Ototoxicity Monitoring using Automated Extended High-Frequency Audiometry and the Sensitive Range of Ototoxicity in Patients with MDR-TB

by

WILDINE MARION GREEFF

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Mrs. Lucretia Petersen

Department of Health and Rehabilitation Sciences

University of Cape Town

Ms. Vera-Genevey Hlayisi

Department of Health and Rehabilitation Sciences

University of Cape Town

DECLARATION

I, **Wildine Marion Greeff**, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Background: Disabling hearing loss is a global burden. This burden is worsened by the emergence of multi-drug resistant tuberculosis (MDR-TB). Some of the medications used to treat MDR-TB are damaging to the cochlea and auditory nerve (ototoxic) and can lead to permanent hearing loss and/or balance disorders. Ototoxicity monitoring aims to reduce this burden by preventing or minimising the damage caused by ototoxic treatment as it can progress and worsen speech perception difficulties. However, the proposed test battery for ototoxicity monitoring is lengthy and demands active participation which is not ideal for ill patients (such as those on MDR-TB treatment). The Sensitive Range of Ototoxicity (SRO) technique is recommended to shorten the test time. The SRO consists of seven consecutive relatively high frequencies determined from the highest frequency the participant responded to. The SRO technique is time efficient. Although the SRO technique provides the prospect of a shortened test battery, there is still a global lack of audiologists. Automated audiometry is a vital application for testing especially when audiologists are not available to physically do the test. Automated audiometry has been previously validated. Clinically, automated audiometry is objective and allows for standardisation. Even though automated audiometry helps improve access to monitoring more patients, patient preference is an important factor when using automated audiometry to ensure patient-centred care is not compromised.

Aims and Objectives: This study aimed to investigate the specificity and sensitivity of the SRO technique with automated audiometry compared to the gold standard (manual audiometry). This comparison was made by firstly, determining the testing time efficiency and the correlation of thresholds obtained with the different test methods and, secondly, testing the diagnostic value of automated audiometry using the SRO technique. The incidence of an ototoxicity-induced hearing loss was described by determining the time interval between starting ototoxic MDR-TB treatment and the onset of a significant threshold shift (STS) according to ASHA's criteria. Lastly, the test method preference of the participants with MDR-TB was described and compared using a short exit survey.

Study Design: A prospective repeated-measures study design was used. Participants were chosen based on a risk factor (i.e. exposure to ototoxic medication) for an outcome of interest (i.e. the presence or absence of an STS). With a repeated measures study, multiple tests using different test methods can be compared with the same sample.

Participants: Twenty-seven in-patients at Brooklyn Chest Hospital and DP Marais TB Hospital with normal hearing and on MDR-TB medication were included in the study. Their age range was from 19 to 51 years old with an average age of 33 years old. Non-probability convenience sampling was used as it was cost-effective, reduced data collection time and was relatively easy to execute.

Data collection materials and procedures: The procedure for data collection included weekly follow-up testing for a maximum of four weeks. The test battery was as follows: an auditory symptom questionnaire, otoscopy examination, and manual and automated audiometry using the SRO technique with a fifteen-minute break in between. Participants were tested with the KUDUwave ™ in a non-sound treated room. The frequency range was determined with the SRO technique. If an STS was obtained, the patient was discharged from the study after completing an exit survey.

Statistics: Analysis included descriptive statistics and inferential statistics. A Bonferroni corrected *p*-value (initially $p \leq 0.05$) was used. Manual and automated audiometry thresholds were compared using the Pearson's Correlation Coefficient test. Manual and automated audiometry testing time and threshold means were compared using paired sample's *t*-tests. The diagnostic value of automated audiometry with the SRO technique was assessed with Receiver Operating Characteristics (ROC) Curves.

Results: Manual audiometry was statistically more time-efficient compared to automated audiometry by an average of one minute and ten seconds (t (94) = -5.44; $p< 0.003$). There was a strong positive correlation for both left and right ears between the thresholds' obtained from manual and automated audiometry at 8kHz to 16 kHz ($df> 28 = r > 0.70$, $p< 0.003$). Automated audiometry was found to be a fair diagnostic test (area under the curve was 0.75; $p= 0.002$). Also, the ROC curve revealed that automated audiometry had a sensitivity of 61% and specificity of 90% when compared to manual audiometry (gold standard). Only participants that started data collection within 31 days after starting their MDR-TB treatment were included in the analysis of determining the incidence of an ototoxicity-induced hearing loss (n= 24 ears). This study found that 41.67% of ears (n= 10) had an ototoxicity-induced hearing loss. A box and whisker plot revealed that data was skewed to the right (i.e. more variation in data between the median and the maximum values) and that the median number of days for an ototoxicity-induced hearing loss to appear was 33 days. Secondly, 55.55% of participants (n=15 out of 27) reported auditory symptoms before data collection commencement. Aural fullness was the most reported symptom (n= eight out of 15). Ten out of 15 (66.66%) participants that reported auditory symptoms obtained an ototoxicity-induced hearing loss. Lastly, most participants (i.e. 13 out of 19; 68.42%) that completed the exit survey had no preference between manual or automated audiometry. The common rationale among these participants was "No difference noted."

Conclusion: This research study has revealed that manual audiometry was more time-efficient compared to automated audiometry in patients with MDR-TB. Also, automated audiometry was a fair diagnostic test. It may aid in reducing the disproportionate audiologist to patient ratio, especially in a

developing country. However, manual audiometry (with the SRO technique) is more clinically appropriate in patients that are difficult-to-test. Secondly, audiometric settings can be changed to accommodate testing frequencies in 1/6 octaves so that the SRO technique can be clinically adopted. An ototoxicity-induced hearing loss seems to appear 33 days after ototoxic MDR-TB treatment commencement. Aural fullness was a commonly reported symptom among participants with MDR-TB. Aural fullness is omnipresent in peripheral auditory pathologies. Therefore, auditory symptoms reported by patients' needs a comprehensive audiological investigation. Lastly, more research is needed on how patients (and clinicians) experience the advances in technology innovation especially in audiology where technology innovation is continuously evolving.

Keywords: Sensitive Range of Ototoxicity (SRO) technique, automated audiometry, ototoxicity, multi-drug resistant tuberculosis (MDR-TB), sensitivity, specificity

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Chapter 1 **Background**

This chapter discusses the global burden of a disabling hearing loss and how the tuberculosis epidemic and the emergence of MDR-TB negatively affects this burden. Furthermore, the negative effects of MDR-TB treatment (i.e. ototoxicity) are explained. Lastly, the importance of ototoxicity monitoring and the ototoxicity monitoring guidelines in developing countries are reviewed.

1.1 Burden of Disabling hearing loss & MDR TB

There is a global burden of disabling hearing loss (Olusanya, Neumann, & Saunders, 2014). A hearing loss is defined as hearing thresholds worse than 25 decibel Hearing Level (dB HL) in both ears and a disabling hearing loss is a hearing loss in the better ear that is permanent and unaided at 40 dB HL or worse (World Health Organization (WHO), 2018). Globally, 5.3% of the world's population have a disabling hearing loss (WHO, 2018). This burden is worse in developing countries, like South Africa with the Tuberculosis (TB) epidemic resulting in the increased use of ototoxic medication which contributes to this burden (Olusanya et al., 2014; WHO, 2018).

The emergence of multi-drug resistant tuberculosis (MDR-TB) is the primary reason for the current TB epidemic (Appana, Joseph, & Paken, 2016). In a 2018 statistical report, the incidence of TB was 301 000 in South Africa (WHO, 2019). MDR-TB is TB strains that are resistant to first-line TB treatment such as rifampicin and isoniazid (Farley et al., 2011). For example, in 2016, 600 000 new cases of DR-TB cases were reported globally of which 490 000 were MDR-TB (WHO, 2017). Moreover, South Africa was reported as one of the world's highest TB burden countries in 2019 where the incidence of MDR-TB was 11 000 (WHO, 2019). The emergence of MDR-TB presents a challenge in controlling the global TB burden as a more aggressive medication is needed to treat it (WHO, 2017).

MDR-TB treatment options are limited (Zumla et al., 2014). Regulatory authorities have approved two new treatment options for MDR-TB, bedaquiline and delamanid (Zumla et al., 2014). South Africa has announced the availability of bedaquiline as a new treatment option for patients with MDR-TB that meet the criteria (e.g., patients with rifampicin-resistant TB) ("Bedaquiline roll-out," 2018). Bedaquiline is prized for having fewer side effects (e.g., less ototoxic) compared to traditional injectable medication (i.e. aminoglycosides) ("Bedaquiline roll-out," 2018; Khoza-Shangase, 2017; WHO, 2018). Bedaquiline is a newly developed drug and its potential ototoxic effects still need to be tested in different contexts (Khoza-Shangase, 2017). In addition, resistance to bedaquiline is a possibility (Pontali, Sotgiu, D'Ambrosio, Centis, & Migliori, 2016). Aminoglycosides are one of the more traditional choices of treatment for MDR-TB (Zimmerman & Lahav, 2013), especially to those patients that do not meet the criteria to be treated with a less aggressive treatment such as bedaquiline

("Bedaquiline roll-out," 2018). Aminoglycosides are endorsed by WHO (Adeyemo, Oluwatosin, & Omotade, 2016) as cost-effective and efficient in alleviating resistant bacterial infections (Zimmerman & Lahav, 2013). This is especially important in developing countries where cost-effective treatment is an economic necessity (Zimmerman & Lahav, 2013). Although aminoglycosides are useful in treating MDR-TB (Sagwa et al., 2015), they are toxic to the auditory nerve and the inner ear (Zimmerman & Lahav, 2013). Damage to the inner ear due to medication is described as ototoxicity (Govender & Paken, 2015) and can cause a permanent hearing loss (Paken, Govender, Pillay, & Sewram, 2016). Aminoglycosides usually damage the cochlear regions necessary for hearing high-frequencies first then it progresses to cochlear regions necessary for hearing low-frequencies (Adeyemo et al., 2016).

1.2 Impact of Disabling Hearing loss & MDR TB

A permanent hearing loss has numerous negative effects on the individual and society at large (Adeyemo et al., 2016; Sagwa et al., 2015; WHO, 2017). A hearing loss negatively affects speech perception and the ability to locate a sound source (Arlinger, 2003). It also compromises (spoken) communication abilities in post-lingual individuals (Appana et al., 2016). All these difficulties negatively affect the effective communication of the individual with a hearing loss (Arlinger, 2003; WHO, 2018). The individual's frequent communication partners also face the same difficulty and frustration (Manrique-Huarte, Calavia, Huarte Irujo, Girón, & Manrique-Rodríguez, 2016). In some instances, this hearing loss and its negative effects can be managed by hearing assistive devices and/or aural rehabilitation. However, management can be costly especially in developing countries (Sagwa et al., 2015; WHO, 2018).

Besides the negative effects a hearing loss has on speech perception, a hearing loss and MDR-TB negatively affect the individual's quality of life and well-being (Appana et al., 2016; Sagwa et al., 2015). When a hearing loss is not managed it leads to a decreased quality of life due to stigmatization, social isolation, depression, low self-esteem, etc. (Adeyemo et al., 2016; Gates & Mills, 2005; Manrique-Huarte et al., 2016; WHO, 2018). Individuals with MDR-TB may encounter the same stigmatization and psychological distress (Bauer, Leavens, & Schwartzman, 2013). Both a hearing loss and MDR-TB are financial burdens as individuals may have a narrower scope of employment opportunities (Adeyemo et al., 2016; Bauer et al., 2013). This may be due to communication difficulties and MDR-TB may affect how well individuals do their job (Adeyemo et al., 2016; Bauer et al., 2013). Having a hearing loss and MDR-TB are also financial burdens to the economy (WHO, 2018). For example, WHO (2017) indicated that treatment costs for TB have increased and funding demands are still prevalent. For example, health departments in developing countries may accept treatment options even though it has a less than favourable risk/benefit ratio due to affordability (Khoza-

Shangase, 2017). WHO (2018) indicated that unaddressed hearing loss presents 750 billion international dollars in annual global costs. Moreover, the South African TB treatment budget for 2019 was reported to be 240 million US dollars (WHO, 2019). Secondly, ototoxicity causes a permanent irreversible hearing loss with its own economic demands to both the individual affected and the government (Khoza-Shangase, 2017). For example, loss of hearing may result in loss of employment and secondly rehabilitation costs such as amplification and aural rehabilitation (Khoza-Shangase, 2017).

1.3 Ototoxicity Monitoring

Ototoxicity monitoring provides the means to minimise the impact of hearing loss through early identification, which could enable early management (Khoza-Shangase, 2017). Ototoxicity monitoring entails regular hearing sensitivity evaluations to detect the early onset of hearing loss and thereby preventing it from progressing to areas important for communication but contribute to speech in noise perception (Paken et al., 2016). Ototoxicity monitoring helps in optimizing aural rehabilitation and further management (Crundwell, Gomersall, & Baguley, 2016) reducing the contribution to the financial burden of unaddressed hearing losses (WHO, 2018) and preserving quality of life (Konrad-Martin, Reavis, McMillan, Helt, & Dille, 2014). There is evidence showing the effectiveness of ototoxicity monitoring in preventing further ototoxic damage (Duggal & Sarkar, 2007). If a significant threshold shift (STS) in hearing sensitivity has been identified, the prescribed aminoglycoside treatment will be altered to reduce its effects on the auditory nerve and inner ear (Crundwell et al., 2016). According to the American Speech-Language-Hearing Association (ASHA), this alteration includes dosage lowering, dosage stopping and/or changing to less ototoxic medication (ASHA, 1994). This will be done to minimize further damage, motivate for counselling and encourage further management (Crundwell et al., 2016). An ototoxicity monitoring protocol is essential in preventing a hearing loss from becoming disabling (Govender & Paken, 2015) and, in turn, minimising the hearing loss's added impact on the quality of life (of patients with MDR-TB) (Appana et al., 2016).

Ototoxicity monitoring guidelines devised for developed countries (e.g., ASHA, 1994) provide a structured protocol that may not be practical for the South African context (Govender & Paken, 2015). This impracticality is due to several reasons. Firstly, there is limited staff to execute testing (Govender & Paken, 2015; Konrad-Martin et al., 2014). Secondly, there is also limited appropriate audiological equipment (such as sound-treated rooms, sensitive audiometers, etc.) (Govender & Paken, 2015; Konrad-Martin et al., 2014). Both limitations in (human and equipment) resources are due to funding demands leading to competing health demands (von Groote, Bickenbach, & Gutenbrunner, 2011). There is also a lack of appropriate infection control (Govender & Paken, 2015).

Appropriate infection control is relevant to ototoxicity monitoring guidelines because MDR-TB is particularly transmissible in under-resourced healthcare facilities as seen in developing countries (Bock, Jensen, Miller, & Nardell, 2007). This then increases the probability of hospital staff being infected with MDR-TB (Von Delft et al., 2015). There is also limited funding for ototoxicity monitoring programs, improper referral systems and a lack of consistency among South African audiologists with ototoxicity monitoring protocols (Govender & Paken, 2015; Konrad-Martin et al., 2014). For example, there is a lack of awareness among South African audiologists about national ototoxicity monitoring guidelines (Govender & Paken, 2015). There are also discrepancies in the ototoxicity monitoring protocol used among audiologists in South Africa (Govender & Paken, 2015). These discrepancies include conducting baseline assessments, the interval between hearing evaluations of patients with MDR-TB (which vary between one-month and whenever the patient experiences symptoms) and/or using sensitive test methods to detect ototoxic damage (Govender & Paken, 2015). Some audiologists only use conventional pure tone audiometry which is not a sensitive test method to detect an ototoxicity-induced hearing loss (ASHA, 1994). These challenges need to be resolved for the successful implementation of a practical ototoxicity monitoring program in developing countries (Konrad-Martin et al., 2014).

This research study aimed to determine the feasibility of using automation (i.e. automated audiometry) and a shortened test battery (i.e. the sensitive range of ototoxicity; SRO technique) in patients with MDR-TB. The objectives for this aim was to investigate the sensitivity, specificity, diagnostic value and time efficiency of automated audiometry with the SRO technique compared to manual audiometry. Secondly, the type of auditory symptoms and the time interval for a significant threshold shift to appear after starting MDR-TB medication were described. Lastly, the test method preference between automated and manual audiometry of patients on MDR-TB were explored.

Chapter 2 **Literature Review**

This chapter delves deeper into the different aspects of ototoxicity monitoring, such as monitoring interval frequency, length and testing techniques used. It also discusses the practicality of ototoxicity monitoring guidelines in developing countries in detail. The short comings of developing countries with regards to the field of audiology is high-lighted and how new advances in technology aims to circumvent this. Lastly, the importance of patient-centred care is discussed.

2.1 Ototoxicity Monitoring Hearing Evaluations

Ototoxicity monitoring guidelines require that patients be monitored every two to three days or at least once every week (ASHA, 1994). This is because a significant threshold shift (STS) in hearing sensitivity can occur immediately after the commencement of ototoxic medication (Sara, Teh, & Friedland, 2014). De Jager and Van Altena (2002) indicated that an ototoxicity-induced hearing loss appears five days after ototoxic MDR-TB treatment commencement. However, conventional audiometry was used, which is not as sensitive as high-frequency audiometry (Durrant et al., 2009; Paken et al., 2016). Secondly, not all participant baseline information was available to conclude whether the presence of a hearing loss was due to ototoxicity and not pre-existing (De Jager & Van Altena, 2002). In contrast to this study, a longitudinal study by Appana et al. (2016) indicated that an STS in hearing sensitivity appears one month after ototoxic MDR-TB treatment commencement. However, participants were monitored monthly (Appana et al., 2016). Other studies indicate that the onset of an ototoxicity-induced hearing loss may appear post-treatment (Kolinsky, Hayashi, Karzon, Mao, & Hayashi, 2010). These studies demonstrate conflicting evidence for the onset of an ototoxicity-induced hearing loss. Therefore, this research investigated the incidence of an ototoxicity-induced hearing loss indicated by an STS in hearing sensitivity. The time it takes for an ototoxicity-induced hearing loss to emerge once treatment has commenced as well as the associated symptoms experienced were described. This may indicate the regular intervals of hearing evaluations needed for the successful identification of an ototoxicity-induced hearing loss.

2.2 Current Ototoxicity Monitoring Protocol

The ototoxicity monitoring protocol followed in most Western Cape public health facilities, which is based on ASHA's guidelines (1994), are as follows: brief case history, otoscopy examination, tympanometry testing, conventional and extended high-frequency air conduction pure tone audiometry for baseline testing (K. Gangerdine, personal communication, October, 23, 2018). Follow-up testing procedures include otoscopy and conventional and extended high-frequency air conduction pure tone audiometry only (K. Gangerdine, personal communication, October, 23, 2018). If a

significant change in hearing has been detected during follow-up testing, tympanometry and bone conduction pure tone audiometry is completed during the same session (K. Gangerdine, personal communication, October, 23, 2018). The patient is then required to be tested every two weeks until hearing sensitivity stabilises (K. Gangerdine, personal communication, October, 23, 2018). If no change in hearing has been identified, the patient is then tested once a month (K. Gangerdine, personal communication, October, 23, 2018).

The current ototoxicity monitoring protocol is comprehensive and lengthy (Konrad-Martin, 2014). Patients taking aminoglycosides may not be able to concentrate for long periods of time during audiological testing (Paken et al., 2016). Aminoglycosides strain the body due to their negative side effects such as nausea, vomiting, anorexia, etc. (Schacht, Talaska, & Rybak, 2012). It takes approximately eight minutes to do conventional audiometry testing excluding other audiological tests such as otoscopy, immittance testing, speech audiometry and extended-high frequency audiometry (Swanepoel, Mngemane, Molemong, Mkwanazi, & Tutshini, 2010). The quality and the quantity of the information from behavioural testing is greatly affected by health status, energy level and testee co-operation (Brooks, & Knight, 2018). Distortion-Product Otoacoustic Emissions (DPOAE) testing is an objective, relatively time-efficient and an ear-specific way to monitor ototoxicity (Brooks, & Knight, 2018). They can also test extended high frequencies up to 10 000 Hz (Reavis et al., 2011). Ototoxicity damage in DPOAE testing may be an amplitude decrease and/or a reduced signal-to-noise ratio or no response when measuring the outer hair cell response from the cochlea (Brooks, & Knight, 2018). However, there are no widely accepted norms for a significant ototoxicity change in DPOAE testing (Brooks, & Knight, 2018). This limits the clinical utility of DPOAE testing to be used in isolation (Brooks, & Knight, 2018).2.3 Disproportionate Audiologist-to-Patient Ratio

In addition to the time consuming ototoxicity monitoring test battery (Konrad-Martin, 2014), there is a global lack of audiologists to conduct testing (Brennan-Jones, Eikelboom, Swanepoel, Friedland, & Atlas, 2016). The disproportionate audiologist-to-patient ratio results in high-patient caseloads and a low coverage rate for patients in need and is worse in developing countries in the presence of the TB epidemic increasing the patient load (Swanepoel & Biagio, 2011). For example, a cross-sectional population study (N = 850) done in the Limpopo province of South Africa investigated the prevalence of hearing loss (i.e. hearing thresholds above 25 dB HL) in the Elias Motsoaledi Local Municipal (Joubert & Botha, 2019). This study revealed that the prevalence rate of a hearing impairment was 19.88% where a disabling hearing loss was 8.94% (Joubert & Botha, 2019). Secondly, a cross-sectional household survey (N= 2494) was conducted in the Cape Town Metropolitan area on the prevalence of a hearing loss (Ramma & Sebothoma, 2016). This study revealed that 12.35% of the

population had a hearing impairment and that 4.57% had a disabling hearing impairment (Ramma & Sebothoma, 2016). As from 06 March 2020, there were only 783 audiologists registered with the Health Professions Council of South Africa (HPCSA) (Y. Daffue, personal communication, April 02, 2020). A shortened test battery and test automation may be a solution for the disproportionate audiologist-to-patient ratio and the constantly increasing caseload.

2.4 The Sensitivitve Range of Ototoxicity (SRO) Technique

The purpose of the SRO technique is to identify an STS in hearing sensitivity in a shortened and customised frequency range of relatively high-frequencies (Fausti et al., 1999; Konrad-Martin et al., 2014). This range consists of seven consecutive frequencies that are ⅙ octaves apart (Konrad-Martin et al., 2014; Paken et al., 2016). The SRO is a range that extends over one octave within reach of the patients functionally determined high-frequency hearing boundary (Fausti et al., 1999; Konrad-Martin et al., 2014). This high-frequency hearing boundary is where the threshold is obtained at or below 100 dB sound pressure level (SPL) (Fausti et al., 1999; Konrad-Martin et al., 2014). The theoretical basis for using (relatively) high-frequencies in this technique is the notion that the basilar membrane of the cochlea that processes the high-frequencies are more vulnerable to ototoxic damage (Konrad-Martin et al., 2014). The SRO technique may be helpful as an addition to the current ASHA ototoxicity monitoring test battery guidelines for patients on MDR-TB treatment (Schacht et al., 2012).

Previous studies have shown that the SRO technique can be used to be effective and more time efficient as it uses a shortened frequency range to detect an STS (Fausti et al., 1999; Konrad-Martin et al., 2014). For example, a study done by Jacobs et al. (2012) has shown that the SRO technique is effective in ototoxicity monitoring. Secondly, Fausti et al. (1999) used a retrospective analysis to show that the SRO technique is sensitive to an ototoxicity-induced hearing loss and its reliability in patients receiving aminoglycoside treatment. Lastly, Konrad-Martin et al. (2014) stated that the SRO technique significantly reduces testing time compared to conventional full-diagnostic hearing evaluations.

Despite the SRO technique's reliability and validity, it has not been adopted clinically (Konrad-Martin et al., 2014). This may be due to lack of equipment settings to test in 1/6 octave frequencies when ototoxicity monitoring guidelines were established (Konrad-Martin et al., 2014). However, these guidelines do recommend high-frequency testing (Konrad-Martin et al., 2014). The key thing to consider is the value of the SRO technique in developing countries. For example, patients will not be

required to concentrate for longer than necessary and it minimizes testing time allowing for more patients to access this service (Fausti et al., 1999; Konrad-Martin et al., 2014). On average, it takes approximately eight minutes to test six conventional pure tone frequencies (i.e. 250 to 8 000Hz) bilaterally for normal hearing patients (Swanepoel, Mngemane, et al., 2010). During ototoxicity monitoring, conventional (with two additional inter-octave frequencies) and extended high-frequency audiometry (i.e. 9000 to 16 000 Hz) need to be tested; this is approximately twelve frequencies per ear (ASHA, 1994) as opposed to only testing seven frequencies per ear with the SRO technique (Fausti et al., 1999; Konrad-Martin et al., 2014). In relation to this matter, this research aimed to explore the feasibility of the SRO technique in ototoxicity monitoring for patients receiving ototoxic MDR-TB medication within a developing country context.

2.5 Automated Audiometry

These studies did not use the SRO technique in conjunction with automated audiometry (Fausti et al., 1999; Konrad-Martin et al., 2014). Automation can contribute to the improvement of hearing healthcare and patient access to services as well as sustainable and cost-effective hearing healthcare services (Swanepoel, Clark, et al., 2010). Of importance to this research is the benefits of automated audiometry in ototoxicity monitoring in developing countries such as South Africa (Maclennan-Smith, Swanepoel, & Hall III, 2013). Automated audiometry is pure tone audiometry testing completed by a computer-based system and not by an audiologist (unlike manual audiometry) (Swanepoel & Hall III, 2010). Automated audiometry could be advantageous for assessing patients that have highly infectious diseases like MDR-TB (Maclennan-Smith et al., 2013; Swanepoel & Biagio, 2011). For example, a study by O'Donnell et al. (2010) has found that South African healthcare professionals are more likely to get infected with MDR-TB compared to the general population due to occupational exposure (O'Donnell, 2010)

In a South African context, automated audiometry will help to alleviate the high-patient caseloads, time constraints and limited staffing resources (Brennan-Jones et al., 2016). It may also aid in minimizing infection transmission as audiologists do not have to be present for testing to be conducted (Swanepoel & Biagio, 2011). However, automated pure tone audiometers are less useful in difficult-to-test patients (Swanepoel & Biagio, 2011). This is because, with manual testing, the tester uses his/her own discretion during testing when considering what are true responses to acoustic stimuli (Dille, Jacobs, Gordon, Helt, & McMillan, 2013). Previous research has validated automated audiometry in normal hearing and heterogenous patients (Brennan-Jones et al., 2016; Maclennan-Smith et al., 2013). The current focus of this research was to investigate the diagnostic value and

sensitivity and specificity of automated audiometry in the ototoxicity monitoring of patients with MDR-TB using the extended high-frequency range and the SRO technique in South Africa.

2.6 Patient-Centred Care

The area of automation is evolving the way patients are cared for in the healthcare system (Cox et al., 2017). Patient experience information about a healthcare service allows for a holistic assessment of its quality (Auras & Geraedts, 2010). Positive patient experiences with healthcare services are important to ensure that quality of care is given to patients (de Silva, 2013). That is why healthcare has become more patient-centred (Grenness, Hickson, Laplante-Lévesque, & Davidson, 2014). There is a lack of research with regard to patient-centred care in the field of audiology (Laplante-Lévesque, Hickson, & Grenness, 2014). Patient-centred care is where patients are cared for holistically and their inputs into their healthcare are valued (Pelzang, 2010; Ponte et al., 2003). The quality of the patient and healthcare professional's interaction is a key contributor to patient-centred care (Grenness et al., 2014). Unfortunately, automated audiometry limits this interaction (Swanepoel & Biagio, 2011). Patient-centred care is directly proportional to patient satisfaction and adherence (Grenness et al., 2014). Patient adherence is improved if the automation (in audiometry) is perceived as useful and easy to use (Or et al., 2011). Automated audiometry requires the same patient instruction as manual audiometry (Maclennan-Smith et al., 2013). However, patient satisfaction is complex (Grenness et al., 2014). This research focused on patient preference as a branch of patient satisfaction.

The majority of research about patient satisfaction and preference in health care are done in developed countries that have better infrastructure and less pressure on the health care system (Wang & Fung, 2014). Insufficient resources and an increase in the demand for health care services fuel the rise in medical disputes (Wang & Fung, 2014). Therefore, it is vital to provide feasible and effective health care services while not compromising on quality of care and patient satisfaction (Wang & Fung, 2014). Patient preference has been shown to improve patient satisfaction in health care (Wang & Fung, 2014).

Patient preference has been researched in the field of audiology (Kelly, Stadler, Nelson, Runge, & Friedland, 2018). In a study by Kelly et al. (2018), patients were neutral on their preference between automated audiometry and traditional manual audiometry testing. However, in a study by Konrad-Martin et al. (2014), patients preferred automated audiometry compared to manual audiometry (Konrad-Martin et al., 2014). The preference for automated audiometry may be due to the predictability of acoustic stimuli presentation (Swanepoel, Mngemane, et al., 2010). Unpredictable

acoustic stimuli presentations are more desirable to reduce false responses (Swanepoel, Mngemane, et al., 2010). To aid in ensuring that patient-centred care is not compromised in automated audiometry, the current focus of this research study was to investigate patient preference with automated audiometry in a South African context.

2.7 Problem Statement

According to Fausti et al. (1999) and Konrad-Martin et al. (2014), the SRO technique provides a fast and effective way of conducting hearing evaluations and detecting an ototoxicity-induced hearing loss in patients on ototoxic medication (Fausti et al., 1999; Konrad-Martin et al., 2014). Despite stated literature, there is still a lack of the clinical adoption of the SRO technique (Konrad-Martin et al., 2014). Furthermore, Swanepoel and Biagio (2011) and Dille et al. (2013) demonstrated the importance of automated audiometry in situations where audiologists are not available. Current hearing evaluation interval protocols practised among South African audiologists (i.e. one-month intervals) are also not according to ototoxicity monitoring guidelines due to high-patient caseloads (Govender & Paken, 2015). There is an increase in the TB epidemic (Appana et al., 2016), therefore, there is a need for the investigation of the feasibility of using the SRO technique with automated audiometry in a developing country context such as South Africa. This may promote the clinical adoption of the SRO technique and automated audiometry in developing countries that use ototoxic medication to treat MDR-TB (Adeyemo et al., 2016).

2.8 Research Rationale

The results of this investigation have the potential to contribute to the development of an appropriate ototoxicity monitoring protocol for the South Africa context. The Department of Health (2010) has indicated the need for context-specific evidence to create such a protocol (*Management of drug-resistant tuberculosis: policy guidelines*, 2010). Results on the incidence of an ototoxicity-induced hearing loss (such as the time it takes for an ototoxicity-induced hearing loss to emerge once treatment has commenced) may provide evidence for the appropriate and practical time interval between follow-up testing in the ototoxicity monitoring guidelines (Fausti et al., 1999). The reliable use of automated audiometry in ototoxicity monitoring may aid in minimizing the high-patient caseloads and circumvent the challenge of an insufficient number of audiologists to conduct testing (Appana et al., 2016). The practicality and feasibility of using the SRO technique might contribute to a shortened and more appropriate test protocol (Fausti et al., 1999). This will ensure that testing is appropriate for ill patients (with MDR-TB) and allow more access to ototoxicity monitoring services (Fausti et al., 1999; Schacht et al., 2012). Patient preference between automated and manual

audiometry is essential for ensuring that patient-centred care is not compromised (Grenness et al., 2014).

Conclusion

The impracticality of ototoxicity monitoring guidelines in South Africa need to be addressed. These impracticalities include appropriate testing time intervals, appropriate testing time length especially for ill patients and the lack of audiologists to conduct testing. The current test battery is comprehensive and too lengthy for fatigued patients to cope with it. However, automation and the SRO technique may aid in circumventing challenges currently faced with ototoxicity monitoring protocols in South Africa. The current clinical audiological guidelines may benefit from adopting the SRO technique and automated audiometry. Lastly, to ensure that new advances in technology does not compromise on patient-centred care, aspects such as patient satisfaction, adherence and preference needs to be taken into consideration.

Chapter 3 **: Methodology**

This chapter will outline the aims and objectives of this research study where the feasibility of the automated audiometry with the SRO technique was the main aim. The various procedures used to achieve these aims and objectives are focused on. The research design used will be explained. The geographic location of the research study will be touched on. The inclusion and exclusion criteria for participants will be outlined in detail and rationale given for each criterion. The power of the sample size will be calculated, and a description of the participants recruited for the study will be described. The recruitment and sampling process will be explained. The instrumentation used during data collection and the data collection procedure (and test battery) was discussed in detail. Issues regarding validity and reliability, ethical considerations, and data management were addressed. Lastly, the process of data analysis was explained.

3.1 Aims and Objectives

In patients with MDR-TB:

1. Compare the feasibility of the SRO technique in detecting an ototoxicity-induced hearing loss with automated and manual (gold standard) audiometry. Objectives:
   1.1. Compare the testing time efficiency of manual and automated audiometry in conjunction with the SRO technique.
   1.2. Determine the parallel forms reliability of thresholds obtained using the different test methods (i.e. manual and automated).
   1.3. Determine the diagnostic value and the sensitivity and specificity of automated audiometry in conjunction with the SRO technique compared to manual testing methods (gold standard).
2. Describe the incidence of hearing loss (determined through an STS). Objectives:
   2.1. Determine the time between ototoxic MDR-TB treatment commencement and the onset of a hearing loss.
   2.2. Describe the associated auditory symptoms such as tinnitus and aural fullness experienced by patients with MDR-TB.
3. Describe and compare the participants' test method preference (i.e. automated or manual audiometry).

3.2 Research Design

A prospective repeated-measures design was used. With a prospective repeated-measures study, participants were followed (and measured) over a period to see what ensues (Pole &

Bondy, 2010). Participants were chosen based on a risk factor (e.g. ototoxic medication exposure) for a certain pathology or possible outcome of interest (e.g. ototoxicity-induced hearing loss) (Pole & Bondy, 2010). The occurrence or non-occurrence (i.e. incidence) of the certain pathology or possible outcome of interest was then measured over time (i.e. repeated measures) (Pole & Bondy, 2010). The time difference between the documented risk factor' onset and outcome of interest was an essential element of this research (Pole & Bondy, 2010).

A prospective study design allowed for comparisons between the results of one or more diagnostic tools (e.g., automated pure tone audiometry) to a gold standard (manual pure tone audiometry) on the same population of interest (e.g., patients with MDR-TB) (Bossuyt et al., 2003). This type of design minimised recall bias and increased the accuracy of risk factor exposure information (i.e. ototoxic medication exposure) (Sedgwick, 2013).

The limitations of the prospective repeated-measures study design were that it was time consuming, difficult to maintain contact with participants with a large sample and data collection time was extensive (Sedgwick, 2013). Bias may have been introduced to the study due to some participants being lost as a result of being discharged from hospital or succumbing to MDR-TB (Sedgwick, 2013).

3.3 Research setting

Data collection was completed at Brooklyn Chest Hospital (BCH) and D.P Marais TB Hospital. These TB hospitals are situated in Cape Town, Western Cape Province. BCH is a public TB hospital with 349 beds in several wards for the management of patients with MDR-TB (Harris et al., 2012). DP Marais Hospital is a specialised public district TB hospital in the Metro region's South Peninsula Health District ("DP Marais SANTA Hospital," 2017).

3.4 Participants

3.4.1 Inclusion criteria

1) Participants that have been diagnosed with MDR-TB and have started aminoglycoside or bedaquiline treatment prescribed by a physician. This information was available in their medical records.

    a) Aminoglycosides and bedaquiline are used to treat MDR-TB (Khoza-Shangase, 2017; Zimmerman & Lahav, 2013). Aminoglycosides are known to have adverse ototoxic effects and bedaquiline has been found to be less ototoxic than aminoglycosides (Khoza-Shangase, 2017; Zimmerman & Lahav, 2013).

2) Participants with MDR-TB that are in-patients and are responsive and cooperative during comprehensive audiological testing. Participant responsiveness and cooperativeness was assessed through their ability to complete comprehensive baseline testing.

    a) Majority of the countries have implemented the in-patient care model at specialised TB hospitals (Loveday et al., 2015).

    b) Patients in the ototoxicity monitoring program that have limited responsiveness need additional modifications to testing such as fewer testing frequencies or objective testing (ASHA, 1994).

3) Normal hearing participants (i.e. hearing thresholds better than or equal to 25dB HL at frequencies 250 – 8 000 Hz (WHO, 2018). This information was available in their medical records.

    a) This research aimed to look at the incidence of an ototoxicity-induced hearing loss.

4) Participants should be able to understand and speak isiXhosa, English or Afrikaans.

    a) An exit survey was administered in isiXhosa, Afrikaans or English, depending on participant's preference.

    b) Participants had to be able to understand instructions as incorrect thresholds will be obtained from the participant's responses if instructions are misunderstood (Schlauch & Nelson, 2015).

3.4.2 Exclusion criteria

1) Exposure to harmful occupational/recreational noise (i.e. 75 A-weighted dB; dBA) without hearing protection 24-72 hours prior to testing. Although it is a noncontrollable factor, participants were asked about exposure to noise loud enough to decrease speech perception prior to each test.

    a) The human ear can sustain damage if a stimulus intensity is above 75 dB As (Fligor, Chasin & Neitzel, 2015) and this noise-induced damage can confound assessment results.

2) Participants on aminoglycoside medication in addition to other ototoxic medication such as Cancer treatment.

    a) The interference of other ototoxic medication act as confounding variables to the outcome of interest.

3.5 Sample size

Data was analysed from 54 ears of 27 participants. According to the G*Power 3.1.9.4 calculation application (Faul, 2008), the power for this research study was 0.99. The statistical information that was used in this estimate is seen in Table 1.

Table **1**

Statistical Power Information

Parameter	Value
Tails	Two-tailed
Effect Size	0.50
Type 1 error probability	0.05
Sample size	54 (i.e. ears)

3.6 Participant description

There were twenty-seven participants in this study (23 males and 4 females). All participants were in-patients. The age range of the participants was from 19 to 51 years old with an average age of 33 years old. MDR-TB was diagnosed in twenty-five participants and two participants were diagnosed with pre-extensively drug resistant (XDR)-TB. Only one participant was treated with amikacin and kanamycin (aminoglycosides) while the rest of the twenty-six participants were treated with bedaquiline. Thirteen participants started their ototoxicity treatment less than a month before data collection started (i.e., < 31-day interval between starting treatment and starting data collection). Fourteen participants started their ototoxicity treatment more than a month before data collection started. All participants had an audiogram baseline from 250 – 16 000 Hz with normal hearing thresholds (i.e. 25 dB HL or better) at 250 – 8 000 Hz. Twenty-six out of the 27 participants had responses at all baseline frequencies (i.e. 250 – 16 000Hz). Therefore, the SRO (seven frequency range) was from 16 through to 8 kHz for 26 participants. One participant had an SRO from 12.5 down to 4 kHz because the participant did not have threshold responses at 14 and 16 kHz.

3.7 Recruitment

The researcher had assistance from the audiology and nursing department/staff in identifying patients with MDR-TB that met the requirement for normal hearing. For example, the resident audiologist would refer potential participants that had normal hearing (at conventional frequencies; 250 – 8 000 Hz) during baseline testing. The researcher then identified the rest of the potential participants that met all criteria by looking through patient hospital records (specifically ototoxicity monitoring baseline assessments from 250 – 16 000 Hz). The researcher approached potential participants and explained the study using the informed consent form as a guide and asked potential participants to participate. Those potential participants that were willing to participate had to sign an informed consent form prior to engaging in data collection.

3.8 Sampling

Non-probability convenience sampling was used as it allowed for reduced costs, reduced data collection time and easy data collection (Etikan, Musa, & Alkassim, 2016). Convenience sampling depended on participant availability and willingness to participate (Durrheim & Painter, 2014) under the assumption of homogeneity among members of the population (Etikan et al., 2016). However, non-probability convenience sampling may have introduced sampling bias and as a result the sample may not be representative of the population (Etikan et al., 2016). The possible presence of sampling bias may have compromised external validity (Etikan et al., 2016).

3.9 Data Collection

Instrumentation:

1) Audiological Case History: According to Beck (2015), anatomical and physiological information needs to be constructed and construed within the context of a patient's case history for an appropriate diagnosis to be made (Beck, 2015).

2) Standard Welch Allyn otoscope: According to ASHA's audiometry guidelines, the pinna, ear canal and tympanic membrane should be visualised and inspected for foreign objects, occlusive wax, active infections and potential collapsing ear canals that may affect results (ASHA, 2005).

3) Portable KUDUwave ™ audiometer: This audiometer has been developed by a South African company called GeoAxon Holdings (Storey, Muñoz, Nelson, Larsen, & White, 2014). This instrument contains sound-reduction headphones with a fully-fledged audiometer inside the headset compartment (Storey et al., 2014). Foam insert earphones are also used (Storey et al., 2014). This audiometer has an automated and manual function (and the function to test remotely)

and covers a frequency range sensitive for the early detection of an ototoxicity-induced hearing loss (Reavis et al., 2011; Yu et al., 2014). The portable KUDUwave ™ audiometer allows hearing assessments to be conducted in suboptimal acoustic environments that are not in soundproof/treated booths (Swanepoel & Biagio, 2011). This is made possible by the instrument continuously monitoring the level of ambient noise and attenuating sound where necessary (Storey et al., 2014). Here internal and external sound level meters are used to assist with ambient noise monitoring (Storey et al., 2014). Hearing thresholds are then only tested once ambient noise falls below the pre-determined noise floor (Storey et al., 2014). However, the level of attenuation is somewhat lower than that of a sound booth (Storey et al., 2014).

4) Stopwatch: A smartphone stopwatch was used to determine the duration of the audiometric testing time for both manual and automated modes.

5) ASHA's STS criteria: This criteria states that a threshold shift is significant when, firstly, there is a 20 dB decrease in hearing threshold at one frequency (ASHA, 1994). Secondly, when there is a 10 dB decrease in hearing threshold at two consecutive frequencies (ASHA, 1994). Lastly, when there are no responses at three adjacent frequencies where a response was previously present (ASHA, 1994). The aim of the ASHA criteria was to reveal an STS in most patients, choosing to reveal false positives rather than delaying the detection of in a change hearing status (Waissbluth, Peleva, & Daniel, 2017).

6) Short exit survey: This short exit survey was specially designed for this research by the researcher. The types of questions that were asked were test preference in multiple choice format and an open-ended question about the rationale for their test preference (see appendix A). This is because patient preference is related to patient-centred care (Grenness et al., 2014). These questions aided in evaluating whether patient-centred care is compromised with the use of automated audiometry. Pertinent to this research is the fact that surveys are essential in collecting information on individual perspectives (Jones, Baxter, & Khanduja, 2013). Closed-ended survey questions are easy to analyse and present (Jones et al., 2013). Although an interview-based questionnaire is time consuming and requires training to avoid bias, it results in higher response rates and allows more complex questions to be asked (Jones et al., 2013). The researcher conducted this survey in the form of an interview in English, Afrikaans and/or IsiXhosa (depending on which language the participant preferred). The researcher had a predetermined number of ways to explain each question to reduce bias. Manual note taking was used during the short survey interview.

3.10 Procedure

Before data collection commenced the researcher had to obtain approval from: 1) the University of Cape Town's Faculty of Health Sciences' Human Research Ethics Committee (reference number: 614/2018), 2) the Western Cape Government: Department of Health (reference number: WC_201902_004) 3) and from the clinical manager of the metro TB Hospital centre (DP Marais Hospital) and BCH (appendix B, C and D respectively). Participant recruitment involved the researcher (a master's student) with the assistance of facility staff members.

During recruitment, participants were assessed on whether they fit the inclusion and exclusion criteria. The participants' medical records were reviewed by the researcher to see whether they are solely on the ototoxic drug of interest (i.e. aminoglycoside or bedaquiline medication). Understanding and speaking English, Afrikaans or IsiXhosa was assessed by asking the participant whether they understood and could speak any of the languages mentioned. The medical records were also reviewed to see whether the participant had normal hearing (i.e. thresholds of 25 dB HL or better (Schlauch & Nelson, 2015)) at baseline testing. If the participant had normal hearing, they were recruited and progressed to stage two of the data collection (see the data collection flow diagram in Figure 1).

After recruitment, the participants were tested (follow-up testing) on a weekly basis for, at most, four weeks (as per ASHA's ototoxicity monitoring guidelines if every two to three days are not feasible (Adeyemo et al., 2016). Participants were asked to attend weekly testing sessions for research purposes only as some South African audiologists do follow-up testing on a monthly (and not weekly basis) (Govender & Paken, 2015). As soon as a significant change in participant test results were seen and confirmed upon a retest, no further audiological testing was required. If no significant change in participant test results were seen during the last week of testing (week four), no further audiological testing was required for data collection. The participant, then, filled in an exit survey and exited the study.

During data collection, the only new test that was added to the test procedures followed by most public facilities in the Western Cape are automated extended high–frequency pure tone audiometry and the use of the SRO technique. The test battery used for data collection was as follows (see the data collection test battery in figure 2): a brief auditory symptom onset questionnaire (see appendix E), otoscopic examination, manual extended high-frequency audiometry using the SRO technique, a fifteen-minute break then automated extended high-frequency audiometry using the SRO technique. If a significant change in hearing sensitivity has been identified during a session, the

following test procedures were added to the follow-up test battery: tympanometry and conventional air and bone conduction manual pure tone audiometry and speech audiometry.

The Modified Hughson and Westlake threshold searching technique was used to obtain hearing thresholds with both manual and automated audiometry. The Modified Hughson and Westlake technique is threshold searching by decreasing in 10 dB steps and increasing in 5 dB steps (Poling, Kunnel, & Dhar, 2016). Additionally, thresholds are only ascertained when ascending (Poling et al., 2016). This technique is the standard clinical procedure and was the focal point of preceding investigations with regards to tester bias (Poling et al., 2016). Manual audiometry started testing at 30 dB HL for 1000 Hz only and at the previous threshold obtained for subsequent frequencies. Automated audiometry started testing each frequency at 30 dB HL.

According to Appana et al. (2016), ototoxic damage occurs approximately one-month post treatment commencement; therefore, testing concluded after a month (four weeks) per participant (Appana et al., 2016). Late onset ototoxicity-induced hearing loss may also occur post treatment (Kolinsky et al., 2010). ASHA's ototoxicity monitoring guidelines require follow-up testing to occur at least six months post treatment (ASHA, 1994). Due to time constraints, the researcher only tested a participant for one month maximum. When a significant decrease in hearing (as per ASHA's 1994 STS criteria) or a change in ear status (i.e. an outer or middle ear pathology characterised by an abnormal tympanogram and/or abnormal otoscopy results) was identified, a retest was conducted within 24 hours to confirm the result as per ASHA's ototoxicity monitoring guidelines (ASHA, 1994). According to ASHA (1994), there is a high probability of a true STS if an STS relative to baseline thresholds is confirmed by a re-test (ASHA, 1994).

The resident physician and audiologist were informed via medical record notes when participants had a decrease in hearing or change in ear status. If a middle ear pathology (i.e. change in ear status) has been identified and confirmed, the participant was required to exit the study. This is because middle ear pathologies may result in elevated extended high-frequency thresholds (Sharma, Munjal, & Panda, 2012). The participant was also required to exit the study upon confirmation of a decrease in hearing (i.e. an STS was obtained). If no decrease in hearing or ear status has been identified, the participant exited the study after four weeks. Upon exiting study, each participant completed the exit survey (using manual note-taking) and was referred to the resident audiologist for management and ototoxicity monitoring as per respective health facility protocol, i.e. monthly or every two-weeks follow-up testing (Govender & Paken, 2015). In the event of a missed appointment/testing session, participants were required to attend their next follow-up session. They could miss up to two sessions.

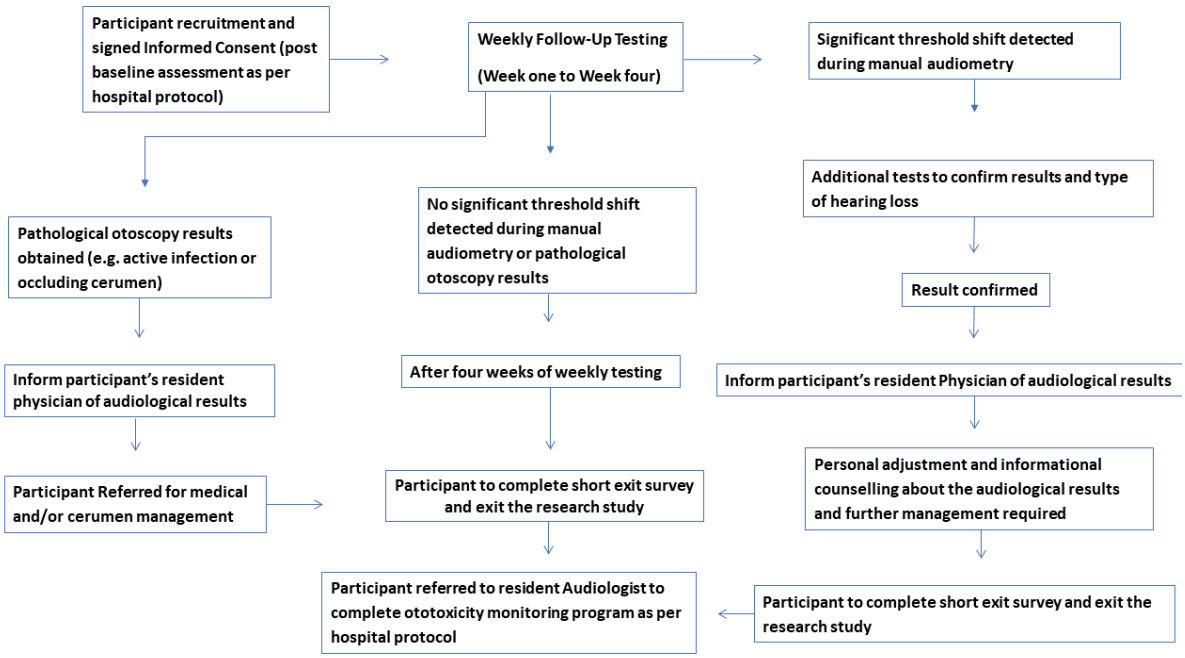


Figure 1. Data Collection Test Procedure Flow Diagram

Data Collection Test Battery

Case history about auditory symptoms

↓

Otoscopy examination

↓

Manual extended high frequency audiometry (i.e., 12 500* – 16 000 Hz) with SRO technique.

↓

15 minute break

↓

Automated extended high frequency audiometry (i.e., 12 500 – 16 000 Hz) with SRO technique.

*One participant's SRO started from 12.5 down to 4 kHz because they had no thresholds/responses at 14 and 16 kHz according to their baseline assessment.

Figure 2. Data Collection Test Battery

Participants were tested on the facility's premises in an area designated by the facility manager. Testing was done in the TB ward at DP Marais TB Hospital and in the audiology department at BCH. The researcher recorded audiological results on the recording sheet (see appendix F). The researcher kept the recording sheet with the participant's name on it on the facility's premises until data collection was completed for that participant. The facility manager or facility staff (e.g., audiological department or resident physician) was asked to assist with a secure location to keep the identifying patient information. After each testing session, participant results were transferred to a password protected OneDrive cloud under a non-identifiable numerical code for data analysis. The recording sheets of the participants are kept at the researcher's supervisors' office in a locked cabinet once data collection was completed. After five years, these documents will be shredded.

3.11 Validity and Reliability

One limitation of audiometry is test-retest inconsistency (Schlauch & Nelson, 2015). The amount of threshold variability allowed is 5 dB (Schlauch & Nelson, 2015); thus, test-retest thresholds needed to be within 5 dB to be considered reliable (Campbell, Hammill, Hoffer, Kil, & Le Prell, 2016). One frequency was retested within the same test session for each audiometric test method (i.e. automated and manual). Calibrated equipment was used. A tester (a master's student) trained to use audiology equipment conducted testing. Researchers found that the portable KUDUwave ™ audiometer was reliable and valid in its manual and automated-mode of audiometric testing (Brennan-Jones et al., 2016). For example, the portable KUDUwave ™ audiometer has been validated (in normal hearing participants) outside a sound-treated room (Maclennan-Smith et al., 2013), in a controlled noise environment (Storey et al., 2014) and in an environment that was not sound-treated with a heterogeneous population (Brennan-Jones et al., 2016). Additionally, it has been demonstrated that extended high-frequency audiometry testing and DPOAE testing are both sensitive to the early detection of an ototoxicity-induced hearing loss and complement each other well (Reavis et al., 2011; Yu et al., 2014). However, it should be noted that both Reavis et al. (2011) and Yu et al. (2014) used behavioural extended high frequency audiometry 0.5- to 20 kHz and DPOAE testing between 1 to 10 kHz.

The inclusion and exclusion criteria of this research study helped reduce confounding variables. Participant effects on results (such as inattentiveness and fatigue) was decreased by rest periods between audiometry testing. Testing time was decreased by testing only seven relatively (depending on the highest high frequency that the participant responded to) high frequencies. The tester instructed participants and used procedures according to the ASHA (2005) standard audiometry guidelines. External validity was compromised with non-probability convenience sampling as the

sample might not be representative of the population (Etikan et al., 2016). This research could only generalise results to members of the population that resemble the sample. The effectiveness of using the extended high-frequency audiometry in patients using ototoxic medication was well documented (Valiente, Fidalgo, Villarreal, & Berrocal, 2016). This corresponded to the theoretical basis indicating cochlear regions containing high-frequencies are more vulnerable to ototoxic damage (Konrad-Martin et al., 2014). It was, thus, the choice of test in ototoxicity monitoring (Reavis et al., 2011; Yu et al., 2014).

3.12 Ethical Considerations

The ethical considerations of this research study were guided by the Declaration of Helsinki (WMA, 2013). The World Medical Association (WMA) states that the ethical principles of the declaration of Helsinki should be used as a guide in medical research that involves humans (WMA, 2013).

Informed consent. The standard elements of informed consent are as follows: appropriate information regarding the research study, participant comprehension of this information, voluntary participation, freedom to withdraw after data collection has commenced and a written document of the consent (Wassenaar, 2014). The researcher verbally informed and gave participants a written copy about all the information that might influence their participation in the study (see appendix G). This consent form was written in English, Afrikaans and IsiXhosa. The information included the study's purpose, procedure, benefits and risks, refusal and termination rights, confidentiality and contact information. Participants had the right to withdraw from this study at any point in time without providing a reason. Participants had the option to receive results from the study once the study has been completed.

Justice. Participants need to be treated equal and fairly during all stages of the research (Wassenaar, 2014). The rationale for the inclusion and exclusion criteria was evidence-based to maintain the principle of justice. Every potential participant that met the criteria were included in this study.

Misrepresentation. According to the WMA, the researcher is accountable to the accurateness and completeness of the reports on human participants (WMA, 2013). Results obtained during data collection were not fabricated. Information used from the works of others are cited according to the American Psychological Association's (APA) sixth edition.

Loss of privacy and confidentiality. This study required some form of participant identification (such as patient name) as participants were tested on multiple occasions. The protection of participant

confidentiality is fundamental to respect for persons (Wassenaar, 2014). Once data collection was complete, each participant was assigned a numerical code and their personal details erased. Participant information (numerical code used and not participant name) and results were entered onto a password protected cloud such as *Microsoft OneDrive* as data is collected. This ensured that confidentiality was still maintained during adverse events such as theft. Any hard copies of the participant information are kept in a locked cabinet in the researcher's supervisor's office. This information will be shredded after for five years.

Beneficence. Caution needs to be taken when evaluating the potential risks and benefits to human participants in medical research (Wassenaar, 2014). In accordance with the Declaration of Helsinki (WMA, 2013), the risks were continuously monitored throughout the study.

Risks and benefits.

- Participants may have been overexerted while being tested with audiometry twice within an hour on a weekly basis. The time interval between tests was a maximum of fifteen minutes allowing participants enough time to rest in between tests. Each audiometric test was reduced from twelve frequencies (as per ASHA's protocol) to testing only seven frequencies per ear.
- Participants may have experienced distress when hearing that they have developed a hearing loss. Counselling and a referral to the resident audiologist and physician for management (part of routine hospital care) was provided in such instances.
- The researcher had the risk of contracting MDR-TB. Precautions such as wearing an appropriate TB mask, wearing gloves when evaluating participants and making sure that the windows of the test room were always open was taken.
- Direct participant benefit:
    - Participants were compensated with R50 for each session attended to cover associative costs (such as travelling fare to and from the hospital if the participant was discharged from hospital) related to participating in the study.
    - Participant satisfaction of being involved in a scientific study (Cozby, 2009).
- General/professional benefit:
    - Contribution to practical ototoxicity monitoring guidelines in developing countries such as South Africa.

- Evidence for a feasible ototoxicity monitoring protocol such as automation with the SRO technique.
- Test time reduction (to seven frequencies) making test battery more appropriate for weak patients such as those with MDR-TB.
- Reduction of high caseloads allowing more access to health care through automation.

3.13 Data Management

The data collected for this research study was recorded on a hard copy during the testing session. The raw data recorded included: 1) a participant identification code (i.e. 1,2, etc.), age and gender, 2) the name of the MDR-TB treatment previously and/or currently being received and the date that it started (e.g., amikacin, kanamycin, bedaquiline, etc.), 3) the auditory symptoms participants reported (ear specific where possible), 4) otoscopic results, 5) tympanometry results, 5) the date and time frame for each audiometric test, 6) the hearing thresholds for both manual and automated audiometry, 7) the state of the participants (e.g., fatigued) for each session, and 8) the exit survey multiple choice option and rationale given by the participant. The participant's name and respective identification code were recorded on a separate sheet.

After each session, the data was stored as a portable document file (PDF) and uploaded onto a password-protected cloud, *Microsoft OneDrive*. The data was also recorded on an excel spreadsheet, on *Microsoft OneDrive. Each objective had a different* excel spreadsheet. Each spreadsheet had an introductory page that outlined the objective and described the type of variable and data needed to answer the objective. Each spreadsheet was formatted in a way that made reading and analysing the data convenient.

Data entry was done on the same day as data collection. Each facility requested that test results be recorded in the participants' medical files. Data entered was rechecked for errors at the end of each week. Data entry checks were also done at the end of data collection for each participant on two separate occasions. The PDF and hard copies of the data were given to the research supervisor to store on her password-protected computer and locked cabinet in her office. The data will be shredded after five years.

3.14 Data Analysis

The research study's data was analysed using descriptive and inferential statistical methods. The sample demographics was expressed using descriptive statistical methods such as frequency distribution tables. Descriptive statistics is used to describe the data or describe the relationship

among the data (Durrheim, 2014). Inferential statistics is used to make judgements and conclusions based on the data acquired from a sample (Durrheim, 2014). A Bonferroni corrected *p*-value was used because numerous independent or dependent inferential statistical tests were being made simultaneously using one sample (Napierala, 2012). This was the case for this research study. The formula for the Bonferroni corrected *p*-value is *p*-value (for this study it was 0.05) divided by the amount of comparisons made (Napierala, 2012). Table 2 shows how results were analysed.

Table **2**

Data Analysis Table

Aim/Objective	**Type of data**	**Variable**	**Descriptive Statistics**	**Inferential Statistics**
1.1 Testing time efficiency between manual and automated audiometry using the SRO technique	Ratio	Test duration (in minutes)	• Mean • Standard deviation • Subtraction (i.e. mean difference)	• Paired samples *t*-tests
1.2 Test-retest reliability of hearing thresholds between manual and automated audiometry	Interval	Hearing thresholds	• None	• Pearson's correlation coefficient • Paired sample's t-test
1.3 Diagnostic value and the sensitivity, and specificity of automated audiometry with the SRO technique compared to manual audiometry	Binary	Absence of presence of an STS	• None	• Receiver operating characteristic (ROC) curve • 2x2 table for sensitivity and specificity

2.1 Time interval of the onset of an STS after starting MDR-TB treatment	Ratio	Time (in days)	• Frequency distribution bar graph • Box and whisker plot • Percentiles	• None
2.2 Associated auditory symptoms	Categorical	Reported symptom	• Frequency distribution bar graph • Percentiles	• None
3. Patient with MDR-TB's test method preference	Categorical	Multiple choice option and rationale theme	• Frequency distribution bar graph • Percentiles	• None

Objective 1.1: the variable of interest was time (in minutes) and this was expressed as ratio data. The average (mean) test duration (in minutes) of manual and automated audiometry was measured. The standard deviation for each test method was calculated to see how widely spread individual test durations are from the mean (i.e. central tendency) of each test method (Durrheim, 2014). The mean values of each test method were subtracted from one another to indicate which test method was more time efficient (i.e. shorter test duration). Paired samples *t*-tests were used to see whether the difference in testing time between the test methods were significant. A paired sample's *t*-test is used to compare the means of two samples where sample data was obtained from the same sample group (Nunez, 2013).

Objective 1.2: the variable of interest was hearing thresholds in dB HL and this was expressed as interval data. The paired sample's *t*-test was used to compare the thresholds obtained between manual and automated audiometry. This analysis was frequency (i.e. 4 – 16 kHz) and ear specific. The Pearson's Correlation Coefficient test (*r*) was used to calculate the strength of the relationship between thresholds obtained through manual and automated audiometry for each frequency tested (Lachenicht, 2013).

Objective 1.3: the variable of interest was the presence or absence of an STS and this was expressed as binary data. Receiver Operating Characteristic Curves are essential in evaluating a diagnostic tools ability to accurately detect a true result (i.e. the area under the ROC curve) (Altman & Bland, 1994; Hajian-Tilaki, 2013). ROC characteristics measure the diagnostic value of a test compared to a gold standard (Kumar & Indrayan, 2011). According to Hajian-Tilaki (2013), if the area under the curve is 1 it is near perfect detecting the presence or absence of a disease (Hajian-Tilaki, 2013). However, if the area under the curve is 0.5 or below that means that there was a chance discrimination during classification of the presence or absence of a disease (Hajian-Tilaki, 2013). Lastly, if the area under the curve is 0, the test incorrectly classifies the presence or absence of a disease (Hajian-Tilaki, 2013). Here, the presence or absence of an STS was coded as '1' and '0' respectively. This was done for both manual and automated audiometry. A 2x2 table was also used to evaluate the sensitivity and specificity of a test (i.e. automated audiometry with the SRO technique compared to manual audiometry) (Shaikh, 2011). The formula for sensitivity was as follows: number of true positive (TP) results divided by the number of TP results added to the number of false negative (FN) results (i.e. TP/(TP+FN)) (Shaikh, 2011). The formula for specificity was as follows: number of true negative (TN) results divided by the number of TN results added to the number of false positive (FP) results (i.e. TN/(TN+FP)) (Shaikh, 2011).

Objective 2.1: the variable of interest was time (in days), and this was expressed as ratio data. A frequency distribution table and percentiles were used to show the frequency with which a certain time (in days) difference of ototoxicity-induced hearing loss onset occurred. A box and whisker plot showing the time difference obtained was measured. This gave the researcher an indication of the data set's central tendency (Tredoux & Durrheim, 2013). There were no inferential statistical measurements for this objective.

Objective 2.2: the variable of interest was auditory symptoms, and this was expressed as categorical data. A frequency distribution bar graph and percentiles were used to show the frequency with which a certain auditory symptom was reported among participants with MDR-TB. There were no inferential statistical measurements for this objective.

Aim 3: the variable of interest was test preference, and this was expressed as categorical data. A frequency distribution table and percentiles were used to show the frequency of multiple options that correspond to the preference of manual, automated, none or both test methods. The rationale given by participants were also expressed in the table. There were no inferential statistical measurements for this aim.

Chapter 4 **Results**

This chapter will report on the results obtained for each objective. The testing time efficiency, hearing threshold parallel forms reliability, diagnostic test value and the specificity and sensitivity of automated audiometry and manual audiometry analysis will be shown under the first aim. The incidence of an STS (i.e. the time it takes for an STS to occur) and the associated auditory symptoms of ototoxicity will be described under the second aim. Lastly, the test method preference will be described under the last aim.

4.1 Aim 1: Compare the feasibility of the SRO technique in detecting an ototoxicity-induced hearing loss with automated and manual (gold standard) audiometry.

- **Testing time efficiency between manual and automated audiometry.**

On average, manual audiometry had a faster testing time (*M*= six minutes and five seconds) compared to automated audiometry (*M*= seven minutes 14 seconds) by one minute and ten seconds. Manual audiometry was more varied in testing time (*SD*= two minutes and 25 seconds) compared to automated audiometry (*SD*= one minute and 36 seconds). The difference between manual audiometry testing time and automated audiometry testing time obtained revealed a statistically significant difference using a paired samples *t*-test where t (94) = -5.44; $p < 0.003$.

- **Reliability of thresholds obtained using the different test methods**

At all frequencies, there was a strong positive correlation for both left and right ears between the thresholds obtained from manual and automated audiometry ($r(28) > 0.70$, $p < 0.003$ excluding 4 and 6 kHz) (see table 3). This correlation is statistically significant ($p < 0.003$; alpha level based on Bonferroni correction) at 8, 9, 10, 11.2, 12.5, 14 and 16 kHz. However, the correlation is not statistically significant at 4 and 6 kHz for both left and right ears ($p > 0.003$). This is because the results of one participant was used to analyse parallel forms of reliability at 4 and 6 kHz as only one participant had an SRO that included these two frequencies. The results obtained for 4 and 6 kHz are excluded from the discussion of the results due to limited number of pairs contributing to the analysis of the data. Results were excluded from analyses when no response was obtained during testing.

Table **3**

Correlations Between Thresholds Obtained from Manual and Automated Audiometry

Frequency	***N****	***r***	***p* (two-tailed)**
4 kHz Right Ear	4	0.88	0.12

4 kHz Left Ear	4	0.92	0.08
6 kHz Right Ear	3	0.88	0.32
6 kHz Left Ear	2	0.91	0.28
8 kHz Right Ear	95	0.92	0.000
8 kHz Left Ear	95	0.86	0.000
9 kHz Right Ear	95	0.89	0.000
9 kHz Left Ear	95	0.91	0.000
10 kHz Right Ear	92	0.92	0.000
10 kHz Left Ear	92	0.93	0.000
11.2 kHz Right Ear	91	0.90	0.000
11.2 kHz Left Ear	91	0.95	0.000
12.5 kHz Right Ear	87	0.95	0.000
12.5 kHz Left Ear	87	0.96	0.000
14 kHz Right Ear	74	0.94	0.000
14 kHz Left Ear	74	0.94	0.000
16 kHz Right Ear	30	0.98	0.000
16 kHz Left Ear	30	0.94	0.000

Note. Bonferroni corrected *p*-value = 0.05/18 = 0.003.

**N* was derived from the number of times a frequency was tested among all participants.

The difference between thresholds obtained from manual audiometry and automated audiometry are not statistically significant for the left and right ear results at all frequencies tested (paired samples *t*-test; *p*> 0.003). (see table 4). On average, poorer thresholds were obtained with automated audiometry compared to manual audiometry.

Table **4**

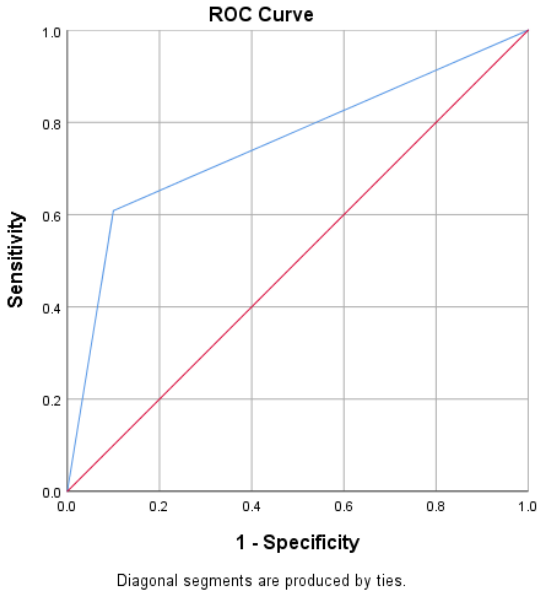
Differences Between Thresholds Obtained from Manual and Automated Audiometry

Frequency	***M***	***SD***	**Standard Error**	**95% *CIs***	***t***	***df***	***p* (2-tailed)**
4 kHz Right Ear	-6.25	9.46	4.73	-21.31, 8.81	-1.32	3	0.278
4 kHz Left Ear	-6.25	12.5	6.25	-26.14, 13.64	-1.00	3	0.391
6 kHz Right Ear	-10	17.32	10	-53.03, 33.03	-1.00	2	0.423
6 kHz Left Ear	-6.67	11.55	6.67	-35.35, 22.02	-1.00	2	0.423
8 kHz Right Ear	-0.89	5.74	0.59	-2.03, 0.27	-1.52	94	0.132
8 kHz Left Ear	-0.79	8.51	0.87	-2.52, 0.95	-0.90	94	0.368
9 kHz Right Ear	-1.42	7.84	0.80	-3.02, 0.18	-1.77	94	0.081
9 kHz Left Ear	-0.84	7.60	0.78	-2.39, 0.71	-1.08	94	0.283
10 kHz Right Ear	-0.27	7.00	0.73	-1.72, 1.18	-0.37	91	0.711
10 kHz Left Ear	-0.49	6.50	0.68	-1.84, 0.86	-0.72	91	0.473
11.2 kHz Right Ear	-0.88	8.01	0.84	-2.55, 0.79	-1.05	90	0.298
11.2 kHz Left Ear	0.16	6.64	0.70	-2.22, 1.55	0.24	90	0.813
12.5 kHz Right Ear	-0.63	5.75	0.62	-1.86, 0.59	-1.03	86	0.308
12.5 kHz Left Ear	-0.63	5.64	0.61	-1.84, 0.57	-1.05	86	0.299
14 kHz Right Ear	-0.41	6.34	0.74	-1.88, 1.06	-0.55	73	0.584
14 kHz Left Ear	1.42	7.61	0.88	-0.34, 3.18	1.60	73	0.113
16 kHz Right Ear	0.83	3.73	0.68	-0.56, 2.23	1.22	29	0.231
16 kHz Left Ear	-0.50	6.48	1.18	-2.92, 1.92	-0.42	29	0.676

- **The diagnostic value and the sensitivity and specificity comparisons of automated audiometry to manual testing**

The ROC curve revealed that automated audiometry is a fair diagnostic test (area > 0.7). This can be seen by the area under the curve being 0.75 (*SE* = 0.07, 95% *CI* (0.62, 0.89), *p* = 0.002).

Moreover, both automated and manual audiometry agree 61% of the time when a significant change in hearing sensitivity has occurred (i.e. sensitivity) and agree 90% of the time when no significant change in hearing sensitivity has occurred (i.e. specificity) (see figure 3).



Blue line: ROC curve; Red line: Reference line indicating no sensitivity and no specificity

Figure 3. Sensitivity and specificity of automated audiometry with the SRO technique in detecting an STS

Table 5 describes the frequencies at which automated and manual audiometry give the same and different diagnostic results. The sensitivity (i.e. (TP/(TP+FN))*100) was 61% and specificity (i.e. (TN/(TN+FP))*100) was 90%.

Table **5**

Correspondence between automated and manual audiometry to determine an STS

	Manual – STS	**Manual – no STS**
Automated – STS	14True Positive (TP)	3False Positive (FP)
Automated – no STS	9False Negative (FN)	28True Negative (TN)

4.2 Aim 2: Describe the incidence of hearing loss (determined through an STS).

- **The time between MDR-TB treatment commencement and the onset of a hearing loss.**

Only participants that started MDR-TB treatment at most 31 days before data collection commenced were included in the analysis of this objective (n=13 out of 14 participants). Baseline assessments were either done within week one (three participants; 23%), week two (four participants; 30%), week three (23% of participants) or within the fourth week (23% of participants) after starting MDR-TB treatment. Of these thirteen participants, only eight participants had an STS during data collection. However not all participants had a bilateral STS, therefore, each ear with an STS (i.e., 10 ears) was analysed separately (see table 6).

Table **6**

Frequency Distribution of the Time Interval of the Onset an STS

Variable (Time in Days)	Number of Ears	Percentage of Participants with an STS (%)
1-9	0	0%
10-19	2	20%
20-29	2	20%
30-39	2	20%
40-49	3	30%
50 and above	1	10%

Note. Ears without an STS were excluded from the analysis (n=16 ears).

The time interval between the onset of an STS and the start of MDR-TB treatment data was skewed to the right as the data varied more between the median and the maximum value than the minimum and the median (see figure 4). An STS indicating an ototoxicity-induced hearing loss was noted in 38.46% of ears (n=10 out of 16). A median of 33 days was observed (skewed data).

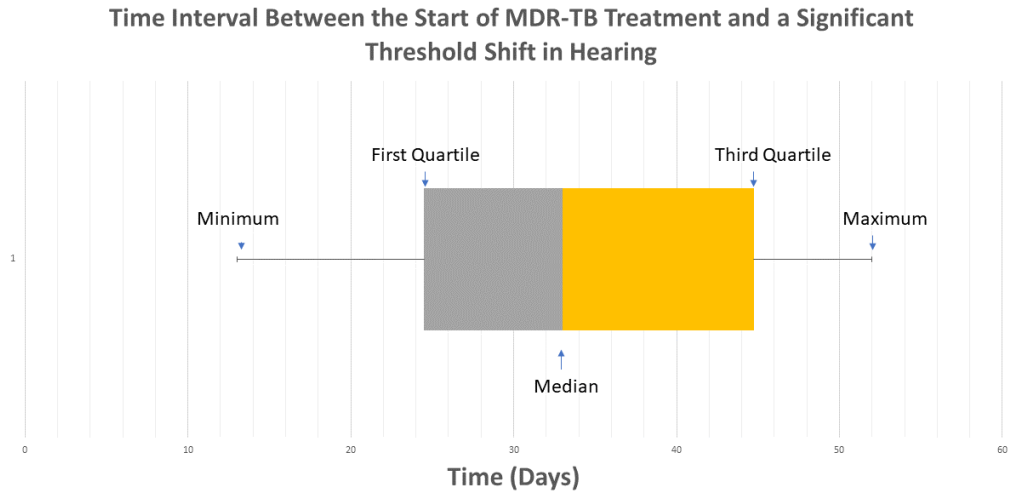


Figure 4. STS onset time interval (in days) graph

- **Associated auditory symptoms reported**

Figure 5 displays the frequency of auditory symptoms among participants before hearing tests were conducted. Fifty-six percent of participants (n=15 out of 27) reported auditory symptoms, with aural fullness the most frequently mentioned (53.33%; n=8 out of 15 participants). Case history information revealed that 44.44% (n=12 out of 27) participants had a history of occupational noise exposure (i.e. more than 72 hours prior to data collection). Most of the participants (53.33%; n= eight out of 15) that reported auditory symptoms started their treatment more than a month before data collection. Secondly, majority of the participants (67%; n= 10 out of 15) that reported auditory symptoms had an STS. In addition, all participants that reported aural fullness (n=8) had an STS. No new symptoms were reported throughout the data collection.

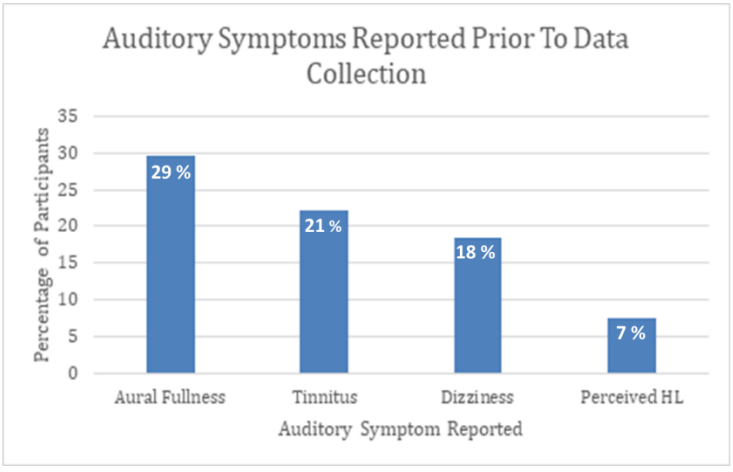


*Figure **5**.* Frequency of other Reported Symptoms

4.3 Aim 3: Ototoxicity Monitoring Test Method Preference (Manual Versus Automated Audiometry)

The exit survey was completed by 19 (70.37%) participants. Eight participants (29.63%) did not complete the exit survey because they were discharged before data collection was completed (see table 7). Most participants had no preference between the two testing methods.

Table **7**

Patient Test Method Preference

Preference	**n**	**Rationale**
No Preference	13	“No difference noted”
Manual Audiometry	3	“easier,” “quicker,” or “had a clearer sound”
Automated Audiometry	3	“heard better” or “had a clearer sound”

Chapter 5 **Discussion**

This chapter interprets the results obtained and analysed in chapter four. Each objective is delved into separately. The first three objectives attempt to answer the main aim of the feasibility of the SRO and automated audiometry. The objectives for the secondary aim (i.e. incidence of an STS) and tertiary aim (i.e. test method preference) are discussed subsequently. How results obtained relate to previous studies are described and the implications for future research and clinical guidelines are also discussed. This chapter also discusses the limitations faced by the research study, the conclusion and recommendations for future research.

5.1 SRO testing time efficiency between manual and automated audiometry

Results from this research study showed that manual audiometry was more time efficient compared to automated audiometry. The results of this study did not correlate with Swanepoel, Mngemane et al., (2010), where manual and automated audiometry testing time was found to be similar (7.2 to 7.7 minutes on average) (Swanepoel, Mngemane, et al., 2010). However, Swanepoel, Mngemane et al., (2010), used normal hearing participants. Swanepoel, Mngemane et al., (2010) varied the order in which testing occurred (e.g., Manual than automated audiometry or automated audiometry than manual audiometry). This study did not counterbalance the test order. Secondly, MDR-TB treatment is known to cause fatigue resulting in patients being difficult to test (Swanepoel & Biagio, 2011). MDR-TB treatment has numerous side effects that negatively affect audiometry testing as it requires concentration for long periods of time (Paken et al., 2016; Schacht et al., 2012). Manual audiometry was always tested prior to automated audiometry during data collection. This may have contributed to manual audiometry being more time efficient compared to automated audiometry. This could also have influenced thresholds obtained through automated to be poorer (on average) compared to manual audiometry. Thirdly, although both automated and manual audiometry used the Modified Hughson and Westlake threshold searching technique, manual audiometry started testing at 30 dB HL at 1 000 Hz only while automated audiometry started testing each frequency at 30 dB HL and perhaps why automated audiometry was found to be less time efficient. Based on this finding, future research can look at programming automated audiometry with the same threshold search manner in which manual audiometry is conducted (i.e. starting at 30 dB HL at 1000 Hz only and not at all frequencies) in an attempt for it to be more time efficient. Lastly, the average time difference between manual and automated audiometry using the SRO technique may be statistically significant but both test methods' testing average is more practical than the current test battery for difficult to test patients that have limited concentration.

Furthermore, the SRO technique is more time efficient (with either manual or automated testing) compared to traditional ototoxicity monitoring methods (Fausti et al., 1999). Traditional ototoxicity monitoring tests conventional frequencies (0.25 to 8 kHz; taking approximately eight minutes) plus additional testing such as extended high-frequency testing (9 to 16 kHz) (Swanepoel, Mngemane, et al., 2010). The SRO technique only tests seven frequencies per ear that are separated by 1/6 octaves (Dille et al., 2013). Thus, the SRO technique is beneficial for patients that are too ill to concentrate for extended periods of time (such as that required for traditional ototoxicity monitoring) (Dille et al., 2013).

5.2 Parallel forms reliability between automated and manual audiometry

Thresholds obtained with both manual and automated audiometry were positively correlated in this study. Similar thresholds were obtained from both testing methods. This result correlated with the study done by Swanepoel and Biagio, (2011) and Swanepoel, Mngemane, et al., (2010) that found that the air conduction thresholds obtained with the automated audiometry (using the KUDUwave ™) correlated 90% of the time with standard manual audiometry (Swanepoel & Biagio, 2011; Swanepoel, Mngemane, et al., 2010). Yeung et al. (2013) obtained highly reliable results when using automated audiometry in a sound treated room compared to the conventional testing (Yeung et al., 2013). Similarly, Brennan-Jones et al. (2016) and Maclennan-Smith et al. (2013) validated automated audiometry in normal and heterogenous populations (Brennan-Jones et al., 2016; Maclennan-Smith et al., 2013). Some studies such as Lemkens et al. (2002) deemed a 10 dB HL difference between automated and manual audiometry thresholds as agreeable (Thompson, Sladen, Borst, & Still, 2015). However, this research study considered a maximum of 5 dB HL difference as reliable. Furthermore, all studies reported no statistically significant differences between automated and manual audiometry testing (Mahomed, Swanepoel, Eikelboom, & Soer, 2013).

Automation has the potential to improve the standardisation of testing protocols across health care facilities (Mahomed et al., 2013). A systematic review and meta-analysis done by Mahomed et al. (2013) has found that automated audiometry has the same amount of test-retest variability as manual audiometry does (Mahomed et al., 2013). Automated audiometry cannot supersede the need for an audiologist but a computerised system that can obtain pure tone thresholds just as accurately is beneficial for the disproportionate patient and audiologist ratio (Mahomed et al., 2013). Thus, automated audiometry can form part of the clinical guidelines as it allows for standardisation across testing.

5.3 The sensitivity and specificity of using automated audiometry

The assessment of a diagnostic test is vital in the modern field of health sciences for detecting the presence or absence of a disease (Hajian-Tilaki, 2013). This allows for the high-quality of diagnostic information in a field like audiology (Beck, 2015). This research study found that automated audiometry is a fair diagnostic test (area under ROC is 0.75). This finding correlated with Mahomed et al. (2013) stating that automated audiometry is largely valid (Mahomed et al., 2013). This research study showed that automated audiometry accurately identified the absence of an STS 90% of the time. However, this research study revealed that the presence of an STS was only accurately identified 60.1% of the time. Similar studies comparing automated audiometry with manual audiometry have found a 90% specificity and 88.9% sensitivity in a non-sound treated room with heterogenous participants (Thompson et al., 2015). Yeung et al (2013) found a 93.3% specificity and 94.5% sensitivity in a sound treated room with normal hearing participants (Yeung et al., 2013). In these studies, the reliability of thresholds had to be within 10 dB HL (Lemkens et al., 2002 as cited by Thompson et al., 2015). However, for this research study, a difference within 5 dB HL (which is a more stringent criterion) was needed for a threshold to be considered reliable. Secondly, the presence or absence of an STS (i.e. binary data) was used when calculating the ROC characteristic not hearing thresholds. Thirdly, the ASHA criteria were used to determine the absence or the presence of an STS (Waissbluth et al., 2017). The ASHA criteria were developed to determine most cases of ototoxicity and focuses more on the detection of false positives (i.e. reducing the number of referrals for confirming an STS) (Waissbluth et al., 2017). Fourthly, pure tone audiometry testing is largely affected by the testee's willingness (and ability) to cooperate and respond when a sound is heard (Schlauch & Nelson, 2015). MDR-TB treatment has adverse side effects that strain the body, causes fatigue and a lack of concentration during testing (Paken et al., 2016; Schacht et al., 2012). This leads to difficulty coping with (subjective) audiometry testing (Walker, Cleveland, Davis, & Seales, 2013). For example, if a patient does not respond within a certain time period, the system records it as a ''no response'' and subsequently increases the intensity (Swanepoel, Mngemane, et al., 2010). An audiologist can detect an inaccurate response when no change in hearing is suspected and resolve this while automated audiometry is at a disadvantage as it is algorithm based (Dille et al., 2013). Therefore, when a patient is difficult to test, manual audiometry is best (Dille et al., 2013). However, automated audiometry has better test-retest reliability compared to manual audiometry as threshold-seeking is done frequently without bias (Jerlvall, 1983 as cited by Swanepoel, Mngemane, et al., 2010). Additionally, high-frequency DPOAE testing, an objective test, can be used as an adjunct to automated audiometry (Reavis et al., 2011). Reavis et al. (2011) found that DPOAEs are strong predictors for ototoxicity induced hearing threshold shifts.

5.4 Incidence of an ototoxic-induced hearing loss in participants with MDR-TB

This research study revealed that most of the participants (38.46% of ears; n=10 out of 16) experienced an STS in hearing after an average of 33 days (median of 33 days; data was skewed to the right) after starting MDR-TB treatment. However, a true baseline could not be obtained (i.e. participants could not be tested prior to starting MDR-TB medication). This finding correlates to a longitudinal study done by Appana et al. (2016) stating that an ototoxicity-induced hearing loss appears after one month of starting ototoxic MDR-TB treatment (Appana et al., 2016). However, there is also conflicting literature available that states that an ototoxicity-induced hearing loss can occur immediately after starting MDR-TB treatment, three to four days after starting MDR-TB treatment, or after the completion of MDR-TB treatment (De Jager & Van Altena, 2002; Kolinsky et al., 2010; Sara et al., 2014). The variability regarding the incidence of an ototoxic-induced hearing loss is affected by assessment protocol parameters, participant characteristics and the normative/standard criteria used to determine an STS (Xie, Talaska, & Schacht, 2011). Additionally, the incidence of ototoxicity depends on the duration and dosage of ototoxicity treatment (Xie et al., 2011).

5.5 Other auditory symptoms reported by participants on MDR-TB

Aural fullness was the most reported symptom. All the participants that reported aural fullness (n=8) at the start of data collection obtained an STS (i.e. ototoxic damage) during data collection. This result correlates with Cianfrone et al. (2011)'s findings that state that tinnitus, dizziness, hyperacusis, aural fullness and hearing loss are symptoms associated with ototoxicity. These symptoms vary among individuals and ototoxic drugs (Bisht & Bist, 2011). However, a study done by Javadi et al. (2011) found that individuals typically do not experience any audiological symptoms prior to the onset of an ototoxic-induced hearing loss (Javadi et al., 2011). Moreover, Bisht and Bist (2011) reported that extended high frequency audiometry can detect an ototoxic-induced significant shift in hearing prior to experiencing tinnitus or a perceived hearing loss (Bisht & Bist, 2011). In addition to aural fullness, a history of noise exposure was also reported among participants. This research study found that 44.44% of participants reported a history of noise exposure. Of the 10 ears that were used in the analysis of the incidence of an STS, 38.46% had an STS. Excessive noise can damage the hair cells of the cochlea and cause a permanent hearing loss (Filgor et al., 2015). This is as a result of the metabolic change that occurs in the cochlea (Filgor et al., 2015). A gradual onset of a cochlea hearing loss may also be due to a history of excessive noise exposure that may range from 75 to 78 dBA to 132 dBA (Melnick, 1991 and as cited by Filgor et al., 2015). It should be noted that most participants that had reported auditory symptoms (53.33%; n= eight out of 15) participated in this study's data collection more than a month after starting their MDR-TB treatment. This time delay

between starting MDR-TB treatment and data collection may have contributed to the results. Therefore, future research may need to look at the accurate incidence of auditory symptoms compared to an STS in individuals receiving ototoxic medication with weekly ototoxicity monitoring using the SRO technique. Lastly, aural fullness may indicate a pathology in any part of the peripheral hearing pathway (Park et al., 2012). It is said to be omnipresent (Park et al., 2012). Therefore, patients reporting aural fullness as the primary complaint need to undergo a diagnostic hearing evaluation. Various pathologies may have aural fullness as a symptom (Park et al., 2012).

5.6 Ototoxicity Monitoring Test Method Preference

Most of the participants (n=13) that completed the exit survey had no preference between manual or automated audiometry testing. The common reason was that “no difference was noted.'' This finding correlates with a study done by Kelly et al. (2018), that found that participants had a neutral response between automated and manual audiometry (Kelly et al., 2018). The reason for this could be that automated and manual audiometry have the same instructions and test procedures (Maclennan-Smith et al., 2013). This finding shows automation will be useful in improving the disproportionate audiologist and patient ratio by decreasing the caseload (Swanepoel & Biagio, 2011) without negatively affecting patient satisfaction or possibly compromising on patient-centred care as participants prefer either testing methods (Wang & Fung, 2014). Secondly, the participants that did have a preference were equally distributed (i.e. n=3 each) among automated or manual audiometry. A ''clearer sound” was the reason preferring both automated or manual audiometry. This does not correlate with a similar study done by Konrad-Martin et al. (2014) that found that participants preferred automated audiometry and Swanepoel, Mngemane et al. (2010) suggested that it is due to automated audiometry’s predictable nature when presenting stimuli (Konrad-Martin et al., 2014; Swanepoel, Mngemane, et al., 2010). It should be noted that manual audiometry may have been preferred by some participants as it requires the tester to decide on whether there was a response or not (Schlauch & Nelson, 2015). This finding is especially useful when testing difficult-to-test patients (Swanepoel & Biagio, 2011). As previously mentioned, MDR-TB medication has adverse side effects on individuals with MDR-TB resulting in them having decreased concentration levels (Paken et al., 2016). Also, there is limited research on how patients (and clinicians) experience the advances in technology innovation (especially in the field of audiology) where technology innovation is continuously evolving (Ng, Phelan, Leonard, & Galster, 2017). More in-depth research studies will be beneficial to understand and create more ways to improve on patient satisfaction (Ng et al., 2017).

5.7 Limitations

This research study could not recruit participants that were newly diagnosed with MDR-TB due to a lack of referrals to the health facilities where data was being collected. The participants were still recruited if they had normal hearing. Initially, this study aimed to test patients on amninoglycosides (known to cause ototoxicity), however, most participants with MDR-TB were enrolled in the new MDR-TB treatment regimen where Bedaquiline was used ("Bedaquiline roll-out," 2018; Zimmerman & Lahav, 2013). Therefore, participants on BDQ had to be recruited as well. Most participants had already started MDR-TB treatment more than a week before data collection commenced. This resulted in some participants being excluded when analysing the incidence of an ototoxicity-induced hearing loss. Baseline testing was not done as part of the research study. This degrades the reliability when assessing the incidence of an ototoxicity-induced hearing loss analysis. All participants were in-patients. Contact was lost with the patient as soon as they were discharged from hospital resulting in incomplete data and limited number of participants completing the exit survey. However, the data already collected for these participants were still used during data analysis. Lastly, this research study could have benefited from a pilot study. A pilot study where the test-retest reliability of each test method could have been assessed prior to the prospective repeated-measures design used for this research. A pilot study would have enhanced the reliability of the current research study.

5.8 Conclusion and Recommendations

This study found that manual audiometry was more time efficient compared to automated audiometry. It was discussed that the test method settings in automated audiometry need to be adapted more similarly to how manual tests are currently conducted to obtain similar testing time efficiency results. Ototoxicity monitoring programs could also consider using the SRO technique in patients that are easily fatigued because of MDR-TB medication. The SRO technique has been shown in previous studies (Dille et al., 2013; Swanepoel, Mngemane, et al., 2010) to be more time efficient compared to traditional ototoxicity monitoring methods. Equipment settings can be changed to accommodate testing frequencies in 1/6 octaves so that the SRO technique can be clinically adopted (Konrad-Martin et al., 2014). Automated audiometry is a fair diagnostic test in patients with MDR-TB. However, using automated audiometry in difficult to test patients gives a less accurate sensitivity. Clinically, automated audiometry with the SRO technique is time efficient, objective and it allows for standardisation (Swanepoel, Mngemane, et al., 2010). A true baseline could not be obtained to report accurately on the incidence of an STS. Therefore, the accurate incidence of an STS still needs to be investigated (Bisht & Bist, 2011). Aural fullness was observed to be the most reported symptom

among participants. Aural fullness is one of the symptoms associated with ototoxicity as found in previous studies (e.g., Cianfrone et al., 2011). Aural fullness may be present in both middle ear and/or inner ear pathologie (Park et al., 2012). Therefore, this symptom needs to be investigated fully and may not be a simple/elementary symptom (Park et al., 2012). No test method preference was reported by participants. It seems that the introduction of automated audiometry has not impacted on patient preference and thus patient satisfaction with services provided (Wang & Fung, 2014).

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Chapter 6 **Appendices**

6.1 Appendix A: Short Exit Survey

Exit Survey On Patient Test Method Preference

1) Which test would you like to do in the future?
    a) Automated Test (where the researcher was not present)
    b) Manual Test (where the researcher was doing the testing)
    c) Any of the two tests
2) If you prefer one test over the other, can you provide reasons for your choice?

_____

_____

_____

6.2 Appendix B: Faculty of Health Science Human Research Ethics Committee Approval Document

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

17 October 2018

HREC REF: 614/2018

Ms Lucretia Petersen
Communication Sciences and Disorders
Health and Rehab
F-floor, OMB

Dear Ms Petersen

PROJECT TITLE: OTOTOXICITY MONITORING USING AUTOMATED EXTENDED HIGH-FREQUENCY AUDIOMETRY AND THE SENSITIVITY RANGE OF OTOTOXICITY IN MDR-TB PATIENTS (Masters Candidate - Ms W Greaff)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

Before formal approval, please address the following issues:

Literature Review:

1. Needs to be updated to reflect recent changes to the drug-regimen for MDR-TB (not all patients receive ototoxic drugs for MDR-TB treatment)

Test Procedure:

2. *Patient recruitment:* It is stated that recruitment will involve the researcher, facility admin staff and resident physician and audiology department; give the power asymmetry between the health providers and the patients, this may compromise patient's autonomy to participate in the study. The HREC Suggest that recruitment be done by individuals who are not directly involved in treating or providing health care services to the patients.

3. *Testing:* Participants will be tested "periodically" after two to seven days of their last audiological tests...: Can you please be clear about what you mean by "periodically" (i.e. exact number of planned assessments. Also, will participants be required to come back for assessments after their last audiological test specifically for the purpose of this research study?

4. The series of tests/assessments proposed, which one of those are tests that will be administered to the patients regardless of the study and which ones are specific to the study? Is the researcher familiar with the ototoxicity monitoring protocol at the facility re: types of assessments that patients are done and intervals between different assessments? Also, what ototoxicity monitoring guidelines are currently in place at the facility?

6.3 Appendix C: Western Cape Health Department Approval Document

Western Cape Government
Health

Health impact assessment
Health research sub-directorate
Health.Research@westerncape.gov.za
tel: +27 21 483 0566; fax: +27 21 483 9690
5th Floor, Norton Rose House, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za

REFERENCE: WC_201902_004
ENQUIRIES: Dr Sabela Petros

University of Cape Town

Anzio Road

Observatory

Cape Town

7925

For attention: Mrs Lucretia Petersen, Ms Wildine Greff, Ms Vera Genevey Illayisi

Re: Ototoxicity Monitoring Using Automated Extended High-Frequency Audiometry And The Sensitivity Range of Ototoxicity In MDR-TB Patients

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

Brooklyn Chest Hospital	**Dr Julian te Riele**	**021 508 7446**
DP Marais Hospital	**Dr Julian te Riele**	**021 508 7446**
District 6 CHC	**Mr Theodore Abrahams**	**021 833 5400**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. By being granted access to provincial health facilities, you are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of your project. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

6.4 Appendix D: Clinical Manager of the Metro TB Hospital centre (DP Marais Hospital) and Brooklyn Chest Hospital's approval

RE: Master's Research Project

Julian Te Riele <Julian.teRiele@westerncape.gov.za>
Tue 2019/06/04 12:47
To: Wildine Greeff <GRFWIL003@myuct.ac.za>
Cc: Lucretia Petersen <lucretia.petersen@uct.ac.za>; Vera Hlayisi <vera.hlayisi@uct.ac.za>

Dear Wildine,

Please do. You have site permission from MTBHC

Regards
Julian

Dr Julian te Riele
Clinical manager
Metro TB Hospital Centre
Brooklyn Chest Hospital
(021) 508 7400

From: Wildine Greeff [mailto:GRFWIL003@myuct.ac.za]
Sent: Tuesday, June 04, 2019 10:01 AM
To: Julian Te Riele <Julian.teRiele@westerncape.gov.za>
Cc: Lucretia Petersen <lucretia.petersen@uct.ac.za>; Vera Hlayisi <vera.hlayisi@uct.ac.za>
Subject: RE: Master's Research Project

Dear Dr Julian Te Riele

Thank you for accomodating my research project at Brooklyn Chest And DP Marais Hospital.

I will be sure to give a presentation about my research project and its findings to you.

May I go ahead and arrange with the audiology departments with regards to the logistics of my data collection?

Kind regards,

Wildine Greeff

-------- Original message --------
From: Julian Te Riele <Julian.teRiele@westerncape.gov.za>
Date: 2019/06/03 14:58 (GMT+02:00)
To: Wildine Greeff <GRFWIL003@myuct.ac.za>
Cc: Lucretia Petersen <lucretia.petersen@uct.ac.za>, Vera Hlayisi <vera.hlayisi@uct.ac.za>
Subject: RE: Master's Research Project

Dear Wildine,

Thanks for the email. I have added all your documents to our database. Don't worry about the recorded presentation but if you find yourself in Cape Town please come and give us a talk on your project. Also, we would be interested in your findings and final thesis

6.5 Appendix E: Auditory Symptom Questionnaire

Auditory Symptom Questionnaire

1. Have you had any exposure to loud noise/music (For example, you had to raise your voice to hear yourself speak)?

Yes/No:

2. Are you experiencing any tinnitus sensations (for example, you hear sounds in your ear without the sound coming from the environment)?

Yes/No:

Is yes, is it in both ears, the right ear or the left ear?

3. Does your ear feel blocked?

Yes/No:

Is yes, is it in both ears, the right ear or the left ear?

4. Do you feel dizzy or off balance?

Yes/No:

5. Have you noticed a change in your hearing ability?

Yes/No:

Is yes, is it in both ears, the right ear or the left ear?

6.6 Appendix F: Recording Sheet

Recording Sheet

Numerical code:

Otoscopy result:

Right:

Left:

Tympanometry Results:

Ear	Type	Compliance (ml)	Pressure (daPa)	Ear Canal Volume
Right				
Left				

Pure Tone Audiometry Result:

Date	Test Method	Ear	Threshold (dB HL)						
	Frequencies Tested (SRO)								
	Manual	Right							
		Left							
	Automated	Right							
		Left							
	Manual	Right							
		Left							
	Automated	Right							
		Left							

	Manual	**Right**							
		Left							
	Automated	**Right**							
		Left							
	Manual	**Right**							
		Left							
	Automated	**Right**							
		Left							

6.7 Appendix G: Informed Consent Form

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD
HEALTH SCIENCES

DHRS
Department of Health and Rehabilitation Sciences
FACULTY OF HEALTH SCIENCES

Divisions of Communication Sciences & Disorders • Disability Studies • Nursing & Midwifery • Occupational Therapy • Physiotherapy

F45 Old Main Building, Groote Schuur Hospital
Observatory, Cape Town, South Africa, 7925
Telephone: +27 (0) 21 406 6401
Website: www.dhrs.uct.ac.za

Informed Consent Form

Study Title:

Automated Audiometry and the SRO Technique in Ototoxicity Monitoring

The Researcher:

My name is Wildine Greeff and I am a postgraduate student studying towards my Master's Degree in Audiology at the University of Cape Town. This study will be completed by researchers from the University of Cape Town.

Purpose of the research:

There are many South Africans that have Multi-Drug Resistant Tuberculosis (MDR-TB). Some medication used to treat MDR-TB may damage hearing. That is why each person receiving these MDR-TB medication needs regular hearing tests. These hearing tests can be long and there are not enough audiologists to do these hearing tests on everyone that needs it. With this research I hope to, firstly make these hearing tests shorter. Secondly, I want to help each person receiving these MDR-TB treatments to be tested often by having computers help test patients if the audiologist is unable to.

What the research will involve:

The research that I am doing involves regularly testing the hearing of patients on MDR-TB treatment. During the hearing tests, I will:

- Ask you a few questions about your hearing.
- Look at the health of your eardrum with a light.
- Test the middle part of your ear to see if it is working as it should be.
- Test to see whether you can hear different types of sounds. I will be doing the test myself, after a fifteen-minute break, a computer will do the same test again without my help.

These tests are not harmful, and the location of the hearing tests will be communicated to you. I will be explaining each test before I test you with it. I will show and explain the results to you at the end of each test session. Your test results will stay at the hospital. I will be testing you every week for a month or until I see a change in the hearing test results (for example, a hearing loss or an ear infection). Each test session will take approximately 60 minutes. I will write your follow-up test date on this information page that you will need to keep. I will provide counselling to explain the possible reason for the change in hearing and refer you back to your doctor and audiologist for further management. After this, you need to fill in short questions about the test you preferred (between me testing you or the computer testing you). You will then be seen by your audiologist after you have completed your part in the study. I will also be looking at your medical records for any information that may affect my results (such as other medication that you are on and the results of your first hearing test after starting your MDR-TB medication).

What will happen to your results?

After you have exited the research study, I will remove your name from the results sheet and replace it with a number. I will upload this information to a password protected cloud. I will be the only one that knows this password. I will need to keep the hardcopy of your results in a locked cabinet in my supervisor's office for five years. After that I will destroy the hardcopy. I will compare the results that I have gotten when I tested you with the results the computer has gotten to see whether the results were the same.

You will get the option of choosing whether you want to receive the results of the study or not. If so, please provide your contact details. In addition to you receiving the results, a summary of the results will be sent to the University of Cape Town. I will be providing a conference presentation about the results and publish an internal report about my research. You contribute to this research by expressing your test method preference as explained previously.

Sharing your results:

I will need to share your results with your doctor and audiologist if there has been a change to your hearing (for example, a hearing loss or an ear infection). This is so that your doctor and/or audiologist can manage the change in your hearing so that it does not get worse and affect your communication.

Voluntary participation and right to withdraw from research:

It is your decision to be part of the research. You have the right to exit the study at any time. You do not need to give a reason for your decision to leave the research. The results that we may already have will still be used for the research.

Risks from the research:

You may be tired during testing as you will be tested twice with the same type of test so that I can compare the results. You will get a fifteen-minute break in between tests. You may feel distressed if you discover that there is a change in your hearing. I will provide you with counselling where I will explain why this change has happened and what can be done to help prevent this change from continuing. I will refer you back to your doctor and audiologist for further management.

Benefits from this research:

You will benefit directly from this research by receiving compensation every time you attend a test session at the facility. The research community and, hopefully, South Africa will benefit by this research providing evidence for how the computer that does testing for the audiologist has worked to help test hearing. They will also benefit by having evidence for a shorter way to test hearing.

This research has been reviewed and approved by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (UCT's FHS HREC).

If you feel (at any stage during this research) that your rights as a participant of this study has been undermined/violated, do not hesitate to contact UCT's FHS HREC on 021 650 3002.

If you have any question regarding this research, please do not hesitate to ask or contact me. The UCT FHS Human Research Ethics Committee can be contacted in case you have any questions regarding your rights and welfare as a research participant of this study.

If you would like to participate in this study, please fill in the consent form attached to this letter.

Kind regards,

Ms Wildine Greeff, *Postgraduate Student*

0796231822, Grfwil003@myuct.ac.za

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Mrs Lucretia Petersen, *Senior Lecturer and Research Supervisor*

Lucretia.petersen@uct.ac.za

Ms Vera-Genevey Hlayisi, *Research Co-Supervisor and Lecturer*

Vera.hlayisi@uct.ac.za

University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee

+27 21 650 3002 *(Reception)*

INFORMED CONSENT FORM

Please fill in the following information:

I, _____ hereby give consent for my hearing to be tested for the postgraduate research project done by Wildine Greeff. I have read and understood the above-mentioned information concerning this postgraduate research project. I understand that my hearing test results will be used for research purposes in conforming to the Health Professionals Council of South Africa's Guidelines and the requirements of the University of Cape Town.

_____

Participant Signature

Date:

_____

Witness Signature

Date: