

HISTORY OF TREATMENT FOR PREVIOUS TB DISEASE

10. Has the patient ever received medication for TB disease in the past?
   ☐ No ☑ Yes ☐ Unknown (If no, skip to #13)

11. If the patient was treated for TB please indicate date and type of Tuberculosis the patient was treated for during first episode of tuberculosis:
   11a) Date:ursos-uros-uros-uros
   11b) Type: ☐ Drug susceptible TB (New); ☐ Drug susceptible TB (Retreatment/Previously treated); ☐ Drug Resistant TB

If the patient was treated for TB more than once in the past, please indicate date and type of Tuberculosis the patient was treated for during second episode of tuberculosis:
   11c) Date:ursos-uros-uros-uros
   11d) Type: ☐ Drug susceptible TB (New); ☐ Drug susceptible TB (Retreatment/Previously treated); ☐ Drug Resistant TB

12. Was patient ever treated with streptomycin during any of the previous episode(s) of tuberculosis treatment? ☐ No ☑ Yes

13. Please indicate when TB treatment with streptomycin started and for how long:
   Streptomycin start:ursos-uros-uros-uros
   Duration of Streptomycin: ☐ 1 One month or less; ☐ 2 between one and Two months inclusive; ☐ 3 More than 2 months

CLINICAL SYMPTOMS AT MDR-TB DIAGNOSIS

14. At the time of diagnosis of Drug Resistant, please indicate which of the following symptoms where present

   1. High-grade fever (≥ 38.0 °C) ☐ No ☑ Yes 9. Diarrhea ☐ No ☑ Yes 10. Loss of appetite ☐ No ☑ Yes
   2. Low-grade fever (37.0 - 37.9 °C) ☐ No ☑ Yes 10. Loss of appetite ☐ No ☑ Yes
   3. Sweats ☐ No ☑ Yes 11. Nausea/vomiting ☐ No ☑ Yes
   4. Dry cough ☐ No ☑ Yes 12. Visual problems ☐ No ☑ Yes
   5. Productive cough ☐ No ☑ Yes 13. Dyspnea ☐ No ☑ Yes
   6. Blood spitting ☐ No ☑ Yes 14. Headache ☐ No ☑ Yes
   7. Chest pain ☐ No ☑ Yes 15. Hearing loss ☐ No ☑ Yes
   8. Weakness ☐ No ☑ Yes 16. Weight loss ☐ No ☑ Yes

Respondent’s Number..................  .. Treatment facility..................

17. Thirsty and Drinking a lot of water ☐ No ☑ Yes 18. Other (specify)......... ☐ No ☑ Yes

19. Other (specify)................. ☐ No ☑ Yes 20. Other (specify)................. ☐ No ☑ Yes

14b. At the time of diagnosis of Drug Resistant, please indicate if this was confirmed or presumed
DR-TB:

1 Presumed MDR-TB  2 Confirmed DR-TB

14C. At the time of bacteriological confirmation of Drug Resistant TB, please indicate if the Drug susceptibility testing (DST) indicated revealed the following confirmation of DST:

1 Isoniazid Mono-Resistant DR-TB (IMR)  2 Rifampicin Mono-Resistant DR-TB (RMR)

3 Isoniazid & Rifampicin Resistant DR-TB (MDR)  4 Second Line Resistant (either FLQ or SL Aminoglycoside DR-TB (Pre-XDR)

HIV SEROLOGY RESULTS AT INITIAL DIAGNOSIS OF THIS TB EPISODE

15. HIV test results  0 Negative  1 Positive  99 Not taken

16. Date of HIV test at initial diagnosis of this episode:  dd-mm-yyyy

Date Unknown

16a. Absolute CD4 count

1 < 200

2 200-500  3 > 500

4 Not taken (if not taken, tick & skip to #24c)

16c. The date of absolute CD4 count  dd-mm-yyyy  Unknown

16d. Is the patient currently taking HIV treatment?  1 No treatment  99 Unknown

2 Antiretroviral therapy
17. MDR-TB TREATMENT REGIMEN:

<table>
<thead>
<tr>
<th>K</th>
<th>C</th>
<th>A</th>
<th>S</th>
<th>Ethio</th>
<th>PAS</th>
<th>Cs</th>
<th>Ter</th>
</tr>
</thead>
</table>

18. Date when the current DR-TB treatment regimen prescribed (DATE of THIS MDR REGIMEN):

19. Date when drugs were received and patient started treatment (START DATE of THIS MDR REGIMEN):

<table>
<thead>
<tr>
<th>A. Drug</th>
<th>B. Status</th>
<th>C. Start Date</th>
<th>D. Frequency of dose (#days/wk)</th>
<th>E. Dose (mgs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KANAMYCIN</td>
<td>0</td>
<td>1</td>
<td>5 13</td>
<td></td>
</tr>
<tr>
<td>CAPREOMYCIN</td>
<td>0</td>
<td>1</td>
<td>5 13</td>
<td></td>
</tr>
<tr>
<td>AMIKACIN</td>
<td>0</td>
<td>1</td>
<td>5 13</td>
<td></td>
</tr>
<tr>
<td>ETHIONAMIDE</td>
<td>0</td>
<td>1</td>
<td>5 13</td>
<td></td>
</tr>
<tr>
<td>CYCLOSERINE</td>
<td>0</td>
<td>1</td>
<td>5 13</td>
<td></td>
</tr>
<tr>
<td>TERIZDONE</td>
<td>0</td>
<td>1</td>
<td>5 13</td>
<td></td>
</tr>
<tr>
<td>LEVOFLOXACIN</td>
<td>0</td>
<td>1</td>
<td>5 13</td>
<td></td>
</tr>
<tr>
<td>PAS</td>
<td>0</td>
<td>1</td>
<td>5 13</td>
<td></td>
</tr>
<tr>
<td>PYRAZINAMIDE</td>
<td>0</td>
<td>1</td>
<td>5 13</td>
<td></td>
</tr>
<tr>
<td>Other 1:</td>
<td></td>
<td></td>
<td>5 13</td>
<td></td>
</tr>
<tr>
<td>Other 2:</td>
<td></td>
<td></td>
<td>5 13</td>
<td></td>
</tr>
</tbody>
</table>

20. Duration on the MDR-TB injectable drug at baseline evaluation

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>1</th>
<th>Treatment &lt; 72 hours</th>
<th>2</th>
<th>Treatment 4-7 days</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment 8-14 days</td>
<td>4</td>
<td>Treatment 15-21 days</td>
<td>5</td>
<td>Treatment 22-28 days</td>
<td>6</td>
</tr>
<tr>
<td>Other (specify)</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

21. Duration on the MDR-TB injectable drug at Follow up evaluation (see follow up sheet)

Section C: Medical History
21. Does you suffer from (ever been diagnosed) any of the following conditions?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Status</th>
<th>Duration of condition</th>
<th>Treatment</th>
<th>Duration on treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mont hs</td>
<td>Year s</td>
<td>weeks</td>
<td>Months</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
</tr>
<tr>
<td>Renal disease</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
</tr>
<tr>
<td>Cancer(specify)</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
</tr>
<tr>
<td>Persistent fever</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
</tr>
<tr>
<td>Kaposi Sarcoma</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>☐ 0 No</td>
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<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
</tr>
<tr>
<td>Silicosis</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
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<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
</tr>
<tr>
<td>Other</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
</tr>
<tr>
<td>Other</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
</tr>
</tbody>
</table>

22. Are you currently using or used the following medications in the last 2 weeks for treatment of any of the above conditions?

<table>
<thead>
<tr>
<th>B. Drug</th>
<th>B. Status</th>
<th>C. Start Date</th>
<th>D. Frequency of dose (#days/wk)</th>
<th>E. Dose (mgs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide (oral)</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>dd - mm - yyyy</td>
<td>☐ 7 D ☐ 5</td>
</tr>
<tr>
<td>Furosemide (Inj)</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>dd - mm - yyyy</td>
<td>☐ 7 D ☐ 5</td>
</tr>
<tr>
<td>erythromycin</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>dd - mm - yyyy</td>
<td>☐ 7 D ☐ 5</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>dd - mm - yyyy</td>
<td>☐ 7 D ☐ 5</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>dd - mm - yyyy</td>
<td>☐ 7 D ☐ 5</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>dd - mm - yyyy</td>
<td>☐ 7 D ☐ 5</td>
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<tr>
<td>Aspirin</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>dd - mm - yyyy</td>
<td>☐ 7 D ☐ 5</td>
</tr>
<tr>
<td>Insulin</td>
<td>☐ 0 No</td>
<td>☐ 1 Yes</td>
<td>dd - mm - yyyy</td>
<td>☐ 7 D ☐ 5</td>
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<tr>
<td></td>
<td>C. Drug</td>
<td>B. Status</td>
<td>C. Start Date</td>
<td>D. Frequency of dose (#days/wk)</td>
</tr>
<tr>
<td>---</td>
<td>------------------------------</td>
<td>-----------</td>
<td>---------------</td>
<td>---------------------------------</td>
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<tr>
<td>9</td>
<td>Oral hypoglycaemics</td>
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<td></td>
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<td></td>
<td>No</td>
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<td>Other 1</td>
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<td>11</td>
<td>Other 2</td>
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<tr>
<td></td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Respondent’s Number…………………..**

23. Kaposi Sarcoma Treatment [ ] No [ ] Yes Start Date dd-mm-yyyy
### 24. ARV Treatment

<table>
<thead>
<tr>
<th>A. Drug</th>
<th>B. Status</th>
<th>C. Start Date</th>
<th>D. Frequency of dose (#days/wk)</th>
<th>E. Dose (mgs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AZIDOVUDINE (AZT)</strong></td>
<td>0 No</td>
<td>dd-mm-yyyy</td>
<td>7 D 5 3</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TENOFOVIR</strong></td>
<td>0 No</td>
<td>dd-mm-yyyy</td>
<td>7 D 5 3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3TC</strong></td>
<td>0 No</td>
<td>dd-mm-yyyy</td>
<td>7 D 5 3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STAVUDINE (D4T)</strong></td>
<td>0 No</td>
<td>dd-mm-yyyy</td>
<td>7 D 5 3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NEVIRAPINE (NVP)</strong></td>
<td>0 No</td>
<td>dd-mm-yyyy</td>
<td>7 D 5 3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1 Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NEVIRAPINE (NVP) PMTCT</strong></td>
<td>0 No</td>
<td>dd-mm-yyyy</td>
<td>7 D 5 3</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1 Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EFERVIRENZ (EFV)</strong></td>
<td>0 No</td>
<td>dd-mm-yyyy</td>
<td>7 D 5 3</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1 Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OTHER 1</strong></td>
<td>0 No</td>
<td>dd-mm-yyyy</td>
<td>7 D 5 3</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1 Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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### 25. Any ear infections/disease

| 1 Childhood | 2 Adolescent | 3 Adult |


Section C Life Style and Physical parameters

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
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<tbody>
<tr>
<td>26. Do you smoke?</td>
<td>Current (even if stopped within last 6 months) 1</td>
</tr>
<tr>
<td>27. For current smoker, how many sticks do you smoke per day</td>
<td>&lt;2 per day 1</td>
</tr>
<tr>
<td>28. Do you drink alcohol?</td>
<td>Current (even if stopped within last 6 months) 1</td>
</tr>
<tr>
<td>29. From question 22, if current drinkers indicate drinks per week</td>
<td>&lt;7 per week 1</td>
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<tr>
<td>30. Please indicate how much water and fluids you take per day (minus alcohol)</td>
<td>Less than 500ml per day 1</td>
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<tr>
<td>31. Please indicate commonest source of the fluids you take</td>
<td>Water 1</td>
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<tr>
<td>32. Please indicate level of physical exercise you are engaged in</td>
<td>Yes regularly exercise &gt; 2 times weekly 1</td>
</tr>
<tr>
<td>33. Are you exposed to noise of more than 1 hour at work or leisure activities</td>
<td>Yes, at work 1</td>
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34. Biometry and Physical parameters

<table>
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<tr>
<th>DATE</th>
<th>WEIGHT (Kg)</th>
<th>HEIGHT (m²) (children at follow up)</th>
<th>Body TEMP (°C)</th>
<th>BMI (Weight/Height²)</th>
<th>BLOOD PRESSURE (Systolic/diastolic) mmHg</th>
<th>HYDRATION STATUS (Normal)</th>
<th>Audiometry summary</th>
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<td>Baseline Values</td>
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ANNEXURE B 2

QUESTIONNAIRE 2: HEARING LOSS SCREEN AND AUDIOLOGICAL TESTING

BEST PRACTICE GUIDELINES TO MONITOR AND PREVENT DRUG RESISTANT TUBERCULOSIS TREATMENT RELATED HEARING IMPAIRMENT

Respondent's Number……………………
Date……………………………………

Office Use

# ___________________________ Date:
__________________________

Date of Birth Age Gender M____ F____

Examiner __________________________
Date of Calibration

Self-Assessment of Communication for Prevalent Hearing loss

Please respond by circling the appropriate number ranging from 1 to 5, for the following questions. If you have a hearing aid, please fill out the form according to how you communicate when aid is not in use.

1 = almost never (or never); 2 = occasionally (about one-quarter of the time); 3 = about half of the time; 4 = frequently (about three-quarters of the time); 5 = practically always (or always).

Various Communication Situations

1. Do you experience communication difficulties in situations when speaking with one other person? (For example: at home, at work, in a social situation, with a waitress, a store clerk, a boss, etc.)

1 2 3 4 5 Q1= 

2. Do you experience communication difficulties in situations when conversing with a small group of several persons? (For example: with friends or family, co-workers, in meetings or casual conversations, over dinner, or while playing cards, etc.).

1 2 3 4 5 Q2= 

12
3. Do you experience communication difficulties while listening to someone speak to a large group? (For example, at church or in a civic meeting, in a fraternal or women’s club, at an educational lecture, etc.)

1 2 3 4 5  

Q3=

4. Do you experience communication difficulties while participating in various types of entertainment? (For example: TV, radio, plays, night clubs, musical entertainment, etc.)

1 2 3 4 5  

Q4=

5. Do you experience communication difficulties when you are in an unfavorable listening environment? (For example: at a noisy party, where there is background music, when riding in an auto or a bus, when someone whispers or talk from across the room, etc.)

1 2 3 4 5  

Q5=

6. Do you experience communication difficulties when using or listening to various communication devices? (For example: telephone, telephone ring, doorbell, public address system, warning signals, alarms, etc.)

1 2 3 4 5  

Q6=

Feelings about Communication

7. Do you feel that any difficulty with your hearing limits or hampers your personal or social life?

1 2 3 4 5  

Q7=

8. Does any problem or difficulty with your hearing upset you?

1 2 3 4 5  

Q8=

Other People

9. Do others suggest that you have a hearing problem?

1 2 3 4 5  

Q9=
10. Do others leave you out of conversations or become annoyed because of your hearing?

1 2 3 4 5

Q10=

11. Raw Score __________ (total of circled numbers; normal range: 10–18)

Q11=

Score Interpretation (Schow, Smedley, & Longhurst, 1990):

Raw score Handicap range

10–18 Normal-no handicap

19–26 Slight handicap

27–38 Mild-moderate handicap

39–50 Severe handicap

Case History- Circle most appropriate

12. Do you think you have hearing loss? Yes No

13. Have hearing aids ever been recommended for you Yes No

14. Is you hearing better in one ear Yes No

If yes, which ear

Right

Left

15. Have you ever had sudden deterioration in hearing Yes No

16. Do you have ringing or noises in the ears Yes No

17. Do you consider diuzzines to be a problem Yes No
18. Have you had recent drainage from your ears
   Yes  No

   If yes, which ear
   Right  Left

19. Do you have pain or discomfort in your ears
   Yes  No

20. Have you ever received medical consultation for any ear related problems?
   Yes  No

Visual/otoscopic examination

21. Otoscopic examination (baseline)

1  External appearance of the pinna
   Normal, Malformations, Inflamed

2  External auditory meatus
   Normal, Inflamed
   Occluding Wax
   Foreign body
   Pus discharge
   Other (specified)

3  Appearance of tympanic membrane
   Normal
   Dull
Opacified
Retracted,
Bulging
Redden
Air-fluid level
Scarred
Perforated

4 Tympanic membrane light reflex
Present
Absence
Deranged

5 Status of media ear (if OM perforated)
Normal
Inflamed
Discharge present
other

22. a) Refer for cerumen management __________________________
    b) Refer for medical Management __________________________

23. Screening Pure Tone Screen (25dB HL) (R=Response; NR=No Response)
<table>
<thead>
<tr>
<th>Frequency</th>
<th>1000</th>
<th>2000</th>
<th>4000</th>
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</table>

**Right Ear**

**Left Ear**

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<tr>
<th>Hearing Disability</th>
<th>Present? (tick one)</th>
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</thead>
<tbody>
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24. Type of Hearing Impairment

- **Sensorial** (1)
- **Conductive** (2)
- **Mixed** (3)
- **Other (Specify)**

25. Further Action: (Tick as appropriate)  

- **Medical Examination**  
  - Yes  
  - No
- **Cerumen Management**  
  - Yes  
  - No
- **Counsel**  
  - Yes  
  - No
- **Audiologic evaluation**  
  - Yes  
  - No
- **Include in the study cohort**  
  - Yes  
  - No
26. See audiogram for summary of the results from audiometry testing

27. Hearing status

Q27= [Blue Bar]

0-25 dB = Normal hearing;

26-40 dB = Slight hearing loss;

41-60 dB = Moderate hearing loss;

60-80 dB = Severe hearing loss;

81+ dB = Profound hearing loss.
Follow up sheet: Respondents #............................; Health Facility…………………………………………………………

1. Please indicate date of the follow Biometric and audiometric findings.

<table>
<thead>
<tr>
<th>Follow Up #</th>
<th>DATE</th>
<th>WEIGHT (Kg)</th>
<th>HEIGHT (m)(^2) (children at follow up)</th>
<th>Body TEMP (°C)</th>
<th>BMI (Weight/Height(^2))</th>
<th>BLOOD PRESSURE (Systolic/diastolic) mmHg</th>
<th>HYDRATION STATUS (Normal)</th>
<th>Audiometry summary</th>
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<td>HYDRATION STATUS (Normal)</td>
<td>Audiometry summary</td>
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2. Please indicate date AND intervention if any during the follow up period

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<th></th>
<th>Developed hearing loss; date</th>
<th>Drug adjustment recommended; date</th>
<th>Dose adjustment recommended; date</th>
<th>Hearing aids prescribed; date</th>
<th>Hearing aids fitted; date</th>
<th>Patient trained on sign language; date</th>
<th>Patient’s family counseled on hearing loss; date</th>
<th>Patient’s family trained on sign language; date</th>
<th>Other Intervention (Specify)</th>
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3. For patients develop hearing loss, please indicate period on treatment and date of follow up

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<td>Treatment weeks</td>
<td>29</td>
<td>Treatment weeks</td>
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</table>

4. For patients who die while on treatment, please indicate date of exit from cohort (period on treatment at date of death)

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<thead>
<tr>
<th>Treatment 1 week</th>
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<th>Treatment 2 weeks</th>
<th>2</th>
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<td>Weeks</td>
<td>Treatment</td>
<td>Grading</td>
<td>Intervention (if any)</td>
<td>Date of recording outcome</td>
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</table>

**5. For patients who are lost to follow up, please indicate date of exit from cohort (period on treatment at date of confirmed lost to follow up)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Weeks</th>
<th>Grading</th>
<th>Intervention (if any)</th>
<th>Date of recording outcome</th>
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</table>

**6. Please indicate date AND final audiometric outcome at the end on follow up period (completion of intensive DR-Treatment/ injection phase or at loss to follow up or at death)**

<table>
<thead>
<tr>
<th>Final Audiometric Outcome</th>
<th>Grading</th>
<th>Intervention (if any)</th>
<th>Date of recording outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ 0 Patient did not develop Hearing loss</td>
<td>☐ 0 Normal Hearing ☐ weeks of follow up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ 1 Patient developed</td>
<td>☐ 1 Mild HL</td>
<td></td>
<td></td>
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<tr>
<td>Hearing loss</td>
<td>weeks of follow up</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>2 Mod HL</td>
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<tr>
<td>3 Mod-Severe HL</td>
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<td></td>
<td></td>
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<tr>
<td>4 Severe HL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5 Profound HL</td>
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</tbody>
</table>

| 3 Patient was LOST to Follow up before HL could be detected | 0 Normal Hearing weeks of follow up before lost to follow up |   |

| 3  | 0  |   |
## B3 THE PILOT STUDY CHECKLIST

### Dimension and Aspect tested

#### Aspects tested for feasibility

<table>
<thead>
<tr>
<th>Question</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the anticipated number of patients that can be included in the study?</td>
<td></td>
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<tr>
<td>How many of the potential patients satisfy the inclusion and exclusion criteria?</td>
<td></td>
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<tr>
<td>Will the eligible respondents consent to receive monthly or two weekly audiometric follow up for 8 months of treatment on injectable antibiotics because some patients prefer to receive injections at home or at a clinic closest to them rather than the hospital?</td>
<td></td>
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<tr>
<td>Why may some respondents not want to take part or what are the reasons for drop out?</td>
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<tr>
<td>Are all medical files or information from other data sources retrievable?</td>
<td></td>
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<tr>
<td>Can all measurements be easily implemented and are they not too bothersome for the research respondents?</td>
<td></td>
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<tr>
<td>Is it possible to implement the intervention and/or study in a setting that did not have audiology services before and there were no dedicated staff for audiology services beyond the outreach services?</td>
<td></td>
</tr>
<tr>
<td>How much time does the measurement of hearing status procedure take, and how many patients can be assessed per day?</td>
<td></td>
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</tbody>
</table>

#### Aspects tested for methodological quality that were piloted

<table>
<thead>
<tr>
<th>Question</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are the measurement instruments valid?</td>
<td></td>
</tr>
<tr>
<td>Are the measurements reproducible: Are the research assistants performing the measurements in exactly the same way?</td>
<td></td>
</tr>
<tr>
<td>Was exposure (to HIV) being properly measured?</td>
<td></td>
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</tbody>
</table>

#### Aspects related to data management that were tested

<table>
<thead>
<tr>
<th>Question</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>How much support does the data collector need to accurately document the study related data? It is important during the data collection phase that the data continue to be collected accurately and in a standardised fashion.</td>
<td></td>
</tr>
<tr>
<td>Were the multiple measurements and calibration immediately verified, consistent?</td>
<td></td>
</tr>
<tr>
<td>Were multiple testing (test-retest by the same and/or different data collectors) and, calibration consistent?</td>
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<tr>
<td>Were questionnaires completed consistently and were there difficult questions that need to be modified?</td>
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<tr>
<td>Did the analysis of pilot data necessitate modifications to the test protocol, modifications in the number of respondents to be tested per day, or modifications in patient flow?</td>
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<tr>
<td>Are the systems sufficient for managing longitudinal files?</td>
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</table>
Dear participant, you are being asked to participate in a research study. Below are the details about the research study.

1. **Title of Research:** BEST PRACTICE GUIDELINES TO MONITOR AND PREVENT HEARING IMPAIRMENT AMONG PATIENTS RECEIVING DR-TB TREATMENT IN SWAZILAND

2. **Investigator's Name:** Dr. Samson Haumba,

3. **Research Entity:** University of South Africa

4. **Consenting for the Research Study:**

   This is an important document. If you sign it, you will be authorizing the University South Africa and its researchers involve you as a respondent for a research study. You should take your time and carefully read it.

5. **YOUR RIGHT TO PRIVACY AND CONFIDENTIALITY:**

   Very specific information on your right to privacy and the confidentiality of the use and disclosure of your personal health information can be found at the end of this consent form. We need your authorisation to use and disclose the health information that we may collect about you during this research study. To be in this research study you must read and sign the authorisation of this consent form.

6. **PURPOSE OF RESEARCH:**

   The purpose of this study is to determine incidence ratio and risk factors for MDR-TB treatment hearing loss; establish duration from treatment initiation to hearing loss; develop a local evidence base for development of best practice guidelines for monitoring hearing and prevention of MDR-TB treatment related hearing loss; and guide local policy for integrating hearing loss monitoring and prevention as integral part of the overall MDR-TB treatment strategy. You are being asked to participate in this study because you are on anti TB
medication. This research project is being conducted in partial fulfillment of the requirements for the degree of Doctor of Literature and Philosophy and you have been asked to take part in this study because you meet criteria for participation in this study.

7. **PROCEDURES:**

If you agree to take part in this study:

You will be asked to complete a set of questions that we ask about your health. This study is limited to completing these self-report questions, conducting a hearing measurement using an audiometer and taking all the relevant medical tests normally requested in management of TB or MDR-TB. All questionnaires will be destroyed after the completion of this study.

8. **RISKS AND DISCOMFORTS/CONSTRAINTS:**

Significant psychological or social risks are not anticipated to occur to you. You may experience slight discomfort such as embarrassment, mild fatigue, anxiety, or frustration while completing the items in the questionnaires. You may skip any questions that you do not wish to answer. The questions have been selected and arranged in a manner that will help complete them relatively quickly. If for any reason you decide that you do not want to participate in the study, you may withdraw from the study at any time.

9. **UNFORSEEN RISKS:**

Participation in this study may involve unforeseen risks. The study investigators do not anticipate any unforeseen risks to you in taking part in this study. If any unforeseen risks are noted, the Office of Secretary of the Scientific and Ethics committee in the Ministry of Health will be notified.

10. **BENEFITS:**

For some respondents, completing these questionnaires might provide an opportunity to think about their overall well-being in a more meaningful manner. For others, there may be no direct benefits from participating in this study. It is anticipated that frequent monitoring of your hearing status during the study is a good and recommended practice for all patients on injectable drugs used in the treatment of multi drug resistant TB and may be beneficial to you. It is also anticipated that the results from this study will be used for the common public health good of all patients.

11. **ALTERNATIVE PROCEDURES/TREATMENT:**
No alternative treatment is provided through this study. Only the treatment that will be prescribed by the doctors managing your condition will be provided to you. The alternative is not to participate in the study.

12. **REASONS FOR REMOVAL FROM STUDY:**

You may be required to stop the study before the end for any of the following reasons:

a) Change in medical condition;

b) If all or part of the study is discontinued for any reason by the sponsor, investigator, university authorities, or government agencies; or

c) Other reasons, including new information available to the investigator or harmful unforeseen reactions experienced by the subject or other respondents in this study.

13. **VOLUNTARY PARTICIPATION:**

You understand that being in this study is voluntary. Your health care will not be affected in any way if you decline to be in or later withdraw from the study. Please contact Dr. Samson Haumba at telephone number (268) 7602-6400 if you have questions related to the study.

14. **IN CASE OF INJURY:**

If you have any questions or believe you have been injured in any way by being in this research study, you should contact Dr. Samson Haumba. However, neither the investigator nor University of South Africa will make payment for injury, illness, or other loss resulting from your being in this research project. If you are injured by this research activity, medical care including hospitalisation is available, but may result in costs to you or your insurance company because the University does not agree to pay for such costs.

15. **CONFIDENTIALITY AND PRIVACY:**

This section gives more specific information about the privacy and confidentiality of your health information. It explains what health information about you will be collected during this research study and who may use, give out and receive your health information. It also describes your right to inspect your medical records and how you can revoke this authorisation after you sign it. By signing this form, you agree that your health information may be used and disclosed during this research study. We will only collect information that is needed for the research study. Your health information will only be used and given out as explained in this consent form or as permitted by law. In any publication or presentation of research results, your identity will be kept confidential.
A. Health Information that will be collected: The following personal health information about you will be collected and used during the research study and may be given to others: Information about number of your status in decibel hearing, results of blood tests for liver function, renal function and blood sugar.

B. Who will see and use your health information: The research study investigator and other authorised individuals involved in the research study will see your health information and may give out your health information during the research study. The authorised persons include the research investigator and the research staff and medical staff managing your condition. The institutional review board and their staff, and other people who need to see the information in order to conduct the research study or make sure it is being done properly might also see your information.

C. Why your health information will be used and given out: Your health information will be used by the research investigator and other authorised individuals involved in the research study to evaluate the results of the study and to the medical staff managing your condition to manage your better. Your information may also be used to meet the reporting requirements of governmental agencies.

D. If you do not want to give authorisation to use your health information: You do not have to give your authorisation to use or give out your health information. However, if you do not give authorisation, you cannot participate in this research study.

E. How to cancel your authorisation: At any time you may cancel your authorisation to allow your health information to be used or given out by sending a written notice. If you leave this research study, no new health information about you will be gathered after you leave. However, information gathered before that date may be used or given out if it is needed for the research study or any follow-up.

F. When your authorisation ends: Your authorisation to use and give out your health information will end when the research study is finished. After the research study is finished, your health information will be maintained in a research database. The researcher shall not re-use or re-disclose the health information in this database for other purposes unless you give written authorisation to do so. However, Ministry of Health Scientific and Ethics committee and Institutional Review Board may permit other researchers to see and use your health information under adequate privacy safeguards.

G. Your right to inspect your medical and research records: You have the right to look at your medical records at any time during this research study. However, the investigator does not have to release research information to you if it is not part of your medical record.

16. CONSENT:

- I have been informed of the reasons for this study.
- I have had the study explained to me.
- I have had all of my questions answered.
• I have carefully read this consent form, and have received a signed copy.

• I authorise the use and disclosure of my personal health information as explained in this consent form.

• I give my consent voluntarily.

Subject or Legally Authorised Representative…………………………….. Date……………

Investigator or Individual Obtaining this Consent……………………….. Date……………

Witness to Signature…………………………… Date…………………………………..

Thank you, very much
ANNEXURE D: Supporting documents for guidelines development and dissemination.

**D1:** invitation to participate in the validation of guidelines for monitoring and prevention of hearing loss related to MDR-TB treatment in Swaziland
Dissemination of the draft guidelines for monitoring and prevention of Drug induced Hearing loss among MDR TB patients

Date: 22nd of April 2015     Time: 7:30 am – 9:30 am     Venue: Royal Swazi Spa
Programme Director: Dr Simetlane (Acting SMO, National TB Hospital)

Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Item</th>
<th>Responsible</th>
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<tbody>
<tr>
<td>7:20</td>
<td>Arrival and Registration</td>
<td>Sikhumbuzo Simelane, Hellen Makhanya</td>
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<tr>
<td>7:30</td>
<td>Opening Prayer</td>
<td>Sixolelwe Hlatshwayo</td>
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<td>7:35</td>
<td>Welcome remarks and Introductions</td>
<td>Programme Director</td>
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<td>7:45</td>
<td>– Introductory Remarks</td>
<td>Programme Manager, NTCP</td>
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<tr>
<td>7:55</td>
<td>Opening Remarks</td>
<td>Director of Health Services, MOH</td>
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<tr>
<td>8:15</td>
<td>Burden of Hearing Disability and services in Swaziland</td>
<td>Eunice Haumba/ Nomsa Mabaso</td>
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<td>8:25</td>
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<tr>
<td>8:25</td>
<td>Presentation of Study findings: Incidence of drug induced Hearing Impairment in patients receiving MDR-TB treatment in Swaziland</td>
<td>Samson Haumba/ Dr Simetlane</td>
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<td>8:45</td>
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<tr>
<td>8:45</td>
<td>Presentation of draft guidelines for monitoring and prevention of drug induced hearing loss</td>
<td>Nomcebo Fakudze /Arnold Mafukidze</td>
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<td>9:15</td>
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<tr>
<td>9:15</td>
<td>Discussion and recommendations</td>
<td>Deputy Director of Health Services, MOH</td>
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