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Cochleotoxicity and vestibulotoxicity monitoring in patients receiving chemotherapy in South Africa

by

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"Find what you love to do, and go do it. You will never be successful until you have a plan, and the discipline and determination to go through with that plan" (Julius Williams)

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PUBLICATIONS AND RESEARCH OUTPUTS

This thesis is based on the following articles that were accepted by and published or accepted for review in peer-reviewed journals:

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ABSTRACT

Title: Cochleotoxicity and vestibulotoxicity monitoring in patients receiving chemotherapy in South Africa

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Platinum-based agents can cause ototoxicity, an adverse reaction affecting the inner ear. The ototoxicity is characterised by cochleotoxicity and vestibulotoxicity. Although ototoxic medications play an essential role in modern medicine, they have the capability to cause harm and can have a significant effect on health-related quality of life (HRQoL). Ototoxicity surveillance is vital for possible treatment modifications, early identification and rehabilitation of hearing and vestibular function. Although many ototoxicity monitoring protocols exist and have proved to be effective in identification of ototoxicity, their success of implementation is questionable. One of the major factors affecting current monitoring protocols is the incapacitated state of the cancer patients. Reliable and efficient monitoring protocols that are less labour intensive and time consuming are required. Shortened protocols that target sensitive frequencies for ototoxicity and allow testing outside of traditional settings are required. Technologies need to be validated in order to decentralise services from the traditional models and ensure access for cancer patients at their treatment venue. There is limited knowledge about the current status of ototoxicity monitoring in oncology units in South Africa. This information could guide future practices of ototoxicity monitoring in South Africa.

This project investigated (i) the status of ototoxicity monitoring in South Africa, (ii) the role

of innovative technology to support decentralised ototoxicity monitoring, and, lastly, (iii) potential monitoring of vestibulotoxicity in cancer patients.

Study I investigated (i) the national status of ototoxicity monitoring implemented in private and public cancer facilities, (ii) the knowledge and ototoxicity monitoring approaches implemented, and (iii) reported challenges. A descriptive quantitative survey was conducted in public and private oncology units and audiology referral clinics. Provinces included were Gauteng, Free State, Mpumalanga, Limpopo, North West, Western Cape, Northern Cape, Eastern Cape and KwaZulu-Natal. Private (60%) and public (43%) oncology units that provide platinum-based chemotherapy in South Africa and 54% of audiology referral units were (1) surveyed telephonically to determine if ototoxicity monitoring takes place, and (2) a self-administered survey was sent to qualifying oncology units and audiology referral clinics. All public oncology units reported that ototoxicity monitoring only occurred on referral and was not standard practice. All private oncology units indicated that monitoring was on a patient self-referral basis when symptoms occurred. Poor awareness of ototoxicity monitoring best practice guidelines was reported by all oncology units and 14% of audiology referral clinics. Audiology referral clinics reported adequate knowledge of ototoxicity protocols although they were not widely used, with only 43% following best practice guidelines. The most prominent challenges reported by participants were referral system (67% oncology units; 57% audiology referral clinics), environmental noise (83% oncology units; 86% audiology referral clinics) and the compromised status of cancer patients (67% oncology units; 57% audiology referral clinics). There is significant discrepancy in the manner in which ototoxicity monitoring is conducted across South Africa in both the private and public sector. Effective scheduling and test location are key to a successful monitoring programme. Ototoxic monitoring programmes need to become standard for the care of all patients receiving treatment with ototoxic chemotherapy.

Study II investigated mHealth-enabled surveillance in ototoxicity. A longitudinal study of 32 participants receiving chemotherapy was conducted. Baseline and exit audiograms that included conventional and extended high-frequency (EHF) audiometry were

recorded at the patient's treatment venue using a validated mobile health (mHealth) audiometer. Average hearing thresholds at baseline were within the normal range (81.2% left; 93.8% right), reducing at exit testing (71.9% left; 78.1% right). Half (50%) of participants presented with a threshold shift according to ototoxicity monitoring criteria. Frequencies affected most were between 4000 and 16000 Hz, with left ears significantly ($p < 0.05$) more affected than right ears. During threshold determination, noise levels exceeded the maximum permissible ambient noise levels in up to 43.8% of thresholds determined in low frequencies between 250 and 1000 Hz. Ototoxicity surveillance that included mHealth audiometry and EHF for cancer patients receiving platinum-based chemotherapy proved to be valuable, and testing could take place at the treatment venue. Baseline and exit testing performed could track changes in hearing. Shortened monitoring protocols focusing on high frequencies and EHF may be more efficient, and address the possibility of noise interference in the lower frequencies during testing.

Study III investigated the changes in vestibular and cochlear function in patients receiving platinum-based chemotherapy. A longitudinal study of 32 participants (10-70 years) receiving chemotherapy was conducted. Baseline and exit vestibular and hearing assessments that included video head impulse (VHIT) testing, cervical and ocular vestibular evoked myogenic potentials (VEMP), bedside dynamic visual acuity (DVA) and pure-tone audiometry were performed at the patient's treatment venue. Half (50%) of the participants showed cochleotoxicity from baseline to exit testing according to ototoxicity criteria, with left ears significantly ($p < 0.05$) more affected than right ears. There was no consistent relationship between hearing loss and vestibular dysfunction. DVA yielded normal results at baseline and exit testing in all participants. VEMP responses were absent in 28.1% of participants at baseline, reflecting the possible challenges of using VEMP for vestibulotoxicity monitoring. VEMP and VHIT results showed a statistically significant ($p<0.05$) decline in results from baseline to exit testing; however, participants did not report symptoms related to vestibular dysfunction. As in cocheotoxicity, VHIT also showed left ears significantly ($p<0.05$) more affected than right ears. VEMP results did not show significant differences between the ears. VHIT can easily be performed at the patient's treatment venue. However, VEMP at the patient's treatment venue has proven

to be logistically challenging and time-consuming when performed as part of an ototoxicity monitoring programme. Furthermore, considering that VEMP responses are absent in all patients >60 years, VEMP may not be practical as a vestibulotoxicity monitoring tool for older cancer patients. As patients did not report vestibular symptoms that had a functional impact on daily life, patient self-report of symptoms may be sufficient to monitor vestibulotoxicity in the treatment venue for patients who are ill and incapacitated.

The results from the three studies demonstrated that ototoxicity monitoring was not routinely implemented across oncology units in South Africa. Multidisciplinary teamwork and a decentralised approach to ototoxicity monitoring may improve hearing outcomes for cancer patients. mHealth-supported audiometry proved to be a valuable tool for ototoxicity monitoring at the treatment venue. Changes in hearing sensitivity over time could be tracked, improving surveillance in patients with full treatment schedules and compromised health status. VHIT proved to be a useful measure of changes in vestibular function secondary to ototoxicity. Future investigations should determine vestibulotoxicity criteria and optimal protocols for sensitivity and efficiency in monitoring vestibular functioning during chemotherapy treatment at the patient's treatment venue or hospital ward. This project highlighted that ototoxicity monitoring as standard practice at the patient's treatment venue would relieve the over-burdened treatment schedule of cancer patients. This would ensure that HRQoL is preserved and an opportunity for early intervention and aural rehabilitation is provided.

KEYWORDS

Cancer

Carboplatin

Chemotherapy

Cisplatin

Cochleotoxicity

Hearing loss

mHealth surveillance

Oncology

Ototoxicity

Ototoxicity monitoring

Ototoxicity monitoring protocols

Oxaliplatin

Platinum chemotherapy

Platinum-based compounds

Vestibular dysfunction

Vestibulotoxicity

LIST OF ABBREVIATIONS

AAA	American Academy of Audiology
ASHA	American Speech-Language-Hearing Association
cVEMP	Cervical vestibular evoked myogenic potentials
dB HL	Decibels hearing level
dB	Decibels
DHI	Dizziness handicap inventory
DVA	Dynamic visual acuity
EHF	Extended high frequency
EHFPTA	Extended high-frequency pure-tone average maximum
HFPTA	High-frequency pure-tone average
HL	Hearing loss
HPCSA	Health Professions Council of South Africa mHealth
HRQoL	Health-related quality of life
Hz	Hertz
IARC	International Agency for Research on Cancer
IQR	Interquartile range
LARP	Left anterior right posterior
mHealth	Mobile health
MPANLs	Permissible ambient noise levels
MRL	Minimum response level
OAE	Otoacoustic emission
oVEMP	Ocular vestibular evoked myogenic potentials
PTA	Pure-tone average

QoL	Quality of life
RALP	Right anterior left posterior
SCC	Semi-circular canals
SD	Standard deviation
VEMP	Vestibular evoked myogenic potentials
VHIT	Video head impulse test
VOR	Vestibular-ocular reflex
WHO	World Health Organisation

CHAPTER 1
INTRODUCTION

1.1 Background

Cancer is known to be one of the world's most life-threatening diseases, resulting in an estimated 19.3 million new cancer cases worldwide and almost 10 million cancer deaths in 2020 (International Agency for Research on Cancer [IARC], 2020), causing more deaths than AIDS, tuberculosis and malaria combined (Bray et al., 2015; Sung et al., 2021). The worldwide cancer burden is expected to be 28.4 million cases in 2040; a 47% rise from 2020, with a larger increase in developing (64% to 95%) as opposed to developed (32% to 56%) countries due to demographic changes, although this may be further exacerbated by increasing risk factors associated with globalisation and a growing economy. Approximately 65% of the annual burden will manifest in developing countries within 20 years (Bray, et al., 2015).

Africa is the least prepared continent to deal with this extraordinary growth in the cancer burden (Moodley et al., 2016). It is estimated that there will be 1.27 million cases and 0.97 million deaths in 2030, assuming there is no increase in underlying incidence rates. These figures are determined by the projected increase in the African population from 1.02 billion in 2010 to 1.56 billion in 2030, with about 85% of this total living in sub-Saharan Africa (Sylla & Wild, 2012). Furthermore, the assumption about stable underlying incidence rates is unlikely to remain stable, given the increased exposures to known risk factors such as tobacco, diet, obesity and physical inactivity, chronic infections and altered reproductive patterns (Landier, 2016).

Many adults and children living with and beyond cancer face long-term, and often permanent, physical and psychological adversities from cancer treatment. Platinum-based chemotherapy tends to differentially affect the cochlear (hearing) and/or vestibular (balance) systems and can impair renal, hepatic, neural and blood marrow function (Konrad-Martin et al., 2018). These lasting effects, such as peripheral neuropathy and

ototoxicity, can occur months after treatment and severely impact health-related quality of life (HRQoL) (Baguley et al., 2017; Pearson et al., 2021). The projected increase of cancer rates as well as the progress in cancer therapeutics over the past 40 years, which has remarkably improved survival rates, reveals the need to shift the focus to adverse drug effects and their impact on HRQoL (Horta et al., 2020; Silver et al., 2013). For patients with life-threatening illnesses that necessitate treatment with ototoxic drugs, communication ability is a central HRQoL issue. Therefore, the early identification of ototoxic damage can improve treatment outcomes by minimising hearing loss deterioration (Konrad-Martin et al., 2018). Early identification and monitoring of cochleotoxicity and vestibulotoxicity also provide audiologists with the opportunity to perform suitable rehabilitation during and after chemotherapy treatment (Agrawal et al., 2017; Isaradisaikul, & Chowsilpa, 2020; Konrad-Martin et al., 2018). Furthermore, education and frequent communication with the monitoring audiologist could improve the likelihood that oncologists will use information about cochleotoxic hearing and vestibular changes for the purposes of adapting the treatment regime (when medically appropriate) to avoid disabling hearing loss and preserve vestibular function (Konrad-Martin et al., 2018).

1.2 Cochleotoxicity and vestibulotoxicity in cancer treatment

Ototoxicity is known to be an adverse drug effect in platinum-based cancer chemotherapeutic agents (Landier, 2016; Silver et al., 2013). Ototoxicity is the temporary or permanent functional impairment of the inner ear and eighth cranial nerve after treatment with an ototoxic drug (Konrad-Martin et al., 2018; Paken et al.; 2016). Various antineoplastic medications (medications used to treat cancer) are known to cause ototoxicity (Landier, 2016; Paken et al., 2016). Cisplatin, carboplatin and oxaliplatin are examples of platinum-based compounds (Dreisbach et al., 2017). Platinum-based chemotherapy is a widely used chemotherapeutic agent for the treatment of various malignancies, including testicular, ovarian, bladder, cervical, head and neck, and non-small cell lung cancers (Dreisbach et al., 2017). Cisplatin is known to be one of the most ototoxic drugs, and is used for both palliative and curative purposes across a wide range of cancers; and causes permanent damage to the cochlea and irreversible hearing loss

(Dreisbach et al., 2017). Ototoxic medications can result in either cochleotoxicity or vestibulotoxicity, or both (Landier, 2016).

Unfortunately, patients may overlook ototoxic hearing loss until a communication problem becomes noticeable, meaning that hearing loss within the speech frequency range that is required for speech understanding has occurred (Konrad-Martin, et al., 2018). Similarly, by the time a patient complains of dizziness or imbalance, permanent vestibular system damage has more than likely already occurred (da Silveira & Gonçalves, 2019). Auditory and vestibular dysfunction has the potential to cause severe social, vocational, and educational consequences (Ganesan et al., 2018).

The exact point in time during care at which ototoxicity first occurs may not be possible to define, making it impossible to assess the causality and risk of each therapy provided. Younger age (particularly <5 years) at the time of therapy, diagnosis of a central nervous system tumour, diminished renal function, being male (up to fourfold greater risk), rapid intravenous administration (high risk with high cumulative dose (> 200 mg/m2), high dose per course, and bolus application of platinum compounds), treatment with multiple potentially ototoxic agents (such as aminoglycoside antibiotics and furosemide), anaemia, hypo-albuminaemia, pre-existing sensorineural hearing loss, exposure during pregnancy, previous exposure to head and neck radiation, genetic susceptibility, and family history of ototoxicity can increase the risk of ototoxicity (Camet et al., 2021; Isaradisaikul & Chowsilpa, 2020; Langer et al., 2013; Patatt et al., 2021; Pearson et al., 2019; Phanguphangu & Ramma, 2018; Waissbluth et al., 2018). The risk of ototoxicity also increases in patients who require multimodality therapy, such as those receiving both radiation and platinum-based chemotherapy (Mahdavi et al., 2020).

Symptoms of cochleotoxicity are poorly associated with drug dosage, peak serum levels, and other toxicities, and they do not fully explain the large individual differences in the susceptibility to cisplatin ototoxicity (Patatt et al., 2021). Statistical regression models that predict the risk of developing cisplatin ototoxicity by using the clinical variables of age and cumulative dose do not accurately predict the average risk in a group of patients at a

given age and cumulative dose (Langer et al., 2013). Therefore, the only way to identify ototoxicity is by assessing auditory function directly (Landier, 2016; Rybak et al., 2019).

Cochleotoxicity is any dysfunction of the auditory system, and can result in reversible or irreversible hearing loss. Cisplatin has the potential to cause progressive bilateral irreversible high-frequency sensorineural hearing loss associated with tinnitus, hyperacusis and speech discrimination difficulties, especially in background noise, which may manifest during treatment or be delayed for several months after the completion of therapy (Ganesan, et al., 2018; Landier, 2016; Paken et al., 2021; Romano et al., 2020; Steffens et al., 2014). The primary mechanism of ototoxic hearing loss is the apoptosis of the outer hair cells at the base of the cochlea. This apoptotic pathway is activated secondary to an imbalance between the production of reactive oxygen species, and depletion of antioxidant enzymes induced by cisplatin (Konrad-Martin, et al., 2018; Rybak et al., 2019). Other evidence suggests that spiral ganglion cells and the stria vascularis are affected in addition to damage to the organ of Corti (Rathinam et al., 2015). The incidence of cochleototoxicity is estimated between 3% (Forastiere et al., 1987), 21% (Sánchez-Canteli et al., 2021), 56% (Nalini et al., 2020), and 100% (Kopelman et al.,1988; McKeage, 1995; Paken et al., 2021) in patients receiving high-dose cisplatin (150–225 mg/m2) tested with extended-high frequency audiometry. This inconsistency in ototoxic effect is attributable to audiological testing methods, variability in how ototoxicity is captured and defined in the various studies and to the range of inter-individual susceptibility to cisplatin (King & Brewer, 2018; Paken et al., 2016; Steffens et al., 2014).

Limited research has been published on the potential effects of platinum-based compounds on the vestibular system (da Silveira & Gonçalves, 2019). Furthermore, there is a large variability (0-50%) in the rates of vestibulotoxicity reported by objective tests following treatment with platinum-based chemotherapy (Deutschmann et al., 2017; Isaradisaikul & Chowsilpa, 2020; Prayuenyong et al., 2018). Other limitations of published studies are small sample sizes, various methods of vestibular evaluation and criteria to determine abnormalities in the vestibular system, and outdated studies (da Silveira & Gonçalves, 2019; Prayuenyong et al., 2018). The symptoms are often noted by the

patient several weeks or longer after administration of the platinum compounds. Vestibulotoxicity may exhibit as vertigo and general disequilibrium, unsteadiness when walking, nystagmus and oscillopsia (da Silveira & Gonçalves, 2019). The clinical findings indicate spontaneous and positional nystagmus, abnormal body sway and caloric abnormalities. These symptoms can lead to difficulty driving, working and walking (Pastalove & Pomponio, 2017). Considering the pathophysiology of the cochleotoxic nature of platinum compounds, ototoxicity of the peripheral vestibular system can result in either partial or complete destruction of hair cells or differentiation of the vestibular end organs due to their shared blood supply, resulting in differing degrees of vestibular impairment (Patatt et al., 2021; Ramírez-Camacho et al., 2004).

The major challenge in vestibulotoxicity monitoring is the differentiation of symptoms, which are evident only when patients are mobilised and may be mistakenly attributed to the patient's compromised state and side effects of the treatment (Ganesan et al., 2018). Cancer patients show physical impairments which may limit independence and may increase fall risk due to unidentified vestibular dysfunction (Niederer et al., 2014). Furthermore, the identification of the presence, severity and nature of vestibular manifestations in patients on chemotherapy treatment is of vital importance to healthcare providers, as vestibular symptoms can be debilitating and may negatively affect the patient's HRQoL and activities of daily living as well as economic earning ability after remission (Agrawal et al., 2018; Isaradisaikul & Chowsilpa, 2020).

1.3 Ototoxicity monitoring protocols

Possible prevention of hearing loss is the most appropriate form of rehabilitation. Audiologists are in the best position to establish and manage an effective ototoxicity monitoring programme in cancer patients (Al-Malky, 2016). Clear aims for ototoxicity monitoring should be established by creating collaborative relationships with the multidisciplinary oncology team, describing clear referral routes and monitoring intervals and protocols, as well as criteria for ototoxicity.

The choice of early ototoxicity identification techniques is affected by factors such as the

requirements of a high degree of sensitivity, specificity and reliability, being less time consuming, and being less exhaustive to the patient. This results in many challenges when implementing a monitoring protocol. A stringent protocol with more practicability, including all elements aimed at profiling the effects of ototoxicity and early intervention is urgently needed (Brungart et al., 2018; Ganesan, et al., 2018).

Platinum-based compounds have been demonstrated to cause permanent hearing loss, but their effect on the vestibular system is unclear (Steffens et al., 2014). In addition, current protocols for assessment and monitoring of cochleo- and vestibulotoxicity are inappropriate or lacking in South Africa. No single protocol is appropriate, due to a multitude of patient variables when monitoring ototoxicity in patients receiving chemotherapy. Furthermore, there are no generally accepted vestibulotoxicity monitoring protocols that are efficient, reliable, and completely suitable for application with ill patients (Konrad-Martin et al., 2018; Pastalove & Pomponio, 2017).

The implementation of standardised audiologic monitoring protocols has the potential to enable the early detection of ototoxicity in patients receiving therapy for cancer, and thus also may provide an opportunity for treatment modification, if possible, before auditory damage becomes severe (Konrad-Martin et al., 2018; Paken et al., 2020). Even when no reasonable alternative is available and therapy with the ototoxic agent must continue, monitoring may still be of value by enabling early intervention and auditory rehabilitation as well as for emotional preparation and auditory counselling (Landier, 2016; Paken et al., 2021). It remains vital to focus on HRQoL.

Ototoxicity monitoring programmes are currently directed by guideline documents (American Speech-Language-Hearing Association (ASHA), 1994; American Academy of Audiology (AAA), 2009, Health Professions Council of South Africa (HPCSA), 2018). Monitoring programmes compare baseline audiometric and vestibular data, (ideally obtained prior to ototoxic drug administration) to the results of subsequent monitoring tests. In this manner, each patient serves as his or her own control (AAA, 2009; ASHA, 1994). The baseline evaluation should take place no later than 24 hours after the

administration of chemotherapeutic drugs. A confirmation of thresholds within 24 hours of the baseline test can be beneficial for determining patient reliability for pure-tone threshold testing (AAA, 2009; ASHA, 1994; Konrad-Martin et al., 2018; Konrad-Martin et al., 2014). The basic audiologic assessment remains an important part of ototoxicity monitoring at baseline assessment and when any significant changes in hearing occur. Extended high-frequency audiometry (EHF) and otoacoustic emission (OAE) testing has become well-established for ototoxicity monitoring and are often included in monitoring programmes (AAA, 2009; ASHA, 1994; Paken et al., 2021).

Although the vestibulotoxicity of some drugs, particularly certain aminoglycosides, is well established, no widely accepted guidelines for vestibulotoxicity monitoring exist (Ganesan et al., 2018; Landier, 2016; Prayuenyong et al., 2021; Prayuenyong et al., 2018). There is neither an established standard of care in vestibulotoxicity management, nor a test battery well adapted to a combination of bedside evaluations for patients who often are critically ill. Currently, protocols are suggested for patients who are able to be transported and who do not have intravenous lines that must remain active (AAA, 2009). This poses a challenge for effective monitoring programmes for patients receiving platinum-based compounds who are frequently ill at the time of testing.

Although vestibular issues may be common during the course of treatment with some ototoxic drugs, the symptoms are not usually directly addressed in ototoxicity monitoring programmes (Brungart, et al., 2018). Unfortunately, the subjective reports of patients do not correlate well with vestibular testing results (Mudd, 2019; Baguley & Prayuenyong, 2020).). As there is no single test that can identify vestibulotoxicity, screening tests such as dynamic visual acuity (DVA) and head impulse testing (Romberg Condition 4) along with Dizziness Handicap Inventory (DHI) are recommended to monitor patients (Petersen, Straumann, & Weber, 2013; Ganesan, et al., 2018). These bedside screening tests are sufficiently sensitive, easily administered, and have sufficient correlation with the more advanced clinical and diagnostic tests (Gans & Rauterkus, 2019).

Type I hair cells (particularly of the semi-circular canals) are more susceptible to ototoxicity; therefore, video head impulse testing (vHIT) and vestibular evoked myogenic potential (VEMP) testing seem more promising for the early detection of vestibulotoxicity than caloric and rotatory testing (Van Hecke et al., 2017). The vHIT especially serves high-frequency characterisation of the lateral, posterior and anterior semi-circular canals, and seems to activate irregular afferents, which tend to innervate Type I hair cells (Janky et al., 2018). Standard vestibular diagnostic procedures (such as videonystagmography (VNG) with calorics, rotary chair testing, video head impulse testing (VHIT), computerised DVA and computerised dynamic posturography (CDP) are often impractical due to the patient's incapacitated health status (Ganesan et al., 2018; Gans & Rauterkus, 2019; Mudd, 2019). Vestibular tests appropriate for patients receiving ototoxic treatment, who may be in poor health overall, need to be developed and validated (Brungart et al., 2018).

A challenge in vestibular monitoring programmes is an inability to recognise subtle changes in functioning indicative of imminent vestibulotoxicity that does not always correlate with changes in the ability to perform daily activities, due to the gradual onset of vestibular dysfunction and central compensation that occurs. Early identification of signs and symptoms of vestibulotoxicity is essential as the window of time for recovery is often limited (AAA, 2009; Rutka, 2019). For this reason, proper objective and subjective monitoring of vestibular function may help recognise early toxic effects and prevent permanent damage by recommending dosage adjustments and providing vestibular rehabilitation.

The frequency of ototoxicity monitoring depends on the particular treatment regimen, which can be confirmed by consulting the patient's medical chart (ASHA, 1994; HPCSA, 2018). Monitoring evaluations, which may be a shortened version of the baseline evaluation, are performed sporadically throughout treatment, usually prior to each dose for chemotherapy patients (ASHA, 1994; HPCSA, 2018, Sánchez-Canteli et al., 2021). Monitoring and appropriate referrals for further auditory and vestibular testing are also warranted any time a patient reports increased hearing difficulties, tinnitus, aural fullness, or imbalance and dizziness (AAA, 2009). Considering that platinum-based chemotherapy

can cause delayed or progressive hearing loss, a follow-up test should also occur a few months after chemotherapy treatment has been completed to confirm that the hearing loss, if present, is stable (AAA; 2009). Cochleotoxic hearing loss can occur up to six months after platinum-based compound exposure (Konrad-Martin et al., 2018; Konrad-Martin et al., 2014).

1.4 Challenges in ototoxicity monitoring

It is not currently known what number of patients undergoing chemotherapy with cisplatin are systematically monitored for signs of ototoxicity in South Africa. The studies performed have been limited to certain geographical areas or sites. Challenges of implementing an ototoxicity monitoring protocol for patients receiving chemotherapy include fatigue, general acute illness, travel issues and priority issues (Konrad-Martin et al., 2018). Current guidelines for ototoxicity monitoring include extensive test protocols performed by an audiologist in a sound-treated room (Brungart et al., 2018). Furthermore, too often, audiological testing is arranged only once debilitating hearing loss is already apparent to the patient or multidisciplinary team. This testing must then be coordinated with a patient's already overburdened treatment schedule and in audiology clinic time slots that are routinely scheduled months in advance. This approach is comprehensive, but it may be demanding for patients suffering from life-threatening illnesses and expensive if it requires several follow-up appointments. With the use of mobile technology, testing outside of the confines of the sound-treated room may be possible, which could create more efficient and less taxing ototoxicity monitoring programmes (Chirtes & Albu, 2014; Brungart et al., 2018).

Audiology equipment and staffing limitations need to be overcome in order to consistently identify those patients who face the greatest risk of preventable hearing loss and to ensure early intervention when hearing loss is identified. In developing countries such as sub-Saharan Africa, there is a lack of hearing care and appropriate equipment in order to successfully implement hearing screening and monitoring programmes (Dille et al., 2015; Sandström et al., 2016; WHO, 2013). The number of audiologists on the African continent has been reported to be one of the lowest, with an estimate of one audiologist for every

million people in sub-Saharan Africa (Sandström et al., 2016; WHO, 2013). Furthermore, audiologists are likely to enter the private healthcare sector, resulting in unequal distribution of audiologists and especially in the public sector, which serves approximately 85% of the population in South Africa (Clark & Swanepoel, 2014; Sandström et al., 2016). In addition, the high costs associated with screening equipment and the necessity for the equipment to be operated by trained personnel such as audiologists further burden the implementation of effective screening programmes for early detection and intervention (Clark & Swanepoel, 2014). Furthermore, the mechanisms for tracking patients throughout the system need to be explored to ensure that patients receive the audiological services they may need at various stages of cancer treatment and survivorship (Konrad-Martin et al., 2014).

Considering these challenges, professional bodies such as the Health Professions Council of South Africa (HPCSA), American Speech-Language-Hearing Association (ASHA) and American Academy of Audiology (AAA) have guidelines that provide flexibility for shortened screening protocols to be used for ototoxicity monitoring. Since most changes are observed to occur within the high frequency range in ototoxicity, a shortened, serial monitoring protocol has been proposed. Consequently, targeting the higher frequencies for serial monitoring improves clinical efficiency by decreasing test time (AAA 2009; ASHA, 1994; HPCSA, 2018). Although audiologic evaluation is ideally performed in a sound-treated room, the ASHA guidelines acknowledge that, even with shortened protocols, audiometric monitoring performed in a sound-treated room may not be practical in all clinical environments. Therefore, audiometry in which threshold results are the goal, but which is not conducted in a sound-treated room, requires technology that utilises standards for environmental noise tolerances by frequency (Brungart, et al., 2018). Interest in portable audiometry and testing hearing in less-than-ideal environments has grown, resulting in application-based audiometric systems, as portable audiometers are often still required to be operated by an audiologist (Dille et al., 2015; Sandström et al., 2016). The need for audiometry to be conducted in the absence of a sound-treated room has arisen from improvements to philanthropic efforts, school-based screenings, hearing conservation programmes, tele-audiology and ototoxicity monitoring programmes

(Brungart et al., 2018; Dille et al., 2015).

The World Report on Hearing (2021) suggests task-shifting as a strategy to make services more accessible. Tasks traditionally performed by audiologists in the field of ear and hearing care can be undertaken by non-specialists, such as community health workers, health aides, nurses and technicians using automated and mobile technologies. Task shifting results in more efficient use of human resources, saves costs, and makes services more accessible (World Report on Hearing, 2021). The use of automated and mobile technologies that are simple to operate by minimally trained health workers has proved to be effective (Bright et al., 2019; Dawood et al., 2020).

1.5 Ototoxicity monitoring using connected mobile health solutions

Mobile health solutions for hearing assessment have been shown to be effective (Manganella et al., 2018; Van der Aerschot et al., 2016). These technologies could improve access to hearing health services in an ototoxicity monitoring programme by providing an alternative to conventional audiological screening that requires the patient to attend an audiology clinic (Manganella et al., 2018).

Automated audiometry is useful for screening programmes and can be conducted by non-specialist personnel, thereby reducing the cost of testing and reaching more people who require hearing screening (Manganella et al., 2018). By using mHealth tools with cellular phones and networks, audiological services could be more readily available and data management systems could track patient hearing status (Louw et al., 2017). Examples of mobile applications for hearing screening include the uHear™ and EarTrumpet, which are iOS-based applications that run on iOS devices such as iPod, iPhone and iPad, and are costly in South Africa. The Ototoxicity Identification Device (OtoID) and Creare Wireless Audiometer (Brungart et al., 2018; Foulad et al., 2013; Manganella et al., 2018) that were developed for high-income countries are also available; however, the cost of running these applications is high and restricts accessibility in low- to middle-income countries such as South Africa; and the reliability and validity of these applications require further research (Brungart et al., 2018; Dille et al., 2015; Peer & Fagan, 2014). Practical

considerations in the selection and use of portable systems for ototoxic monitoring should include self-administered versus provider-administered testing, strategies for background noise monitoring, and management and distribution of patient data (Brungart et al., 2018).

A lower-cost alternative for automated screening protocols is the smartphone- or tablet-based hearTest^{R} certified digital audiometer. The hearTest^{R} is calibrated according to current standards (ANSI/ASA S3.6-2010; ISO389-1, 1998), and demonstrates clinical threshold assessment outcomes (at the conventional frequencies as well as extended high-frequency (EHF) audiometry) comparable to conventional testing with improved efficiency, noise monitoring and quality control (Bornman et al., 2018; Louw et al., 2017; Mahomed-Asmail et al., 2016; Sandström et al., 2016; Swanepoel et al., 2014; Van Tonder et al., 2017). The application allows for remote hearing testing where patient data and results can be uploaded onto centralised servers for data management through cellular networks. The hearTest^{R} application has been validated in underserved primary healthcare contexts and resource- constrained environments (Louw et al., 2017; Mahomed-Asmail et al., 2016; Sandström et al., 2016; Swanepoel, 2016; Swanepoel, 2017; Swanepoel et al., 2016; Swanepoel & Clark, 2019; Yousuf Hussein et al., 2016); however, no validations for ototoxicity monitoring in patients receiving chemotherapy have been performed.

1.6 Study rationale and aims

Although ototoxic medications play an essential role in modern medicine, they have the capability to cause harm and can have a significant effect on HRQoL. The implementation of ototoxicity monitoring is vital for possible treatment modifications, early identification and rehabilitation of hearing and vestibular function. Although many ototoxicity monitoring protocols exist and have proved to be effective in the identification of ototoxicity, the success of their implementation is questionable. One of the major factors affecting current monitoring protocols is the incapacitated state of the cancer patients. Reliable and efficient monitoring protocols that are less labour intensive and time consuming are required. Shortened protocols that target sensitive frequencies for ototoxicity and allow testing outside of traditional settings are required. Technologies need to be validated in

order to decentralise services from the traditional models and ensure access for cancer patients at their treatment venue. Knowledge of the current status of ototoxicity monitoring in oncology units in South Africa is limited. This information could guide future practices in ototoxicity surveillance in South Africa.

The research project consists of three original studies. This project investigated (i) the status of ototoxicity monitoring in South Africa, (ii) the role of innovative technology to support decentralised ototoxicity monitoring, and, lastly, (iii) potential monitoring of vestibulotoxicity in cancer patients.

CHAPTER 2
METHODOLOGY

This chapter aims to describe the research objectives, design and ethical considerations. Furthermore, participants, equipment and materials, as well as data collection procedures and analysis, are discussed.

2.1 Research objectives and design

The aim of the research was to determine the cochleotoxicity and vestibulotoxicity in patients receiving platinum-based compounds chemotherapy and to survey current ototoxicity monitoring conducted in South Africa. A novel mHealth approach to monitoring hearing was investigated, as was the practicality of the vestibular assessments performed. The main aim was divided into three objectives and each objective was addressed with a study. Each study was summarised in an article for publication in a peer-reviewed journal. The studies are summarised in Table 2.1 according to the proposed main aims, sub-aims, research design, journal and publication status, and corresponding chapter in the thesis.

Table 2.1 Proposed aims, research design, journal and publication status and corresponding chapter in thesis

Study	I	II	III
Title	Ototoxicity monitoring in South African cancer facilities: A national survey	Surveillance for ototoxicity in platinum-based chemotherapy using mHealth audiometry with extended high frequencies	Changes in vestibular and cochlear function following platinum-based chemotherapy
Research objectives	To determine the national status of ototoxicity monitoring in South Africa	To investigate mHealth-enabled surveillance for ototoxicity	To determine the changes in vestibular and cochlear function longitudinally in patients receiving platinum-based chemotherapy
Sub-aims	To determine (1) the national status of ototoxicity monitoring implemented in private and public cancer facilities, (2) the knowledge of and ototoxicity monitoring approaches implemented and (3) reported challenges	To describe the nature and incidence of hearing loss with conventional and extended high-frequency audiometry in patients receiving platinum-based chemotherapy using a mHealth-validated audiometer	To describe the incidence and nature of vestibular and cochlear function in patients receiving platinum-based chemotherapy using VHIT, VEMP, DVA and pure-tone audiometry
Research design	Cross-sectional quantitative survey	Descriptive, longitudinal research design using quantitative data	Descriptive, longitudinal research design using quantitative data
Journal	South African Journal of Communication Disorders	Journal of Laryngology and Otology	Hearing, Balance and Communication
Publication status	Published https://doi.org/ 10.4102/sajcd.v68i1.846	Submitted to journal. In review process.	Submitted to journal. In review process.
Corresponding chapter in thesis	**3**	**4**	**5**

2.2 Ethical considerations

Research is subject to ethical standards that promote respect for all human beings and protect their health and rights (South African National Health Act, 2003; World Medical Association, 2013). The current study was conducted by adhering to the ethical guidelines set out in the Guidelines of Practice in the Conduct of Clinical Trials in Human Subjects in South Africa (South African Department of Health, 2000) and in the South African

National Health Act (Act 61 of 2003). The researcher obtained ethical clearance from the Research Ethics Committee of the Faculty of Health Sciences and Faulty of Humanities prior to any data collection (Appendix A). Table 2.3 below describes the ethical framework applied.

Table 2.3 Ethical framework

Ethical principles	Adherence to ethical principles	Relevance to the study
Protection from harm	The right, safety and well-being of the participants are the most important considerations and should prevail over the interest of science and society. Foreseeable risks and inconveniences should be weighed against the anticipated benefit for participants and society. A study should only be initiated and continued if the anticipated benefits justify the risks.	There was direct benefit (ototoxicity monitoring and referral for intervention) to the participants. No medical risks or discomforts were associated with this study. Rescheduling was arranged if a patient was too ill at the time of testing. Clear instructions were given and the benefits of participation were explained. The benefit for the study population was hearing and vestibular monitoring provided throughout their treatment in order to preserve hearing, balance and HRQoL. Furthermore, the development of a novel service delivery model for cancer patients was verified, providing a cost-effective approach for future ototoxicity monitoring programmes in South Africa.
Informed consent	Research or experimentation on an individual may only be conducted after the participant has been informed of the objectives of the research or experimentation and any possible positive or negative consequences on his or her health. Freely given informed consent was obtained from every participant prior to clinical trial participation. The participant was informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. For children between 12 and 18 years, parents gave consent for their child to participate in the study and the child gave assent.	Prior to the commencement of the study participants were informed of the nature of the study as well as their level of involvement in the study. Informed consent letters were available in English. Interpreters (nursing staff or research assistants) were used for patients speaking African languages who were not proficient in English or Afrikaans. Furthermore, when the *hearTest*^{R} application is opened, it requests that informed consent/assent be obtained from the participant prior to commencing the test. The participant was made aware of the nature of the service being provided and that the data collected would be used for research purposes. Testing began only once freely given informed consent/assent had been obtained. All participants were informed that their participation was voluntary and that they could withdraw from the study at any time without any repercussions (Appendix B).

Ethical principles	Adherence to ethical principles	Relevance to the study
		Approval was obtained from the Research Ethics Committee of the Faculty of Health Sciences and Faculty of Humanities at the University of Pretoria. Furthermore, permission from the National Department of Health, Gauteng Department of Health, Netcare, Mediclinic and Life Healthcare Group as well as hospital management at Doctor George Mukhari Academic Hospital (DGMAH), Unitas Hospital, Muelmed Hospital and Life Groenkloof Hospital was obtained prior to data collection (Appendix C).
Confidentiality and anonymity	The confidentiality of records that could identify participants should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).	For study 1, participants were requested to complete the questionnaire anonymously, and no identifying information was documented. For studies 2 and 3, each participant was provided with a coded number, which ensured confidentiality. The identity of the participant represented by this code was known only to the researcher.
Reliability and validity	A preliminary study was conducted in compliance with the protocol that had received prior institutional review board ethics committee approval. The pilot study was conducted in order to evaluate feasibility, time, cost and adverse events, and to improve on the study design prior to data collection (Leedy & Ormrod, 2010).	For study 1, the questionnaire was conducted on five participants, and their results were not included in the study. No changes to the questionnaire were required after the pilot study. During studies 2 and 3, testing took take place in an isolated area or room in the ward or outpatient treatment venue. Sufficient breaks (if possible) were provided during testing to ensure that fatigue did not affect the reliability and validity of the results obtained.
Patient rights	Participants have the right to know their health status and researchers are obligated to disseminate results in a timely and competent manner (South African National Health Act 61 of 2003).	The researcher conveyed the results of hearing and vestibular assessment to participants directly after completion of testing as well as to the treating doctor. Appropriate referrals were made based on the results in order to ensure timely intervention such as referral for hearing aid assessment and aural rehabilitation, treatment dosage adjustments and vestibular rehabilitation.

2.3 Study 1: A national survey of ototoxicity monitoring in South African cancer facilities

2.3.1 Research design

A cross-sectional quantitative survey was implemented. The study was descriptive and quantitative in nature and aimed to provide a broad overview of a representative sample of a larger population. The study involved the investigation of data from the representative population at one specific point in time. The participants in this study were selected based on variables of interest (Brynard et al., 2014; Mouton, 2000).

2.3.2 Research context

All public hospitals and private care hospitals in South Africa with cancer units were targeted. Of the 388 public hospitals, 64% are district hospitals. Secondary and specialised hospitals make up 16% each of the total number. Together, provincial and national hospitals comprise less than 4% of all hospitals in the public sector (National Department of Health (NDOH), 2019).

There are 55 cancer units in private hospitals in South Africa. The cancer units per province are as follows: Eastern Cape: 2, Free State: 1, Gauteng: 23, KwaZulu-Natal: 8, Limpopo: 2, Northern Cape: 2, North West: 2, Mpumalanga: 2 and Western Cape: 13 (Independent Clinical Oncology Network (ICON), 2017; Hospitals in South Africa, 2018; Medpages, 2018).

2.3.3 Research participants

Probability sampling was applied (Brynard et al., 2014). The participants included healthcare professionals (general practitioners (GPs), oncologists, nurses, pharmacists and audiologists) working in private and public healthcare oncology units and audiology referral clinics in South Africa. All public hospitals were accessed via the National Department of Health website (NDOH, 2019). Private oncology units were accessed via www.medpages.co.za (Medpages, 2018) and the Independent Clinical Oncology

Network (ICON, 2017). Public provincial tertiary and central/academic hospitals were included, as these hospitals consist of specialised referral units, which together provide an environment for multi-specialty clinical services, innovation and research, such as oncology. There are 29 tertiary hospitals and 10 major teaching hospitals in South Africa, but not all hospitals provide platinum-based oncology treatment or were able to participate in the research. Fifty-five private oncology units were identified in South Africa. The oncology units were contacted telephonically to confirm their eligibility and willingness to participate. Information was obtained from the practice manager or nurse in charge. Once consent for participation had been obtained, questionnaires were sent to the oncology units where a healthcare professional (GP, oncologist, nurse, or pharmacist) representing the oncology units completed the questionnaire.

Audiology referral clinics (n=13) in the same hospital as the oncology units were contacted for participation in the study. Participants therefore included an audiologist representing the audiology referral clinics in the private and public sector across South Africa and/or mentioned by oncology units as referral centres. Questionnaires were sent to the audiology referral clinics for completion. Figure 2.1 describes the research sites, participant description and sampling procedure.

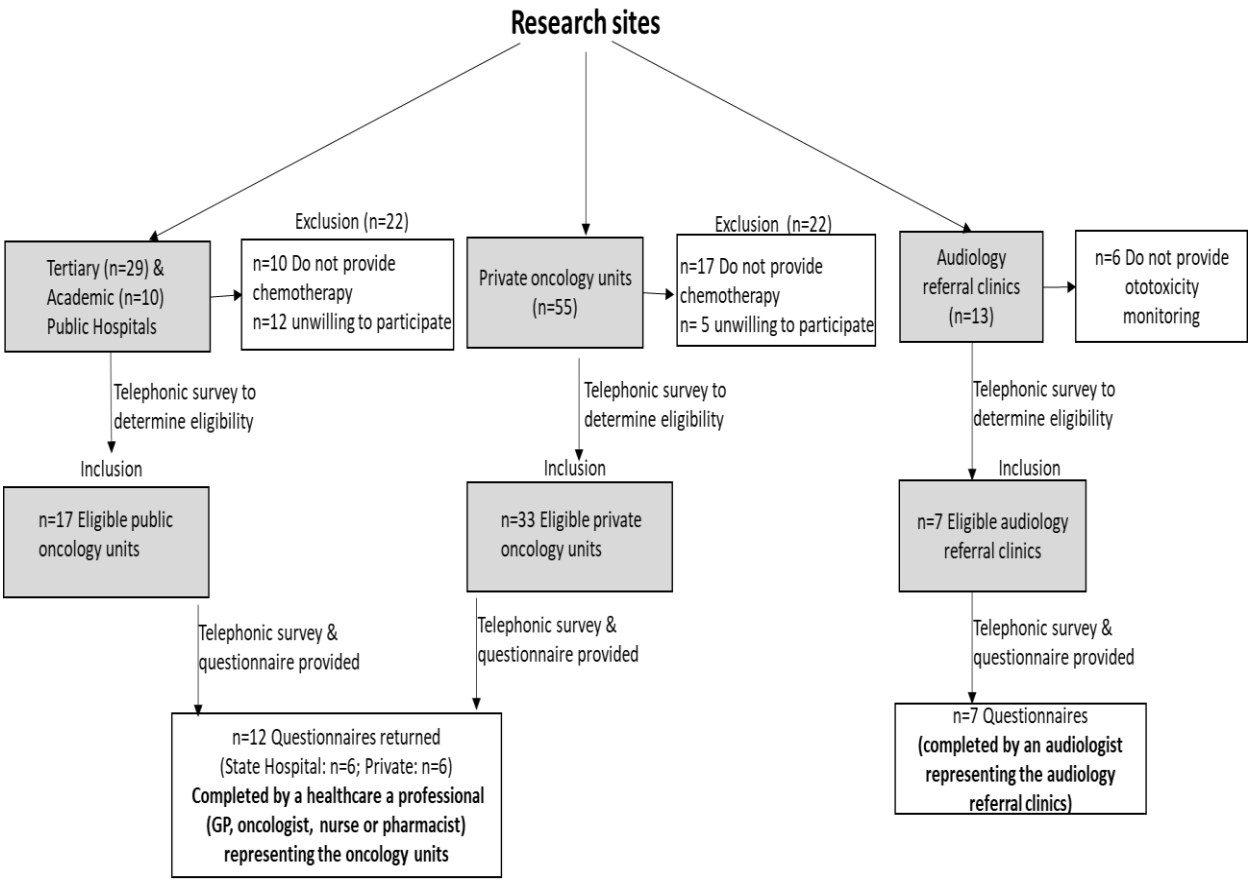

Figure 2.1: Research sites, participant description and sampling procedure

2.3.4 Material and apparatus for data collection

A structured, self-administered questionnaire was used for both oncology units and audiology referral clinics. The questionnaire was administered once off to determine the characteristics of the ototoxicity monitoring protocols currently implemented in oncology units and audiology referral clinics in South Africa as well as the challenges experienced. The same questionnaire was used for all healthcare professionals, as the questionnaire included general aspects regarding ototoxicity, ototoxicity monitoring, and challenges. There was a section to be completed only by audiologists that included aspects such as testing protocols and procedures followed during ototoxicity monitoring. The questionnaire was adapted from Steffens et al. (2014) by adding answer options to choose from, resulting in more closed-ended questions with an option of providing additional information. The original study (Steffens et al., 2014) had only open-ended

questions, which were interview-based.

The questionnaire included a range of open- and closed-ended questions (multiple-choice format) in three broad categories: (i) demographic information, (ii) knowledge of and general perceptions towards ototoxicity monitoring, (iii) challenges, (iv) ototoxicity monitoring protocols (to be completed only by audiology referral clinics) and (v) views on potential improvements to ototoxicity monitoring. The Qualtrics survey platform was used for ease of completion and automatic data storage (Appendix D).

2.3.5 Data collection procedure

Firstly, private oncology units (n=55) and public hospitals (n=29) with cancer units were contacted telephonically to determine whether they offered platinum-based chemotherapy as a treatment option. Oncology units who offered platinum-based chemotherapy and were willing to participate in the study were surveyed telephonically. During the telephonic survey, nursing managers and/or oncologists in the units provided information regarding ototoxicity monitoring practices within the cancer units. The telephonic survey confirmed (i) if platinum-based chemotherapy agents were offered in the unit, (ii) if ototoxicity monitoring was done as standard practice for all patients receiving ototoxic chemotherapy, if ototoxicity monitoring was only done when referred by a healthcare professional, or if patients arranged their own hearing evaluation when ototoxicity symptoms or hearing loss became apparent, and (iii) where patients were referred for ototoxicity monitoring. The second part of the research study included a self-administered questionnaire. An electronic questionnaire was sent to the oncology units to determine their knowledge of, monitoring approaches, protocols and challenges of implementing ototoxicity monitoring. Nurses, oncologists, general practitioners and pharmacists were some of the healthcare professionals who completed the electronic questionnaires on behalf of the oncology units.

Audiology departments in public hospitals with cancer units and private practice audiologists in close proximity to private oncology units, as well as those mentioned as referral centres, were contacted for information on ototoxicity monitoring practices. The

telephonic survey confirmed whether ototoxicity monitoring was performed for patients receiving ototoxic chemotherapy. The electronic questionnaire was sent to the identified audiology referral clinics for completion. Audiologists completed the questionnaire on behalf of the audiology referral centres.

2.3.6 Data analysis

The data collected from the (i) telephonic surveys and (ii) electronic questionnaires with private and public oncology units and audiology referral clinics were integrated. The data were analysed to yield percentages and frequency distributions nationally and across provinces. The researcher completed the collection and interpretation of the open-ended questions by writing down the exact participant responses (word-for-word). Thematic content analysis was used for open-ended questions.

2.4 Study 2: Surveillance for ototoxicity in platinum-based chemotherapy using mHealth audiometry with extended high frequencies

2.4.1 Research design

This study followed a longitudinal (repeated measures over time) experimental design that was quantitative in nature (Brynard et al., 2014) and aimed to identify changes in hearing abilities using an mHealth audiometer from baseline to exit testing. Testing took place in the participant treatment venue. This design allows for inferring of causality and test-causal relationships, however, small sample sizes make generalisability risky (Mouton, 2000).

2.4.2 Research context

This study was conducted in collaboration with the oncology units at Doctor George Mukhari Academic Hospital (DGMAH), Life Groenkloof Mary Potter Oncology Unit, Unitas Oncology, Muelmed Oncology, and Montana Oncology in Pretoria, Gauteng, South Africa. Hospital groups and oncology units that provided consent and were easily

accessible to the researcher (i.e. in the Tshwane area) were selected for longitudinal data collection. DGMAH is a tertiary healthcare institution situated in the north of Pretoria near the township of Ga-Rankuwa. It is the second largest academic hospital in South Africa and is situated on the doorstep of the Sefako Makgatho Health Sciences University (SMU). The hospital comprises 28 clinical departments, rendering all three levels of service. It is one of four academic institutions in the Gauteng Province and provides a service to the surrounding population of approximately 1.7 million people. This excludes the catchment population from the other provinces it services. The hospital also receives referrals from the Limpopo, North West and Mpumalanga provinces. In addition, this facility receives referrals from Southern African Development Community (SADC) countries, other tertiary academic hospitals, local specialists and general practitioners. The hospital has 1 650 active beds, 20 approved Intensive Care Unit (ICU) beds, 60 high-care beds, 50 oncology beds and 17 theatres (DGMAH, 2015).

Life Groenkloof Hospital is a member of Life Healthcare, one of the largest private hospital groups in South Africa, which operates 63 acute care facilities across the country. The modern, sophisticated facilities include 214 beds and eight theatres. At the Mary Potter Oncology Unit (branches included were the Unitas, Muelmed and Montana oncology units), a dedicated team of oncologists perform stem cell transplants, chemo- and radiotherapy (Life Healthcare, 2017).

2.4.3 Research participants

Patients were recruited at hospital departments (DGMAH and Life Healthcare) and oncology units (Mary Potter, Unitas, Muelmed and Montana) where they received their chemotherapy treatment. Arrangements were made with healthcare professionals (nurses and oncologists) who worked directly with chemotherapy patients to make appropriate referrals for the study. Once consent was obtained, the researcher contacted prospective participants directly for participation in the study.

Inclusion criteria included all participants (aged >10 years) treated with platinum-based compounds (cisplatin, carboplatin and/or oxaliplatin) for the first time in private and public

oncology units and hospitals. Testing was conducted during chemotherapy treatment in oncology clinics or at the hospital bedside. Thirty-two participants (64 ears) participated in the study, taking into account that repeated measures (baseline and exit testing) were performed for each participant.

2.4.4 Ototoxicity monitoring protocol

The ototoxicity monitoring protocol was adapted from AAA (2009), ASHA (1994) and HPCSA (2018). Figure 2.2 describes the monitoring protocol applied in the study to identify cochleotoxicity.

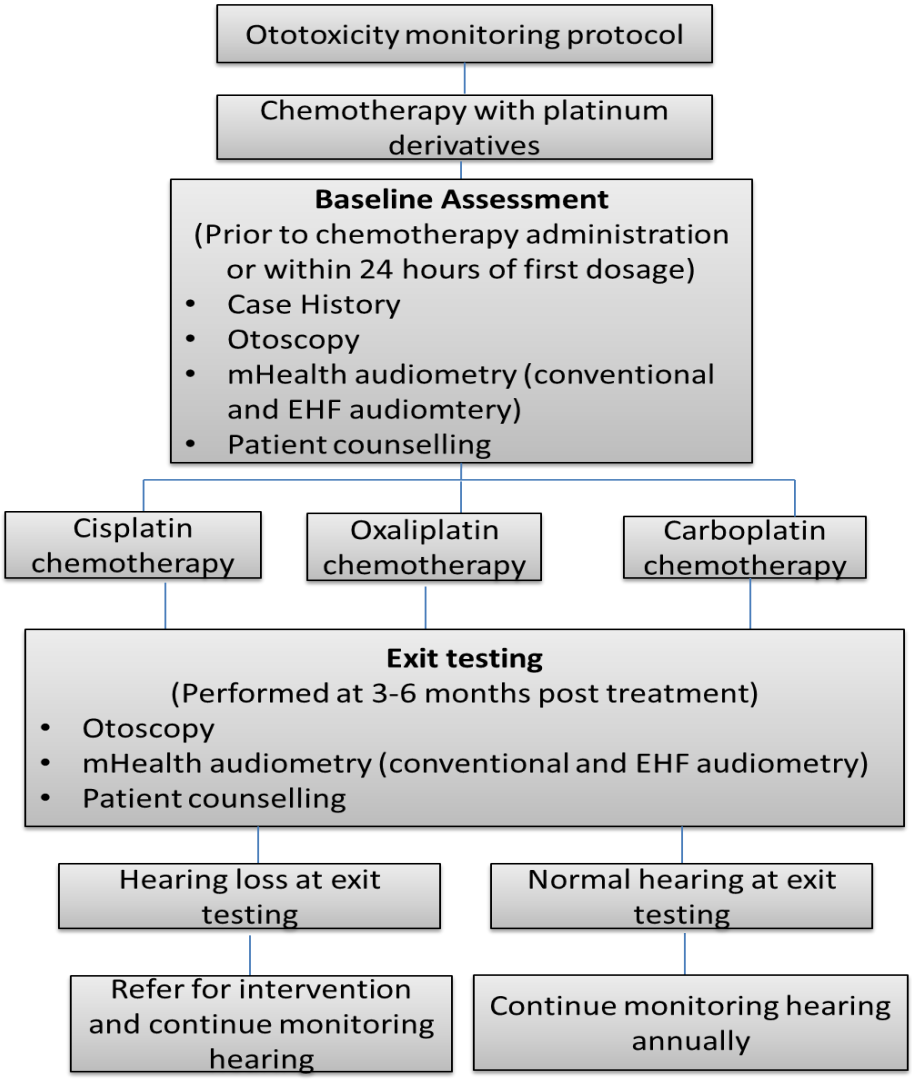

Figure 2.2 Ototoxicity monitoring protocol applied in the study

2.4.5 Material and apparatus for data collection

Ototoxicity monitoring case history interview

The *ototoxicity monitoring case history interview* (adapted from Campbell, 2007; Venter, 2011) was used as a guideline during case history at baseline testing. The case history was used to determine the biographical and background history of the participants (Appendix E).

Otoscopy

An otoscopic examination was used to determine the condition of the external auditory meatus and tympanic membrane, to ensure that there were no obstructions in the external canal or conditions that might influence additional testing procedures (Medwetsky, Burkard, & Hood, 2009). The Heine Mini 3000 Otoscope was used to perform otoscopy prior to pure-tone testing.

Mobile audiometry

The hearTest^{R} certified digital audiometer (IEC 60645-1, hearX Group, South Africa) was used for testing. The hearTest^{R} Extended High Frequencies (EHF) application was used on a Samsung A3 smartphone with the Android version 8.0 operating system (Google, Mountain View, United States of America). Supra-aural Sennheiser HDA 300 headphones (Sennheiser, Wedemark, Germany) calibrated according to prescribed standards (International Organisation for Standardisation, ISO 389–1, 2017), and adhering to equivalent threshold sound pressure levels determined for this headphone were connected to the smartphone. Daily calibration listening checks of headphones were performed. The hearTest^{R} has been validated to monitor noise accurately using the smartphone microphone (Van Tonder, et al., 2016). There was real-time monitoring of noise with the smartphone microphone to alert the user of environmental noise concerns during testing. The maximum permissible ambient noise levels (MPANLs) used for HDA300 headphones were 22.7, 19.4, 22.8, 25.1, 38.8 and 36.2 dB HL for 250, 500, 1000, 2000, 4000 and 8000 Hz respectively (Sennheiser, HDA300), for testing at the

minimum response level (MRL) of 10 dB HL. Automated pre-programmed test sequences (250-16000Hz) were used for improved efficiency, and the reliability of patient responses was monitored throughout (hearX Group, South Africa). Testing commenced and ended at 1000 Hz frequency in each ear. Threshold concern was flagged at 1000 Hz when there was a difference of ≥ 10 dB (hearX Group, South Africa). Patient, test and facility data were consolidated instantly on a secure online database. Data collected by the smartphone were automatically uploaded to a secure cloud-based server once connected to Wi-Fi. Access to the smartphone and cloud-based data was protected by a user password.

2.4.6 Data collection procedures

The researcher conducted the following data collection procedures:

Otoscopy

Outer ear functioning was assessed with an otoscopic examination of the external ear canal and tympanic membrane. Participants with occluded ear canals due to excessive cerumen were referred for cerumen removal prior to testing, or cerumen was removed by the researcher. Otoscopic examination was conducted before further testing could continue.

Pure-tone audiometry

Baseline testing included case history, otoscopy, and pure-tone audiometry (conventional air conduction (250−8000Hz) and EHF (10000−16000Hz). Exit testing included otoscopy and pure-tone audiometry (conventional air conduction (250−8000Hz) and EHF (10000−16000Hz).

Testing was performed outside a sound-treated room in the oncology rooms during chemotherapy appointments or oncology visits as well as in hospital wards. Participants were tested prior to initiation of treatment, during or within 24 hours of treatment initiation (baseline testing). Post-treatment follow-up occurred at three to six months post-

treatment (exit testing). Prior to baseline testing, participants were provided with simple instructions and a demonstration of the testing procedure. An automated hearTest^{R} protocol was employed for baseline and exit testing to determine participant thresholds. The Shortened Threshold Ascending method was used in the automated protocol to obtain thresholds (Van Tonder et al., 2016).

A pure tone average (PTA) refers to the average of hearing threshold levels at a set of specified frequencies. This value gives a description of an individual's hearing level in each ear. The PTA was calculated as the better ear average for four frequencies of 500, 1000, 2000, and 4000 Hz. The WHO grades of hearing impairment were used to determine severity of hearing loss. A PTA of <25 dB HL indicates normal hearing, 26–40 dB HL slight hearing loss, 41–60 dB HL moderate hearing loss, 61–80 dB HL severe hearing loss, and >81 dB HL profound hearing loss (Mathers, Smith & Concha, 2000).

Threshold shifts were regarded as significant if there was 20 dB decrease or greater at one frequency, 10 dB decrease or greater at two adjacent frequencies, and loss of response at three consecutive frequencies where there was a previously recorded response (ASHA, 1994). Participants with changes in hearing were advised to continue monitoring until hearing had stabilised and up to 12 months post treatment (Langer et al., 2013). All participants, even those without a significant shift in threshold, were advised to continue annual monitoring of hearing abilities.

Referral pathway

When cerumen impaction was identified during otoscopy, participants were advised to have cerumen removed. Referrals were made to their general practitioner. When hearing loss was identified, participants were provided with three names of audiologists closest to their residence for further testing, possible hearing aids and aural rehabilitation.

2.4.7 Data analysis

Descriptive statistics (averages and standard deviation) were used to determine the

decline in hearing thresholds from baseline to exit testing. The Shapiro-Wilk test (Field, 2018) was used to test for normality, and since the p-values were less than 0.05, the data differed from normality, and nonparametric tests were used. The correlation between the most common frequencies affected and duration between baseline and exit testing was determined. Within-subject statistical tests (Wilcoxon signed-rank (WSR) test) was used to determine the statistical significance of the hearing threshold shifts from baseline to exit testing. If the p-value was < 0.05, there was a statistically significant difference between baseline and exit. Non-parametric Spearman correlations were used to report on statistically significant (p-value < 0.05) correlations. Since males and females were independent groups, the Mann-Whitney (MW) test was used to determine whether males or females differed significantly (p-value < 0.05) in terms of incidence of ototoxicity.

2.5 Study 3: Changes in vestibular and cochlear function following platinum-based chemotherapy

2.5.1 Research design

This study followed a longitudinal (repeated measures over time) experimental design that was quantitative in nature (Brynard, et al., 2014) and aimed to identify changes in vestibular function from baseline to exit testing using video head impulse test (VHIT), vestibular myogenic evoked potentials (VEMP) and dynamic visual acuity (DVA). Testing took place in the participant treatment venue. This design allows for inferring of causality and test-causal relationships, however, small sample sizes make generalisability risky (Mouton, 2000).

2.5.2 Research context

The research context was exactly the same as in study two, which is described in 2.4.2.

2.5.3 Research participants

The research participants were the same as in study two, which is described in 2.4.3.

2.5.4 Protocol for vestibulotoxicity monitoring

In view of the fact that Type I hair cells (particularly of the semicircular canals) are more susceptible to ototoxicity, vHIT and VEMP testing are useful objective tests for the early detection of vestibulotoxicity (Van Hecke, et al., 2017). VHIT provides quick and objective measurements of the vestibular-ocular reflex (VOR) and efficiently assesses the dizzy patient to determine if the dizziness is related to a vestibular disorder (McGarvie MacDougall, Halmagyi, Burgess, Weber, & Curthoys, 2015; Halmagyi, Chen, MacDougall, Weber, McGarvie, & Curthoys, 2017). VEMP assesses the saccular and utricular functioning in individuals with various vestibular disorders (Sahu & Sinha, 2015). Air conduction cervical VEMP (cVEMP) testing predominantly reflects the function of the saccule and inferior vestibular nerve (Singh, Keloth, & Sinha, 2019), while air conduction ocular VEMP (oVEMP) testing predominantly reflects the function of the utricle and superior vestibular nerve (Singh et al., 2019; Manzari, Burgess, & Curthoys, 2010).

In addition to vHIT and VEMP, DVA was included to assess the functional VOR, which is often compromised in those with bilateral vestibular loss (van de Berg, van Tilburg, & Kingma, 2015). Consequently, a thorough case history, VHIT, VEMP testing and DVA was used to assess vestibular function at baseline and exit testing. Pure-tone audiometry was performed using an mHealth supported device to assess cochleotoxicity.

Vestibular dysfunction was described as abnormal vHIT results and/or abnormal VEMP results. The vHIT results are classified as abnormal when the gain is abnormally low and/or covert or overt saccades are present. The cVEMP and oVEMP results are classified as normal in the presence of identifiable P1 and N1 waveforms and classified as abnormal under the following conditions: (i) the presence of identifiable P1 and N1 waveforms and latencies above the upper limits of the waveform latencies are considered present yet delayed, and considered abnormal; or (ii) the presence of an amplitude AR of ≥40% is considered abnormal, as it indicates amplitude differences between the ears and (iii) absent VEMP responses could not be interpreted and were not valuable for ototoxicity monitoring (Akin & Murnane, 2008). An abnormal DVA confirmed peripheral vestibular pathology. Figure 2.3 describes the vestibulotoxicity monitoring protocol applied in the

study.

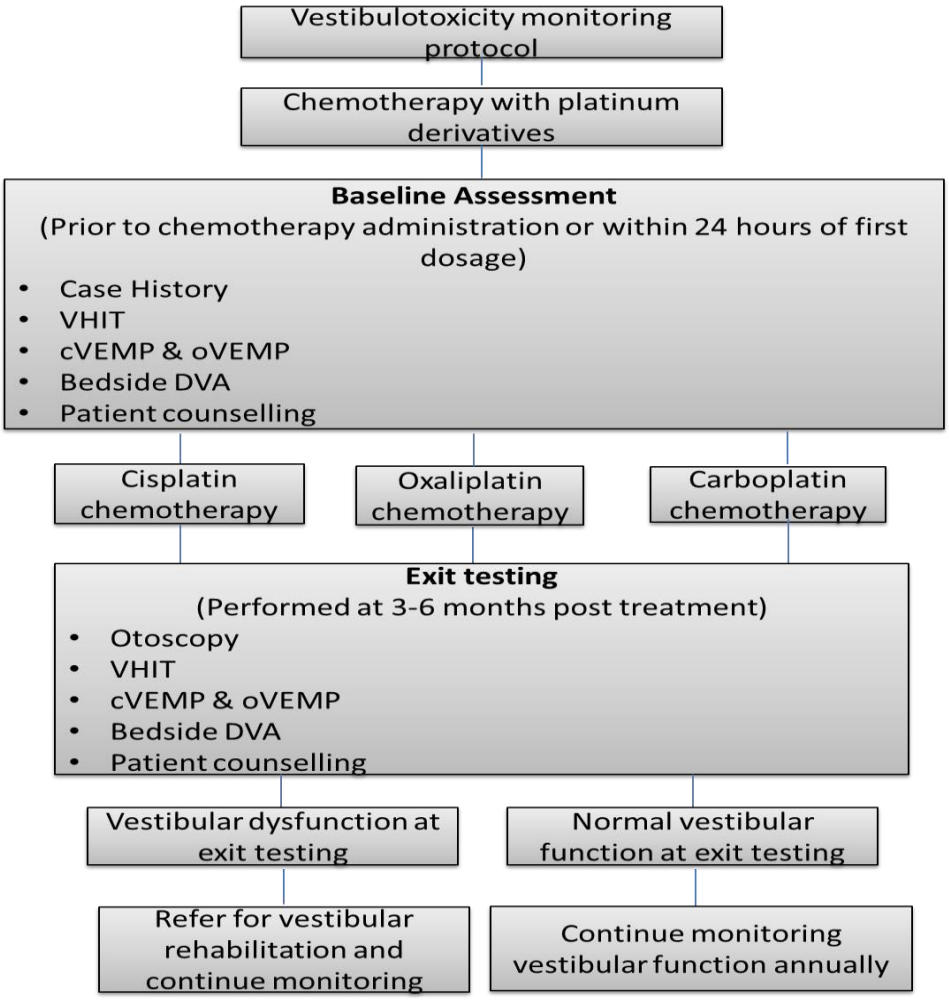

Figure 2.3 Vestibulotoxicity monitoring protocol applied in the study

2.5.5 Material and apparatus for data collection

The ototoxicity monitoring case history interview

The *ototoxicity monitoring case history interview* (adapted from Campbell, 2007; Venter, 2011) was used as a guideline during case history at baseline testing. The case history was used to determine the biographical and background history of the participants (Appendix E).

Mobile audiometry

Hearing testing was performed with the hearTest^{R} certified digital audiometer (IEC 60645-1, hearX Group, South Africa) for baseline and exit testing. Supra-aural Sennheiser HDA 300 headphones (Sennheiser, Wedemark, Germany) calibrated according to prescribed standards (International Organisation for Standardisation, ISO 389–1, 2017), and adhering to equivalent threshold sound pressure levels determined for this headphone were connected to the smartphone. Automated protocols were used to obtain hearing thresholds and monitor cochleotoxicity.

Video head impulse test (VHIT)

The ICS impulse VHIT device (GN-Otometrics, Denmark) and ICS impulse video goggles (GN Otometrics, Taastrup, Denmark) with a camera speed of 250 frames per second, recording motion of the right eye, were used to assess semi-circular canal function. Calibration was performed annually in November 2019, 2020 and 2021.

Vestibular evoked myogenic potentials (VEMP) testing

The SOCRATES Clinical Auditory Evoked Potentials (Hedera Biomedics, Italy) was used to obtain cVEMP and oVEMP measurements. SOCRATES is a computer-based medical device that can detect auditory evoked potentials by using two independent channels. Calibration was performed annually in July 2019, 2020 and 2021.

Bedside dynamic visual acuity (DVA)

A Snellen eye chart was used to conduct bedside DVA.

2.5.6 Data-collection procedures

Testing was performed in the oncology rooms during chemotherapy appointments or oncology visits. Participants were tested prior to initiation of treatment or within 24 hours of treatment initiation (baseline testing). Post-treatment follow-up occurred at three to six months post treatment (exit testing). Participants with changes in vestibular function and

hearing were advised to continue monitoring until vestibular function and hearing had stabilised and up to 12 months post treatment (Langer et al., 2013). All participants, even those without a significant shift in vestibular and hearing function, were advised to continue annual monitoring of hearing and vestibular function.

Pure-tone audiometry

Prior to baseline testing, participants were provided with simple instructions and a demonstration of the testing procedure. An automated hearTest^{R} protocol was employed for baseline and exit testing to determine participant thresholds. Participants were expected to indicate when they heard the tone by pressing a button on the smartphone. The Shortened Threshold Ascending method was used in the automated protocol to obtain thresholds (Van Tonder, et al., 2016).

The pure-tone average (PTA) was calculated as the better ear average for four frequencies of 500, 1000, 2000, and 4000 Hz. The WHO grades of hearing impairment were used to determine severity of hearing loss. A PTA of <25 dB HL indicates normal hearing, 26-40 dB HL slight hearing loss, 41-60 dB HL moderate hearing loss, 61-80 dB HL severe hearing loss and >81dB HL profound hearing loss (Mathers, Smith, & Concha, 2000).

Threshold shifts were regarded as significant if there was 20 dB decrease or greater at one frequency, 10 dB decrease or greater at two adjacent frequencies and loss of response at three consecutive frequencies where there was a previously recorded response (ASHA, 1994).

Video head impulse test (VHIT)

Participants were tested in a well-lit room with an eye-level target at a distance of 1 m in front of them while seated in a chair. Spectacles were removed for this assessment. VHIT goggles were tightened on the head until movement of the goggles at the bridge of the nose was minimal to avoid goggle slippage.

Calibration of the eye position signal was performed with the subject successively fixating on two projected laser dots separated by a known horizontal angle. For each of the canal planes, the researcher aimed to deliver a range of velocities in random order and direction so as to achieve at least 10 artifact-free impulses in each of the following ranges: horizontal: 10 <120°/s, 10 in the range 120–180°/s, and 10 over 180°/s in each direction. For vertical impulses, the ranges were: 10 <110°/s; 10 between 110° and 140°/s; 10 >140°/s.

For the horizontal VHIT stimulus, the researcher delivered small, passive, abrupt horizontal head rotations, with an unpredictable direction and magnitude. All tests were performed by the same right-handed researcher. Horizontal tests were performed with both hands on the top of the head, well away from the goggles strap and forehead skin.

Vertical VHIT included left anterior, right posterior (LARP) and right anterior left posterior (RALP) semi-circular canals. For LARP, the participant's head was rotated 30°–40° to the right of the fixation point. The participant was instructed to keep fixating on the target on the wall. Thereafter, a diagonal head pitch forward (toward the fixation target) activated the left anterior canal and caused an upward eye movement, and a head pitch back (away from the fixation target) activated the right posterior canal and caused a downward eye movement. Similarly, the RALP was performed with the participant's head turned 30°–40° to the left of the target, while still fixating on the target. A head pitch forward activated the right anterior canal, and a head pitch back activated the left posterior canal. The entire VHIT took 10–15 minutes to complete.

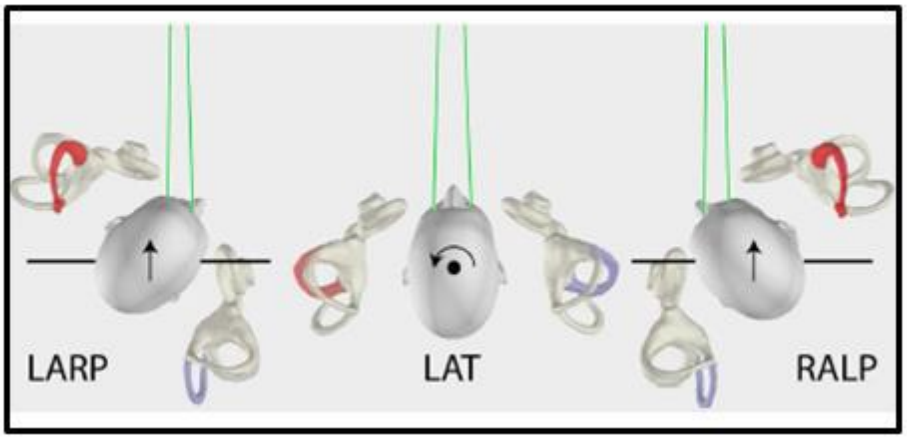

Figure 2.4 Video Head Impulse Test (VHIT) head movement procedures: Lateral (LAT) and vertical (Left Anterior Right Posterior (LARP) & Right Anterior Left Posterior (RALP) semi-circular canals (from McGarvie et al., 2015)

Test results were interpreted as abnormal if i) the VOR gain value <0.8 for lateral canals and <0.7 for vertical canals or ii) if overt (saccades after the head movement) or covert (saccades during the head movement) catch-up saccades were present (McGarvie, et al., 2015; Halmagyi, et al., 2017).

Vestibular evoked myogenic potentials (VEMP) testing

Participants were seated on a standard chair for both cVEMP and oVEMP testing. Ipsilateral electromyography recordings were performed for cVEMP testing. The participants had to obtain sufficient tonicity of the sternocleidomastoid (SCM) muscle with minimum discomfort in order for the cVEMP to be recorded (Isaradisaikul, et al., 2012). The participants turned their head contralateral to the side of stimulation and neck flexion of the SCM muscle was achieved while being instructed to gaze at a target point in order to generate cVEMP with the most robust amplitudes and without premature fatigability. An electromyography (EMG) monitor was used to ensure consistent and sufficient muscle contraction. (Isaradisaikul et al., 2012). Disposable wet-gel electrodes were used for recording after mild scrubbing of the electrode sites. The active (inverting) electrode was positioned on the ipsilateral mid-portion of the SCM muscle of the test ear, the reference (non-inverting) electrode was placed on the sternum, and the ground electrode was

positioned on the forehead (Isaradisaikul et al., 2012; Konukseven et al., 2015). Impedances were kept below 5 kΩ. The stimulus was presented using insert earphones and an air-conduction tone burst stimulus of 500 Hz was presented at an intensity of 97 dB nHL using alternating polarity. A 2-ms rise/fall time and plateau time was used with band pass filters ranging from 10 to 1000 Hz at a repetition rate of 5.1 per second. One hundred sweeps were averaged for each cVEMP test. For the cVEMP waveform interpretation, the first positive peak on the waveform was marked as P1 and the first negative deflection was marked as N1. Normal P1 latency was ≤19 ms and for N1, ≤28 ms was considered normal (Isaradisaikul et al., 2012; Zapala & Brey, 2004). The inter-peak (peak-to-peak) amplitude was the sum of the amplitudes of the repeated cVEMP responses.

Regarding oVEMP testing, electromyography recordings from the extra-ocular muscles in the infra-orbital region are recorded while the stimulus is presented in the contralateral test ear. An upward gaze during the stimulation and recording of oVEMP is required. Participants were asked to maintain their gaze on a stationary target on the ceiling. The active (inverting) electrode was positioned under the opposite eye on the inferior oblique muscle from the test ear. The reference (non-inverting) electrode was placed on the nose bridge, and the ground electrode was positioned on the forehead (Leyssens et al., 2016). A 1-ms rise/fall time and 2-ms plateau time with band pass filters ranging from 2 to 500 Hz. One-hundred and fifty sweeps were averaged for each oVEMP test. For the oVEMP waveform interpretation, the first negative deflection was marked as N1 and the first positive peak was marked as P1 (Leyssens et al., 2016). Normal latencies for N1 were ≤11.1, and a latency of ≤17.6 ms was considered normal for P1. The interpeak amplitude was the sum of the amplitudes of the repeated oVEMP responses (Leyssens et al., 2016).

The VEMP asymmetry ratio (AR) was calculated using the Jongkees formula: (AR): [(AL - AS) / (AL+ AS)] x 100, where “AL” represents the larger P1-N1 amplitude and “AS” the smaller P1-N1 amplitude. In order to confirm the presence of VEMP responses, the responses and the peaks had to be repeated within the correct latencies to test for wave reproducibility and to disregard potential artefacts. The VEMP responses were interpreted

according to the following parameters: (i) the presence of identifiable P1and N1 waveforms and latencies above the upper limits of the waveform were considered present yet delayed, and recorded as abnormal; (ii) the presence of an AR of ≥40% was considered abnormal as it confirms amplitude differences between the ears; and (iii) absent VEMPS could not be interpreted and were not useful for ototoxicity monitoring (Akin & Murnane, 2008).

Bedside dynamic visual acuity (DVA)

The participant was seated approximately 3 m from a Snellen eye chart, which was placed at eye level. Eyeglasses were permitted during this test. To determine static visual acuity, the participant was asked to read the smallest line, while reading all of the letters correctly. After verifying and recording the line of static visual acuity, the examiner stood behind the participant and rotated his/her head side to side, at a speed of 2 Hz to effectively elicit a VOR response. A metronome was used to ensure that the appropriate speed was maintained throughout. To determine the DVA, the participant was again asked to read the smallest line possible in which all of the letters were read correctly, while his/her head was moving. A decline of more than two lines from static head recordings was considered abnormal (Camet et al., 2018).

Referral pathway

Participants identified with hearing loss or vestibular dysfunction were provided with three names of audiologists close to their residence for further testing, hearing aid fitting, aural and vestibular rehabilitation.

2.5.7 Data analysis

SPSS was used for data analysis (IBM SPSS Statistics 27). Descriptive statistics (averages and standard deviation) were used to determine the decline in vestibular function from baseline to exit testing. The Shapiro-Wilk test (Field, 2018) was used to test for normality, and since the p-values were less than 0.05, the data differed from normality, and nonparametric tests were used. Within-subject statistical tests (Wilcoxon signed-rank

(WSR) test) was used to determine the statistical significance of the vestibular function from baseline to exit testing. If the p-value is < 0.05, then there is a statistically significant difference between baseline and exit. Non-parametric Spearman correlations were used to report on statistically significant (p-value < 0.05) correlations. Using G*Power version 3.1.9.4 (Faul et al., 2007), the achieved power for a level of significance of 0.05, a sample size of 32 and an effect size of 0.573 (calculated from the data) equals 0.973. In order to show an association between cochleotoxicity and vestibulotoxicity, correlations were used. If the p>0.05, then there was no significant correlation. On the other hand, if the p< 0.05, the correlation was significant. A positive correlation was used to conclude that as cochleotoxicity increases, so does vestibulotoxicity.

CHAPTER 3

OTOTOXICITY MONITORING IN SOUTH AFRICAN CANCER FACILITIES: A NATIONAL SURVEY

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3.1 Abstract

Background: National information about ototoxicity monitoring practices is limited for patients undergoing chemotherapy in South Africa.

Objectives: To determine: (i) the national status of ototoxicity monitoring implemented in private and public cancer facilities; (ii) the knowledge of ototoxicity monitoring approaches implemented; and (iii) reported challenges.

Method: A descriptive quantitative survey was conducted in public and private oncology units and audiology referral clinics. Private (60%) and public (43%) oncology units that provided platinum-based chemotherapy in South Africa and audiology referral units (54%) were 1) surveyed telephonically to determine if ototoxicity monitoring took place, and 2)

a self-administered survey was sent to qualifying oncology units and audiology referral clinics.

Results: All public oncology units reported that ototoxicity monitoring occurred only on referral and was not standard practice. All private oncology units indicated that monitoring was on a patient self-referral basis when symptoms occurred. Poor awareness of ototoxicity monitoring best practice guidelines was reported by all oncology units and 14% of audiology referral clinics. Audiology referral clinics reported adequate knowledge of ototoxicity protocols although they were not widely used, with only 43% following best practice guidelines. The most prominent challenges reported by participants were referral system (67% oncology units; 57% audiology referral clinics), environmental noise (83% oncology units; 86% audiology referral clinics) and the compromised status of cancer patients (67% oncology units; 57% audiology referral clinics).

Conclusion: Ototoxicity monitoring is not routinely implemented across oncology units in South Africa. Multidisciplinary teamwork and a simplified national ototoxicity monitoring protocol may improve hearing outcomes for patients.

Keywords: cancer; chemotherapy; hearing loss; oncology; ototoxicity; ototoxicity monitoring; ototoxicity monitoring protocols; platinum-based compounds

3.2 Background

Cancer is known to be one of the world's most life-threatening diseases, resulting in approximately 19.3 million new cases and 10 million deaths in 2020 (Sylla & Wild, 2012; World Health Organization, 2020). The projected increase in cancer rates as well as the progress in cancer therapeutics over the past 40 years, which has remarkably improved survival rates, revealed a need to shift the focus to adverse drug effects and their impact on quality of life (QoL). Ototoxicity is known to be an adverse effect in platinum-based cancer chemotherapeutic agents (Rybak & Ramkumar, 2007; Silver, Baima, & Mayer, 2013). Susceptibility to ototoxicity increases with dose and duration of therapy, infusion rate and cumulative lifetime dose, impaired kidney function, which can lead to rapid

accumulation of the ototoxic drug, concurrent administration of another ototoxic drug (such as aminoglycosides and loop diuretics), anaemia, hypoalbuminemia, age, pre-existing sensorineural hearing loss, exposure during pregnancy, previous exposure to head and neck radiation, genetic susceptibility, and family history of ototoxicity. This, in turn, has a significant impact on QoL in a cancer survivor's life (Baguley et al., 2017; Ferlay et al., 2015; Pearson et al., 2019; Silver et al., 2013).

Platinum-based chemotherapy such as cisplatin is a widely used chemotherapeutic agent for the treatment of numerous malignancies, including testicular, ovarian, bladder, cervical, head and neck, and non-small-cell lung cancers (Rybak & Ramkumar, 2007). Ototoxicity results in tinnitus and sensorineural hearing loss, which can be severe to profound after high-dose chemotherapy (Rybak & Ramkumar, 2007). For patients with life-threatening illnesses that necessitate treatment with ototoxic drugs, communication ability is a central QoL issue. Hearing loss and tinnitus are both associated with a greater risk of social isolation, depression, anxiety (Nordvik et al., 2018) and development of dementia (Deal et al., 2017). There is also a substantial risk of cochleotoxicity to be followed by vestibulotoxicity in patients receiving platinum-based chemotherapy (Prayuenyong, et al., 2018). Vestibular dysfunction may have a major effect on the QoL, as balance and mobility impairment are more predominant in cancer survivors, which also increases the risk of falls (Sun et al., 2014; Wildes et al., 2015). Therefore, the early identification of ototoxic damage can improve treatment outcomes by minimising hearing loss progression and vestibular dysfunction, and providing early aural and vestibular rehabilitation where ototoxicity is inevitable (Konrad-Martin et al., 2018).

Although platinum-based chemotherapy ototoxicity is a common adverse occurrence, varying incidence rates are reported in both adults and children, which is partly due to the variability of audiological tests employed in the identification and monitoring of the cancer patient's hearing status (Paken et al., 2020). Considering these challenges, international bodies like the American-Speech-Language-Hearing-Association (ASHA) and American Academy of Audiology (AAA) have guidelines that provide flexibility for shortened screening protocols to be used for ototoxicity monitoring (AAA, 2009; ASHA, 1994; Health

Professions Council of South Africa (HPCSA), 2018). Although audiologic evaluation is ideally conducted in a sound-treated room, the ASHA (1994) guidelines recognise that, even with shortened protocols, full booth-based audiometric monitoring is not always feasible in all clinical environments (Brungart et al., 2018), which contributes to the ineffectiveness of existing screening programmes.

It is currently unknown what proportion of patients undergoing chemotherapy with platinum-based agents are systematically identified and monitored for signs of ototoxicity in South Africa. Too often, audiological testing is arranged only once debilitating hearing loss is already apparent to the patient or multidisciplinary team (Paken, et al., 2020), whereas serial audiological monitoring is critical in ototoxicity monitoring protocols to achieve the desired outcomes (Brungart et al., 2018; HPCSA, 2018). Another challenge is that, while much chemotherapy practice is protocol-based, divergence from protocols is common as treatments may be delayed, modified, or added to in particular circumstances (Baguley et al., 2017). This often affects the audiological monitoring schedules, highlighting that set protocols cannot be followed for all patients receiving chemotherapy. Thus, the identification of a truly homogeneous treatment group may be difficult. While empirical evidence of compliance with such guidelines has not been identified, indications are that the implementation of audiometric monitoring is sporadic (Paken et al., 2020).

In low- and middle-income countries (LMICs) like those in sub-Saharan Africa, there is a lack of hearing care and appropriate equipment to successfully implement hearing screening and monitoring programmes (Chadha, Cieza, & Krug, 2018; Mulwafu, Kuper, & Ensink, 2016). The number of audiologists on the African continent has been reported to be one of the lowest, with an estimate of one audiologist for every million people in sub-Saharan Africa (Mulwafu et al., 2016). In addition, the high costs associated with screening equipment and the necessity for the equipment to be operated by trained personnel such as audiologists further burden the implementation of effective screening programmes for early detection and intervention (Louw et al., 2017). Furthermore, the mechanisms for tracking patients throughout the system need to be explored in order to

ensure that patients receive the audiological services they may need at various stages of cancer treatment and survivorship (Konrad-Martin et al., 2018).

Studies in South Africa (Andrade, Khoza-Shangase, & Hajat, 2009; Khoza-Shangase & Jina, 2013) revealed that oncologists did not fully recognise the effects of ototoxicity, the role of audiologists and the need for their expertise. Furthermore, most general practitioners did not appear to carry out ototoxicity monitoring strategies, despite being aware of their own role in an ototoxicity monitoring programme (Andrade et al., 2009; Garinis et al., 2018; Khoza-Shangase & Jina, 2013).

Early identification of ototoxic effects on hearing ability due to platinum-based therapy provides physicians with an opportunity to adjust the drug therapy in order to minimise or prevent hearing loss and provide early hearing intervention services (Garinis et al., 2018; HPCSA, 2018). An ototoxicity monitoring programme should be context-sensitive without increasing the already over-burdened treatment schedule of cancer patients, identify ototoxic effects early, and include a team of health care professionals (Ganesan et al., 2018). Studies conducted in South Africa indicated that neither had provision been made for ototoxicity monitoring in the chemotherapy protocols nor had any ototoxicity monitoring programmes been implemented, and only half of the participants reported referring patients for audiological management during the chemotherapeutic process (Khoza-Shangase & Jina, 2013; Paken et al., 2020). The studies that have been performed in South Africa are limited to certain geographical areas, and national data on ototoxicity monitoring practices in South Africa is lacking. This study therefore aimed to describe ototoxicity monitoring practices in South Africa in both the private and public healthcare sector.

3.3 Method

The survey aimed to: (i) describe the national status of ototoxicity monitoring implemented in private and public cancer facilities in South Africa; (ii) describe knowledge of ototoxicity monitoring approaches implemented; and (iii) identify challenges to ototoxicity monitoring.

3.3.1 Data collection sites, population and sampling

Probability sampling was applied. The participants included healthcare professionals (general practitioners (GPs), oncologists, nurses, pharmacists and audiologists) working in private and public healthcare oncology units and audiology referral clinics in South Africa. All public hospitals were accessed via the national department of health website http://www.health.gov.za/ (Department of Health, 2019). Private oncology units were accessed via www.medpages.co.za (Medpages, 2018) and the Independent Clinical Oncology Network (ICON) (ICON, 2017). Public provincial tertiary and central or academic hospitals were included, as these hospitals have specialised referral units, which together provide an environment for multi-specialty clinical services, innovation and research, such as oncology. There are 29 tertiary hospitals and ten major teaching hospitals in South Africa, but not all hospitals provide platinum-based oncology treatment or were able to participate in the research. Fifty-five private oncology units were identified in South Africa and were contacted telephonically to confirm their eligibility and willingness to participate. Information was obtained from the practice manager or nurse in charge. Once consent for participation had been obtained, questionnaires were sent to the oncology units, where healthcare professionals (GPs, oncologists, nurses, or pharmacists) representing the oncology units completed the questionnaires.

Audiology referral clinics (n=13) in the same hospital as oncology units were contacted for participation in the study. Participants therefore included an audiologist representing the audiology referral clinics in the private and public sector across South Africa and mentioned by oncology units as referral centres. Questionnaires were sent to the audiology referral clinics for completion. Figure 1 below illustrates the research sites, participant description and sampling procedure.

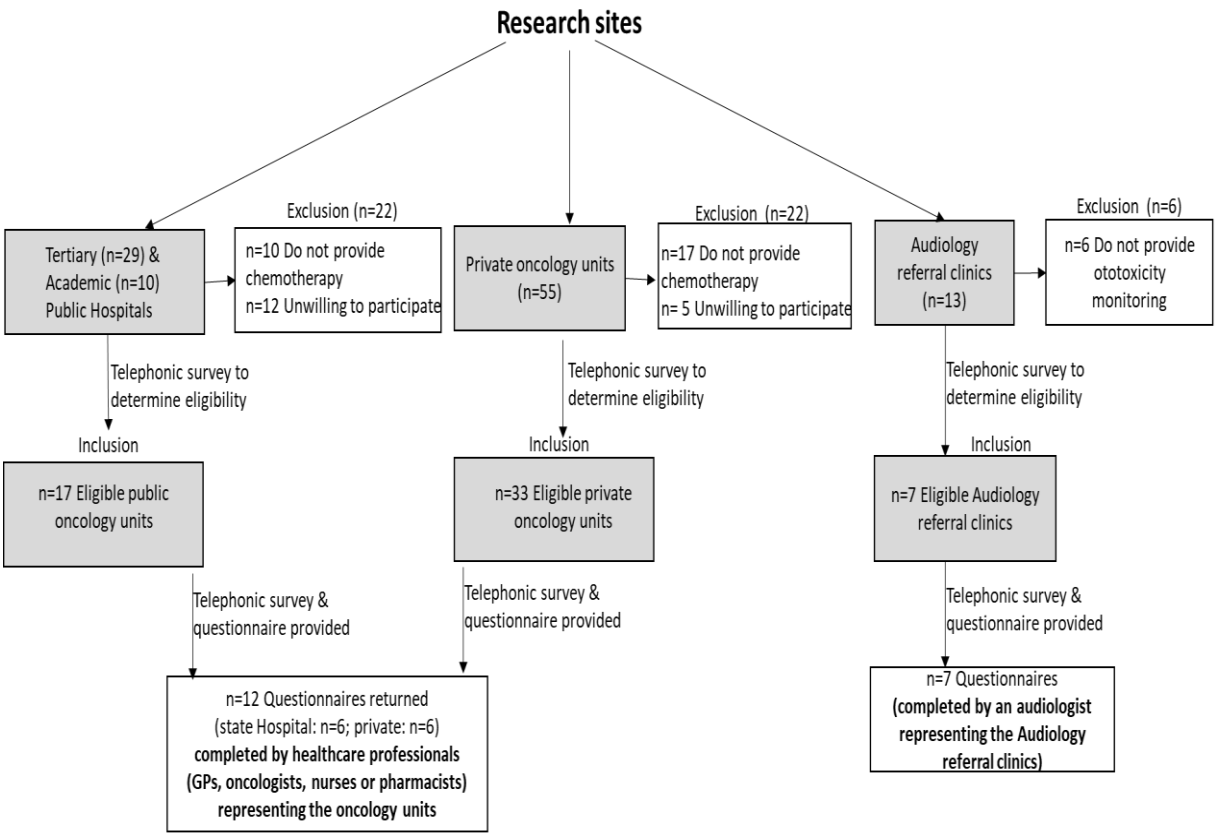

Figure 3.1: Research sites, participant description and sampling procedure

3.3.2 Data collection procedure

Before commencing with the study, ethical clearance was obtained from a university in South Africa.

Firstly, private oncology units (n=55) and public hospitals (n=29) with cancer units were contacted telephonically to determine whether they offered platinum-based chemotherapy as a treatment option. Oncology units who offered platinum-based chemotherapy and were willing to participate in the study were surveyed telephonically. During the telephonic survey, nursing managers and/or oncologists in the units provided information regarding ototoxicity monitoring practices in the cancer units. The telephonic survey confirmed (i) whether platinum-based chemotherapy agents were offered in the unit, (ii) whether ototoxicity monitoring was done as standard practice for all patients receiving ototoxic chemotherapy or whether ototoxicity monitoring was only done when

referred by a healthcare professional or if patients arranged their own hearing evaluation when ototoxicity symptoms or hearing loss was apparent, and (iii) where patients were referred to for ototoxicity monitoring. The second part of the research study included a self-administered questionnaire. An electronic questionnaire was sent to the oncology units to determine the knowledge, monitoring approaches, protocols and challenges of implementing ototoxicity monitoring. Nurses, oncologists, general practitioners and pharmacists were some of the healthcare professionals who completed the electronic questionnaires on behalf of the oncology units.

Audiology departments in public hospitals with cancer units and private practice audiologists in close proximity to private oncology units as well as those mentioned as referral centres were contacted for information on ototoxicity monitoring practices. The telephonic survey confirmed whether ototoxicity monitoring was performed for patients receiving ototoxic chemotherapy. The electronic questionnaire was sent to the identified audiology referral clinics for completion. Audiologists completed the questionnaire on behalf of the audiology referral centres.

3.3.3 Description of electronic questionnaire

A structured, self-administered questionnaire was used for both oncology units and audiology referral clinics. The questionnaire was administered as a single attempt to determine the characteristics of the ototoxicity monitoring protocols currently implemented in oncology units and audiology referral clinics in South Africa, as well as the challenges experienced. The same questionnaire was used for all healthcare professionals as the questionnaire included general aspects regarding ototoxicity, ototoxicity monitoring, and challenges. There was a section for completion by audiologists only, which covered aspects such as testing protocols and procedures followed during ototoxicity monitoring. The questionnaire was adapted from Steffens et al. (2014) by adding answer options to choose from, resulting in more closed-ended questions with an option of providing additional information. The original study (Steffens et al., 2014) had only open-ended questions, which were interview-based.

The questionnaire contained a range of open- and closed-ended questions (multiple-choice format) in three broad categories: (i) demographic information, (ii) knowledge of and general perceptions towards ototoxicity monitoring, (iii) challenges, (iv) ototoxicity monitoring protocols (only to be completed by audiology referral clinics), and (v) views on potential improvements to ototoxicity monitoring. The Qualtrics survey platform was used for ease of completion and automatic data storage (refer to questionnaire in Appendix).

3.3.4 Data analysis

Data collected from the (i) telephonic surveys and (ii) electronic questionnaires administered to private and public oncology units and audiology referral clinics were integrated. The data were analysed to yield percentages and frequency distributions nationally and across provinces. Thematic content analysis was used for open-ended questions.

3.4 Results

Of the 39 hospitals in the public sector who provided chemotherapy oncology services, 44% (n=17) were willing to participate in the research following the telephonic survey. Of the 55 private oncology units, 60% (n=33) were surveyed telephonically and provided platinum-based chemotherapy; some units only provided radiation or were unwilling to participate. A lower response rate was obtained for the questionnaire compared to the telephonic survey, as some of the units did not perform ototoxicity monitoring and did not consent to completing the questionnaire. Furthermore, some oncology units had several branches and responses were only obtained from one branch, as similar ototoxicity monitoring practices were followed at all the branches.

The electronic questionnaire was completed by 26 (46%, n=57) participants, but only n=19 (33%, n=57) complied with the inclusion criteria and could be included in the study. Questionnaires completed by healthcare professionals who were not involved in ototoxicity monitoring and working in/with oncology units were excluded from the study. Therefore, only 36% (n=12) questionnaires were completed and returned by healthcare professionals representing the oncology units. The questionnaires were completed by

54% (n=7) audiologists representing the audiology units. Overall, a response rate of >25% for completion of questionnaires was achieved, which is considered acceptable for mailed surveys (Baruch & Holtom, 2008).

3.4.1 Telephonic survey: Ototoxicity monitoring coverage

Telephonic surveys of ototoxicity monitoring at private and public oncology units demonstrated that it was not standard practice. Cancer patients with ototoxicity complaints such as hearing loss and tinnitus were either referred for an audiological evaluation by a healthcare professional, or had to arrange for audiological evaluations on their own initiative. Table 3.1 provides a breakdown of the ototoxicity monitoring approaches followed.

Table 3.1: Distribution of oncology units and ototoxicity monitoring approaches (n=50) across public and private facilities

			Ototoxicity monitoring approaches	
Province	**No public oncology units**	**Number of private oncology units**	**Public healthcare by professional referral ***	**Private healthcare: Patient self-referrals ****
Gauteng	4	12	4	12
Free State	1	1	1	1
Mpumalanga	1	1	1	1
Limpopo	1	2	1	2
North West	1	2	1	2
Western Cape	4	7	4	7
Northern Cape	1	2	1	2
Eastern Cape	2	2	2	2
KwaZulu-Natal	2	4	2	4
Totals	**17**	**33**	**17**	**33**

**Professional referral refers to referral from a healthcare professional within the oncology unit.*
***Patient self-referral refers to patients making their own appointment with an audiologist when ototoxicity symptoms or hearing loss became apparent.*

3.4.2 Self-administered questionnaire: Ototoxicity perceptions, challenges and testing approaches

Table 3.2 summarises the demographic information of the participants (healthcare professionals representing the oncology units and referral audiology centres).

Table 3.2: Demographic information of the participants

Participant demographics	Oncology units percentage (n=12)*	Audiology referral clinics percentage (n=7)**
Average age		
20-25 years	0	71% (5)
26-30 years	0	0
31-35 years	0	9% (2)
36-40 years	8% (1)	0
41 years +	92% (11)	0
Gender		
Males	17% (2)	14% (1)
Females	83% (10)	85.7% (6)
Years' experience in oncology		
0-5 years	17% (2)	86% (6)
6-10 years	8% (1)	0% (0)
11-16 years:	25% (3)	14% (1)
>21 years:	50% (6)	0% (0)
Current working place		
Public	33% (4)	43% (3)
Private	67% (8)	57% (4)
Profession		
General practitioner	17% (2)	0% (0)
Nurse	42% (5)	0% (0)
Audiologist	0% (0)	100% (7)
Oncologist	25% (3)	0% (0)
Pharmacist	17% (2)	0% (0)
Ototoxicity knowledge acquired (select all that apply)		
University programme	25% (3)	100% (7)
On the job	58% (7)	0% (0)
Own reading	50% (6)	71% (5)
Conferences and workshops	33% (4)	57% (4)

**n=12 healthcare professionals representing the oncology units.*
***n=7 audiologists representing the audiology referral clinics.*

Multiple-choice questions were used to determine general knowledge and perceptions of ototoxicity monitoring. Overall, poor awareness of ototoxicity monitoring protocols or best practice guidelines was reported, as no oncology units reported to have knowledge about protocols. Of the audiology referral clinics, 14% (n=1) had knowledge of best practice guidelines and 86% (n=6) had no knowledge. All participants (100%) from the oncology units and audiology referral clinics described ototoxicity as “a side effect of medicine resulting in auditory and/or vestibular dysfunction resulting in hearing loss and disequilibrium”. The purpose of ototoxicity monitoring was reported as early identification of hearing loss (83%, n=10 oncology units; 86%, n=6 audiology referral clinics), to terminate ototoxic treatment (0%, n=0 oncology units; 14.3%, n=1 audiology referral clinics), to adjust treatment dosages (67%, n=8 oncology units; 86%, n=6 audiology referral clinics), to improve QoL post-treatment (25%, n=3 oncology units; 57%, n=4 oncology referral clinics) and to provide appropriate and timely intervention (83%, n=10 oncology units; 86%, n=6 audiology referral clinics). On the other hand, the benefits of providing ototoxic monitoring to the patient were reported as patient knowledge of ototoxic hearing loss (58%, n=7 oncology units; 43%, n=3 audiology referral clinics) and early identification (100%, n=12 oncology units; 100%, n=7 audiology referral clinics) and intervention (83%, n=10 oncology units, 100%, n=7 audiology referral clinics) in hearing loss. Table 3.3 below describes participants’ knowledge of ototoxicity.

Table 3.3: Participants' general knowledge and perceptions of ototoxicity monitoring

Areas of knowledge about ototoxicity	Oncology units percentage (n=12)*	Audiology referral clinics percentage (n=7)**
Signs of ototoxicity		
Hearing loss (HL)	100% (12)	100% (7)
Disequilibrium	75% (9)	86% (6)
Renal impairment	0% (0)	0% (0)
Cancer drugs causing HL		
Fosfamide	8.3% (1)	14% (1)
Cisplatin	100% (12)	100% (7)
Methotrexate	0% (0)	14% (1)
Configuration of HL from ototoxicity		
High-frequency hearing loss	50% (6)	100% (7)
Unsure	50% (6)	0% (0)
Severity of HL		
Moderate	25% (3)	14% (1)
Severe	8% (1)	29% (2)
Profound	8% (1)	57% (4)
Unsure	58% (7)	0% (0)
% Patients receiving cisplatin will develop HL		
1-24%	25% (3)	0% (0)
25-49%	33% (4)	43% (3)
50-74%	17% (2)	14% (1)
75-99%	8% (1)	29% (2)
100%	17% (2)	14% (1)
Likelihood of tinnitus developing		
Slight likelihood	0% (0)	0% (0)
Moderate likelihood	25% (3)	0% (0)
Very likely	75% (9)	100% (7)
Likelihood of developing vestibular problems		
Slight likelihood	25% (3)	0% (0)
Moderate likelihood	42% (5)	57% (4)
Very likely	33% (4)	43% (3)

HL: Hearing loss
**n=12 healthcare professionals representing the oncology units.*
***n=7 audiologists representing the audiology referral clinics.*

Participants reported on the severity of the possible impact (tinnitus, hearing loss and vestibular problems) of ototoxicity on cancer patients' daily life as presented in Figure 3.2 below.

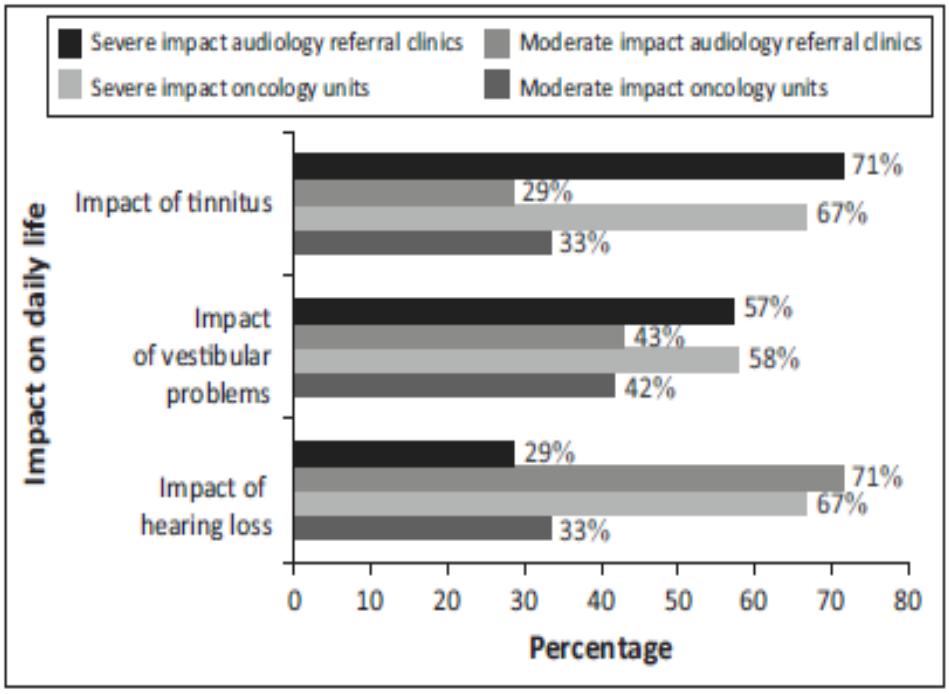

Figure 3.2: Participants' perceptions of the impact of ototoxicity symptoms on daily life (n=12 healthcare professionals representing the oncology units, n=7 audiologists representing the audiology referral clinics)

The questionnaire probed the ototoxicity monitoring protocols followed when cancer patients attend hearing evaluations, as well as the importance of baseline testing. Baseline testing in ototoxicity monitoring was deemed important as 60% (n=7 oncology referral units) and 100% (n=7 audiology referral clinics) reported it as extremely important and 42% (n=5 oncology units) said it was very important. However, this does not seem to be reflected in practice, as the audiology referral clinics reported that only 29% (n=2) of oncology patients received baseline assessments. All participants (100%, n=12 oncology units; n=7 audiology referral clinics) reported that only referred patients received baseline assessments and 17% (n=2 oncology units) reported that baseline assessments were not performed. Section 4 (refer to appendix) of the electronic questionnaire was completed by audiologists only (n=7 audiology referral clinics). Table 3.4 describes the battery of audiological tests included in ototoxic monitoring when patients are referred or self-refer for audiological testing.

Table 3.4: Battery of audiological tests included in ototoxic monitoring by audiology referral clinics (n=7 audiologists)

Audiological tests	Baseline testing % (n=7)	Serial monitoring % (n=7)
Pure-tone audiometry (PT)	100% (7)	100% (7)
Extended high-frequency audiometry (EHF)	71.4% (5)	57.7% (6)
Distortion-product otoacoustic emissions (DPOAEs)	57.1% (4)	71.4% (5)
Vestibular assessments	14.1% (1)	0% (0)
Other (not specified)	28.6% (2)	14.1% (1)

The participants were asked how informed patients were about the ototoxic effects of chemotherapy; 0% (n=0 oncology units) and 71% (n=5 audiology referral clinics) reported patients were uninformed, 8% (n=1 oncology units) and 29% (n=2 audiology referral clinics) reported slightly informed, 83% (n=10 oncology units) reported moderately informed and 8% (n=1 oncology units) reported well informed. The participants reported that patients received this information from oncologists (50%, n=6 oncology units; 57%, n=4 audiology referral clinics) nurses (42%, n=5 oncology units; 71%, n=5 audiology referral clinics), audiologists (25%, n=3 oncology units; 100%, n=7 audiology referral clinics), pharmacists (25%, n=3 oncology units; 14.3%, n=1 audiology referral clinics) and general practitioners (8%, n=1 oncology units; 14.3% n=1 audiology referral clinics). The majority of participants agreed that oncologists (92%, n=11 oncology units; 86%, n=6 audiology referral clinics) and nurses (83%, n=10 oncology units; 86%, n=6 audiology referral clinics) were responsible for informing patients. Audiologists (58%, n=7 oncology units; 57%, n=4 audiology referral clinics), general practitioners (58%, n=7 oncology units; 57% audiology referral clinics) and pharmacists (50%, n=6 oncology units; 43%, n=3 audiology referral clinics) also had a responsibility to inform patients. Although ototoxicity monitoring is not standard practice, but rather based on referral, provision of ototoxicity monitoring services was reported by 25% (n=3 oncology units) and 29% (n=2 audiology referral clinics; 42% (n=5 oncology units), while 43% (n=3 audiology referral clinics) stated no ototoxicity monitoring was provided and 33% (n=4 oncology units) and 29% (n=2 audiology referral clinics) reported that they were unsure.

Of the responses obtained in the section completed only by audiology referral clinics (n=7), only 43% (n=3) reported that the ototoxicity monitoring protocols were documented

and that it was the hospital's protocol of unknown origin, 43% (n=3) were unsure and 14% (n=1) reported that protocols were not documented. Only 14% (n=1) reported that the protocols were compulsory and always followed, 29% (n=2) said the protocols were only a guideline and were sometimes followed, and 57% (n=4) were unsure if protocols were followed. The factors that influenced the protocols followed were reported as follows: 29% (n=2) stated testing was done according to clinical necessity and doctor referrals, 43% (n=3) reported that best practice guidelines were followed, 57% (n=4) mentioned the availability of equipment, 29% (n=2) stated appointment availability, and 57% (n=4) mentioned audiologist training and knowledge as a contributing factor. Audiologist referral units (n=7) reported sending ototoxicity testing and monitoring results to oncologists (71%, n=5) and nurses (14%, n=1) as well as to the patient (29%, n=2). The results provided were believed to influence dosage choices (86%, n=6), to influence treatment choices (57%, n=5), and to result in otoprotective agents being prescribed (29%, n=2), and all audiology referral clinics (100%, n=7) agreed that the results ensured follow-up appointments and frequent visits to the audiologist.

The length of monitoring varied, as 50% (n=6 oncology units) and 43% (n=3 audiology referral clinics) reported that monitoring should continue for 12 months while 42% (n=5 oncology units) and 43% (n=3 audiology referral clinics) were of the opinion that it should continue for the patient's lifespan and only 8.3% (n=1 oncology units) and 14.3% (n=1 audiology referral clinics) indicated that six months of monitoring was sufficient. Most participants (83%, n=10 oncology units; 100%; n=7 audiology referral clinics) agreed that the audiologist should decide for how long monitoring is needed, while 17% (n=2 oncology units) indicated that the oncologist should decide.

3.4.3 Challenges to implementation of ototoxicity monitoring

The final section of the questionnaire surveyed the challenges of implementing ototoxicity monitoring in cancer patients. All (100%, n=12 oncology units and n=7 audiology referral clinics) of the participants reported a greater awareness needed amongst health professionals. However, 25% (n=3 oncology units) reported that awareness amongst oncologists was not needed. When participants were asked if improvements were needed

in ototoxicity monitoring in their workplace, 50% (n=6 oncology units) and 57% (n=4 audiology referral clinics) reported “yes”, 17% (n=2 oncology units), 14% (n=1 audiology referral clinics) reported “no”, and 33% (n=4 oncology units) and 29% (n=2 audiology referral clinics) reported “unsure”. Participants were asked if the referral process for ototoxic monitoring posed a challenge, and 8% (n=1 oncology units) and 14% (n=1 audiology referral clinics) reported “yes”, 33% (n=4 oncology units) and 29% (n=2 audiology referral clinics) reported “no” and 58% (n=7 oncology units) and 57% (n=4) reported “unsure”. An open-ended response in the questionnaire from a referral audiology clinic in the public sector (14%, n=1) was that “an attempt was made to implement a strict ototoxicity monitoring system for all qualifying chemotherapy patients, however, this was unsuccessful”. Oncology referral units indicated that “at-risk patients or patients with hearing loss complaints, rather than all patients, are identified for possible ototoxicity monitoring”. It was also reported that “hearing loss does not seem to be a main complaint in patients seen”. The patient challenges experienced were as follows: too ill to attend the audiology clinic (67%, n=8 oncology units; 57%, n=4 audiology referral clinics), patients tested in wards due to poor immunity and isolation (33%, n=4 oncology units; 57%, n=4 audiology referral clinics), which results in environmental noise (83%, n=10 oncology units; 86%, n=6 audiology referral clinics) and unfavourable testing conditions as well as financial considerations (25%, n=3 oncology units). An open-ended response from the private oncology units was: “The patients are put through a lot very quickly and it is extremely stressful to them. Cost is a big factor”.

As it was clear that ototoxicity monitoring protocols were not followed adequately, 83% (n=10 oncology units; 86%; n=6 audiology referral clinics) were in favour of a national ototoxicity monitoring protocol to be implemented in hospitals; however, 43% (n=3 audiology referral clinics) indicated that they would modify the protocol to suit their setting. A national ototoxicity protocol might also assist with lobbying for equipment in hospitals (57%, n=4 audiology referral clinics); however, 43% (n=3 audiology referral clinics) were unsure if that would help. Of the audiology referral clinics (n=7), 57% (n=4) were in favour of a novel approach to monitoring, such as automated smartphone audiometry, 14% (n=1) were not in favour, and 29% (n=2) were unsure. An open-ended response from the

audiology referral clinics stated that there was “a need for mobile testing equipment”.

3.5 Discussion

This survey is the first to report on the national status of ototoxicity monitoring in cancer patients in the public and private healthcare sectors in South Africa. Ototoxicity monitoring protocols are not followed in either the private or the public healthcare sector. In the public sector, hearing tests are done according to clinician referrals. Clinicians refer if patients complain about hearing-related problems. Some hospitals have attempted to implement a strict protocol to see all qualifying chemotherapy patients, but the constant rotation of doctors has hampered the implementation of a smooth working system between audiology and oncology. Awareness campaigns result in a temporary influx of referrals, but do not remain consistent (Maru & Malky; 2018). In the private sector, patients mostly refer themselves. Often, by this time, a hearing loss is already noticeable and likely irreversible. Similarly, a study in the USA reported that the physicians differed in their approaches to ototoxicity monitoring, from habitual referrals to audiology to relying on patient self-referral (Garinis et al., 2018).

The feedback from the private sector was that the oncology units did not give as much attention to hearing loss as they should. Oncology units claimed that it was not a lack of awareness of ototoxicity, but rather because of the cancer diagnosis; advanced disease, other oncologic emergencies, and emotional, financial and physical constraints that were prioritised (Carrera et al., 2018; Oun et al., 2018). Although platinum-based treatment is an ototoxicity risk in itself and risk-prediction models for platinum-related ototoxicity have been developed based on age and cumulative dose, these models do not accurately predict risk for individual patients (Landier, 2016). Patient risks such as younger age (particularly< 5 years) at the time of therapy, diagnosis of a central nervous system tumour, diminished renal function, rapid intravenous administration, and treatment with multiple potentially ototoxic agents (Oun et al., 2018) are identified as increased risks for ototoxicity. The private oncology units are of the opinion that identifying a patient who has a high risk is more valuable than identifying just anyone on platinum-based treatments, as hearing loss does not seem to be a main complaint in patients seen. This was also

reported in a South African study, where oncologists reported that patients did not complain of the “subtle” symptoms of cisplatin ototoxicity, such as tinnitus (Paken et al., 2020; Whitehorn et al., 2014).

The current study indicates comprehensive understanding of ototoxicity across all disciplines; however, there is limited familiarity with implementing ototoxicity monitoring and referral pathways, and greater awareness amongst healthcare professionals is needed. These findings were similar to previous studies internationally and in South Africa, which found that professionals involved in the care and management of cancer patients needed to improve their awareness of ototoxicity and refer timeously for audiological evaluation (Landier, 2016; Paken et al., 2020; Steffens et al., 2014). All participants in this study indicated that platinum-based chemotherapy could cause hearing loss, tinnitus and vestibular problems which have a moderate to severe impact on daily life. This corresponds with findings in similar research performed in South Africa and internationally (Ganesan et al., 2018; Landier, 2016; Oun et al., 2018; Paken et al., 2020; Whitehorn et al., 2014). Cancer patients, however, undergo significantly variable ototoxicity monitoring; and practices range from no baseline testing and routine monitoring to some form of testing in some patients, which seems to be a common phenomenon in current ototoxicity monitoring practices (Ganesan et al., 2018; Paken et al., 2020). Although survival rates remain the priority in cancer treatment, there needs to be more emphasis on the importance of remaining side effects and long-term symptoms such as hearing loss and tinnitus (Pearson et al., 2019). As the survival rate increases and it becomes clear that there will be a life beyond cancer, QoL becomes increasingly important.

All audiology referral clinics in this study described appropriate ototoxicity protocols that should be followed, but implementation remains a challenge, despite the presence of substantial evidence supporting the significance of early identification of ototoxic-induced hearing loss (Ganesan et al., 2018; HPCSA, 2018; Paken et al., 2020). Pure-tone audiometry, EHF audiometry and DPOAEs were cited as the most crucial tests, as suggested in ototoxicity monitoring guidelines (Ganesan et al., 2018; Landier, 2016;

Paken et al., 2020; Pearson et al., 2019). Although participants reported that vestibular problems may be caused by platinum-based chemotherapy, vestibular assessments are not typically included in monitoring protocols in both this study and internationally (Landier, 2016; Paken et al., 2020; Steffens et al., 2104). No widely accepted guidelines for vestibulotoxicity monitoring exist (Ganesan et al., 2018). The major challenge in vestibulotoxicity monitoring is the identification of these symptoms, which are apparent only when patients are mobilised and may often be incorrectly attributed to the patient's debilitated state. Vestibular diagnostic procedures are also often impractical due to the patient's compromised health status. Furthermore, due to the complex nature of the vestibular system, there is no single test that can identify vestibulotoxicity (Pearson et al., 2019).

Ototoxic testing was reported to continue for six to 12 months post-treatment, with some suggesting follow-up for a person's entire lifespan. Existing protocols suggest six months post-treatment, and annually for at least ten years (Landier, 2016; Pearson et al., 2019; Steffens et al., 2014). More than half of participants in this study indicated that patients were uninformed about the ototoxic effects of chemotherapy. Research suggests that oncologists and nurses should be the custodians for providing this information (Paken et al., 2020; Pearson et al., 2019). A multidisciplinary team and patient-centred approach to ototoxicity are essential, as effective communication between healthcare professionals and greater insight into information about adverse effects and monitoring are needed (Ganesan et al., 2018; Landier, 2016; Pearson et al., 2019). Monitoring outcomes are believed to influence dosage and treatment choices, to result in otoprotective agents being prescribed, and ensure follow-up appointments and frequent visits to the audiologist. This is in accordance with the purpose of ototoxicity monitoring protocols (Konrad-Martin et al., 2018; Landier, 2016; Maru & Malky, 2018; Pearson et al., 2019; Steffens et al., 2014).

The most prominent challenges reported by participants in this study were referral system, environmental noise, multidisciplinary teamwork, lack of equipment, staff availability and the often-compromised status of cancer patients (Konrad-Martin et al.,

2018). More than half of audiology referral clinics in this study were in favour of a novel approach to ototoxicity monitoring. Considering the challenges identified in ototoxicity monitoring, the integration of mobile health (mHealth) tools such as smartphone audiometry is a novel approach that could improve the effectiveness and efficiency of ototoxicity monitoring in cancer patients. mHealth tools have proved to be effective in primary healthcare settings (Sandström et al., 2016) and infectious disease clinics (Brittz et al., 2019), but applications specifically for ototoxicity monitoring in cancer patients require further investigation. An mHealth hearing screening application with automated test sequences, integrated noise monitoring, data capturing and data sharing (Sandström et al., 2016; Yousuf Hussein et al., 2016) makes asynchronous ototoxicity monitoring possible, which would minimise the effect on the already overburdened schedule of cancer patients, as monitoring can take place during in- or outpatient chemotherapy treatments.

3.6 Conclusion

There is significant discrepancy in the manner in which ototoxicity monitoring is conducted across South Africa in both the private and public sector, and the implementation of a national ototoxicity monitoring protocol may improve audiological outcomes for patients receiving ototoxic chemotherapy. HPCSA (2018) ototoxicity monitoring guidelines have been developed and should be used as a guide when implementing ototoxicity monitoring programmes.

Furthermore, effective scheduling and test location are key to a successful monitoring programme. Finally, the need to simplify ototoxic monitoring of hearing and vestibular function to reduce test time and make it less stressful and tiresome for the patient should be considered. Ototoxic monitoring programmes need to become standard of care for all patients receiving treatment with ototoxic medications. Although a multidisciplinary team approach is vital, audiologists must take the lead in implementing programmes that are thorough, efficient, and accurate; and based on patient-centred care. Audiologists need to be proactive and develop exceptional working relationships with the oncologists and nursing staff in the oncology units, ensuring that appropriate referrals are made for

ototoxicity monitoring. The inclusion of ototoxicity monitoring in the oncology treatment programme could also limit the overwhelming costs involved in oncology treatment.

A deeper understanding of how long-term toxicities such as hearing loss, tinnitus and vestibular dysfunction can affect QoL needs to be incorporated into clinical practice for audiology referral centres and oncology units. The risk of these long-term effects being overlooked could be reduced by raising awareness. Once cancer patients have been enrolled in ototoxicity monitoring, they should be guided through the treatment journey and be provided with pertinent and individualised support and intervention for hearing loss, tinnitus and vestibular dysfunction.

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CHAPTER 4

SURVEILLANCE FOR OTOTOXICITY IN PLATINUM-BASED CHEMOTHERAPY USING MHEALTH AUDIOMETRY WITH EXTENDED HIGH FREQUENCIES

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4.1 Abstract

Objective

This study investigated mHealth-enabled surveillance in ototoxicity.

Method

A longitudinal study of 32 participants receiving chemotherapy participated in the study. Baseline and exit audiograms that included conventional and extended high-frequency audiometry were recorded at the patients' treatment venue using a validated mHealth audiometer.

Results

Average hearing thresholds at baseline were in the normal range (81.2% left; 93.8% right) reducing at exit testing (71.9% left; 78.1% right). Fifty percent of the participants presented with a threshold shift according to ototoxicity monitoring criteria. Frequencies affected most were between 4000 and 16000 Hz, with left ears significantly ($p < 0.05$) more affected than right ears. Noise levels exceeded the maximum permissible ambient noise levels in up to 43.8% of low frequencies (250–1000 Hz).

Conclusion

mHealth-supported audiometry proved to be a valuable tool for ototoxicity monitoring at the treatment venue. Changes in hearing ability over time could be tracked, improving surveillance in patients with full treatment schedules.

Keywords: carboplatin; cisplatin; mHealth surveillance; monitoring; ototoxicity; oxaliplatin; platinum chemotherapy

4.2 Introduction

Cancer is known to be one of the most life-threatening illnesses in the world, resulting in about 19.3 million new cases and 10 million deaths in 2020. The overall number of individuals living within five years of a cancer diagnosis, called the five-year prevalence, is estimated to be 50.6 million worldwide.[1] Although cancer appears to be a life-altering diagnosis, there has been an overall decrease of 26% in cancer deaths in the last two decades due to medical advancements.[2] However, treatment outcomes can also lead to survivors having long-term physical and psychological issues.[3] For this reason, there is a need to assess how these long-term consequences affect the health-related quality of life (HRQOL) of those who are transitioning to a life with and beyond cancer.

Ototoxic medications typically used in chemotherapy can result in cochleotoxicity or vestibulotoxicity, or both.[4,5] Ototoxicity refers to any hearing deficit or tinnitus following treatment with an ototoxic drug resulting from acute or permanent inner-ear dysfunction. Platinum-based compounds (cisplatin, carboplatin and oxaliplatin) are used as single agents and in combination with other drugs for the treatment of various types of cancer (such as testicular carcinoma, lung carcinoma, ovarian carcinoma, head and neck carcinomas, melanomas, lymphomas and neuroblastomas).[6,7] The platinum-based drugs combine DNA and result in irreversible changes that prohibit tumour cell division. Common adverse effects of platinum-based drugs include nephrotoxicity and ototoxicity.[8] When ototoxins cross the blood-labyrinth barrier of the auditory system, the barrier breaks down and instantly causes loss of endolymphatic potential that leads to the demise of auditory hair cells in the cochlea.[4] Furthermore, genetic mutations that cause

mitochondrial pathologies are often associated with hearing loss and substances such as cisplatin are known to damage mitochondria,[8] which results in an elevation of sensory thresholds and eventually hearing loss.[4] Hearing changes are typically detected in the highest audible frequencies, progressing to lower frequencies with additional ototoxicity exposure. Consequently, cancer survivors often have difficulties understanding speech in noise.[9]

Unfortunately, ototoxic hearing loss may go unnoticed by patients until a communication problem becomes apparent, suggesting that hearing loss within the frequency range important for speech understanding has already occurred.[10] For patients with life-threatening illnesses that warrant treatment with ototoxic drugs, communication ability is a central QoL issue. These patients have important communication needs in terms of dealing with multiple healthcare professionals and family members during the course of cancer treatment.[11] Therefore, the early identification of ototoxic damage can improve treatment outcomes by minimising hearing loss progression and its associated impact on functioning in daily life.[4] Early identification and monitoring of ototoxicity also provide hearing care professionals with the opportunity to perform appropriate (re)habilitation during and after treatment.[10]

The only way to detect ototoxicity is by assessing auditory function directly.[4] For patients undergoing chemotherapy, the difficulties of introducing an ototoxicity monitoring protocol include fatigue, general acute illness, travel problems and priority issues.[10] Present ototoxicity testing recommendations include detailed test protocols conducted in a sound-treated room by an audiologist.[12] It is usually not feasible to move patients undergoing chemotherapy into a sound-treated room, due to their immunocompromised state and overburdened treatment schedule.[12] This contributes to the ineffectiveness of existing monitoring programmes.

Mobile solutions to test hearing on digital devices like smartphones have proved to be effective for hearing assessment outside conventional clinic environments and provide a low-cost alternative to conventional ototoxicity monitoring that requires the patient to

attend an audiology clinic.[13,14,15] These mHealth technologies are often also designed to be used by minimally trained persons, which could can further improve access to hearing care.[14,16] Automated pure-tone testing protocols using mHealth technologies with calibrated headphones demonstrate clinical hearing threshold assessments (at the conventional frequencies as well as extended high-frequency (EHF) audiometry) comparable to conventional testing with improved efficiency, noise monitoring and quality control.[17] Smartphone audiometry has also provided reliable results in an infectious disease clinic setting and can be used as a baseline and monitoring tool.[13] The use of mHealth tools connected to cloud-based data management systems enables the paperless tracking of patient data and potential threshold shifts.[13] The application allows for remote hearing testing where patient data and results can be uploaded onto centralised cloud-based servers for data management through cellular networks. Patients can also be linked to the closest audiologist for further management.[13]

As cancer patients face unique health problems and side effects throughout the course of platinum-based chemotherapy treatment, a flexible approach to ototoxicity monitoring is required. Hearing testing, particularly in a clinic or hospital setting, is required to overcome patient challenges and to implement a successful ototoxicity monitoring programme. The mobility, quality controls, use by healthcare workers and paperless surveillance in the cloud make mHealth-supported devices ideal for ototoxicity surveillance. Hearing testing during chemotherapy treatment in hospital wards and oncology clinics would relieve the already over-burdened treatment schedule of cancer patients. This study, therefore, investigated platinum-based chemotherapy ototoxicity surveillance using mHealth audiometry.

4.3 Method

Ethical clearance was obtained from the Research Ethics Committee of the Faculty of Health Sciences and Faculty of Humanities of the University of Pretoria on 11 January 2019 (665/2018).

4.3.1 Study design, setting and participants

A longitudinal study design was implemented. Inclusion criteria included all participants (aged >10 years) treated with platinum-based compounds (cisplatin, carboplatin and/or oxaliplatin) for the first time in private and public oncology units and hospitals. Testing was conducted during chemotherapy treatment in oncology clinics or at the hospital bedside. Thirty-two participants (64 ears) above the age of ten years (to ensure reliable behavioural testing) participated in the study, taking into account that repeated measures (baseline and exit testing) were performed for each participant.

4.3.2 Equipment

The *ototoxicity monitoring case history interview* [18,20] was used as a guideline during case history at baseline testing. The Heine Mini 3000 Otoscope was used to perform otoscopy prior to pure-tone testing.

The hearTest^{R} certified digital audiometer (IEC 60645-1, hearX Group, South Africa) was used for testing. The hearTest^{R} Extended High Frequencies (EHF) application was used on a Samsung A3 smartphone with the Android version 8.0 operating system (Google, Mountain View, United States of America). Supra-aural Sennheiser HDA 300 headphones (Sennheiser, Wedemark, Germany)[20] calibrated according to prescribed standards (International Organisation for Standardisation, ISO 389–1, 2017)[21], and adhering to the equivalent threshold sound pressure levels determined for this headphone were connected to the smartphone. Daily calibration listening checks of headphones were performed. The hearTest^{R} has been validated to monitor noise accurately using the smartphone microphone.[22] There was real-time monitoring of noise with the smartphone microphone to alert the user of environmental noise concerns during testing. The maximum permissible ambient noise levels (MPANLs) used for HDA300 headphones were 22.7, 19.4, 22.8, 25.1, 38.8 and 36.2 dB HL for 250, 500, 1000, 2000, 4000 and 8000 Hz respectively (Sennheiser, HDA300), for testing at the minimum response level (MRL) of 10 dB HL. Automated pre-programmed test sequences (250–16000 Hz) were used for improved efficiency, and the reliability of patient responses was monitored throughout (hearX Group, South Africa). Testing commenced and ended at 1000 Hz

frequency in each ear. Threshold concern was flagged at 1000 Hz when there was a difference of ≥ 10 dB indicating possible unreliable participant responses. To ensure quality control and test reliability a re-test was conducted in such cases (hearX Group, South Africa). Patient, test and facility data were consolidated instantly on a secure online database. Data collected by the smartphone were automatically uploaded to a secure cloud-based server as soon as it was connected to Wi-Fi. Access to the smartphone and cloud-based data was protected by a user password.

4.3.3 Data collection procedures

For this study, baseline testing included case history, otoscopy, and pure tone audiometry (conventional air conduction and EHF). Exit testing included otoscopy and pure-tone audiometry (conventional air conduction and EHF).

Testing was performed outside a sound-treated room in the oncology rooms during chemotherapy appointments or oncology visits as well as in hospital wards. Participants were tested prior to initiation of treatment or within 24 hours of treatment initiation (baseline testing). Post-treatment follow-up occurred at three to six months post-treatment (exit testing). Prior to baseline testing, participants were provided with simple instructions and a demonstration of the testing procedure. An automated hearTest^{R} protocol was employed for baseline and exit testing to determine participant thresholds. The shortened threshold ascending method was used in the automated protocol to obtain thresholds.[22]

The pure-tone average (PTA) was calculated as the better ear average for four frequencies of 500, 1000, 2000, and 4000 Hz. The WHO grades of hearing impairment were used to determine severity of hearing loss. A PTA of <25 dB HL indicates normal hearing, 26–40 dB HL slight hearing loss, 41–60 dB HL moderate hearing loss, 61–80 dB HL severe hearing loss, and >81 dB HL profound hearing loss.[23]

Ototoxicity criteria were regarded as significant when there were threshold shifts of 20 dB decrease or greater at one frequency, a 10 dB decrease or greater at two adjacent

frequencies and loss of response at three consecutive frequencies where there was a previously recorded response.[24] Participants with changes in hearing were advised to continue monitoring until hearing had stabilised and up to 12 months post-treatment.[25] All participants, even those without a significant shift in threshold, were advised to continue annual monitoring of hearing abilities.

4.3.4 Data analysis

Descriptive statistics (averages and standard deviation) were used to determine the decline in hearing thresholds from baseline to exit testing. The Shapiro-Wilk test[26] was used to test for normality and since the *p*-values were less than 0.05, the data differed from normality, and nonparametric tests were used. The correlation between the most common frequencies affected and duration between baseline and exit testing were determined. Within-subject statistical tests (Wilcoxon signed-rank (WSR) tests) were used to determine the statistical significance of the hearing threshold shifts from baseline to exit testing. This was only possible for participants where thresholds were obtained. No response thresholds were not useful in determining a shift from baseline to exit testing and were omitted. If the *p*-value was < 0.05, there was a statistically significant difference between baseline and exit. Non-parametric Spearman correlations were used to report on statistically significant (p-value < 0.05) correlations. Since males and females were independent groups, the Mann-Whitney (MW) test was used to determine whether males and females differed significantly (p-value < 0.05) in terms of incidence of ototoxicity.

4.4 Results

Table 4.1 describes the characteristics of participants, including gender, age, type of cancer, treatment and dosages received, time frame between baseline and exit testing, otoscopic results and hearing changes from baseline to exit testing according to ototoxicity monitoring criteria.

Table 4.1: Characteristics of participants (n=32)

Characteristics	
Gender	**n (%)**
Male	16 (50.0%)
Female	16 (50.0%)
Mean age (SD; IQR)	47 (16.7; 22)
Age range 11-70	**n (%)**
11-15 years	3 (9.4%)
25-29 years	3 (9.4%)
30-39 years	3 (9.4%)
41-49 years	7 (21.9%)
50-59 years	9 (28.1%)
61-69 years	4 (12.6%)
70-74 years	3 (9.4%)
Type of cancer (CA)	**n (%)**
Lymphoma	6 (18.8%)
CA Cervix	5 (15.6%)
CA Lung	4 (12.5%)
CA Breast	3 (9.4%)
CA Gastric	3 (9.4%)
CA Colon	3 (9.4%)
CA Oesophagus	2 (6.3%)
CA Breast and lymph	1 (3.1%)
CA Bladder	1 (3.1%)
CA Prostrate	1 (3.1%)
Seminoma	1 (3.1%)
Cholangiocarcinoma	1 (3.1%)
CA tongue	1 (3.1%)
Mean number of days between baseline and exit testing (SD; IQR)	217 days (105.8; 200)
Platinum-based chemotherapy compounds	**n (%)**
Cisplatin	14 (43.8%)
Carboplatin	14 (43.8%)
Oxaliplatin	9 (28.0%)
Of n=32, four were on combination treatments:	
Combination 1 (cisplatin and oxaliplatin)	3 (9.4%)
Combination 2 (cisplatin, carboplatin and oxaliplatin)	1 (3.1%)
Mean dosages of platinum-based compounds	
Cisplatin: Mean dose (SD)	507 mg (194.8)
Dosage range	200-825 mg
Carboplatin: Mean dose (SD)	212.4mg (1325)
Dosage range	169-4338 mg
Oxaliplatin: Mean dose (SD)	948.2 mg (438.8)
Dosage range	180-2040 mg
Otoscopic examination	**n (%)**
Normal outer and middle ear	29 (90.6%)
Cerumen impaction (treated prior to exit testing)	2 (6.2%)
Perforation	1 (3.1%)
Hearing change from baseline to exit testing	**n (%)**
20 dB decrease or greater at one frequency	10 (31.3%)
10 dB decrease or greater at two adjacent frequencies	15 (46.9%)
Loss of response at three consecutive frequencies where there was a previously recorded response	1 (3.1%)

IQR=inter-quartile range, n=number of participants, SD=standard deviation, CA=Cancer, mg=milligrams

Table 4.1 describes the characteristics of the participants (n=32). Case history at baseline testing yielded reports of noise exposure, pre-existing hearing loss and tinnitus. Tinnitus was reported by 34.4% (n=11) of participants prior to chemotherapy treatment and all these participants also reported an increase in tinnitus during the course of treatment. All participants (100%; n=32) reported an awareness of tinnitus during treatment, and 81.3% (n=26) reported tinnitus symptoms at exit testing.

Half the participants (50%; n=16) presented with a threshold shift according to ototoxicity criteria from baseline to exit testing. Table 4.2 summarises the outcomes for pure-tone audiometry at baseline and exit testing. Noise levels exceeded the MPANLs at the lower frequencies (250-1000 Hz). Test-retest checking at 1000 Hz for differences of 10 dB or greater indicated concerns in 17.2% (n=11 by 10 dB) at baseline testing and 10.9% (n=6 by 10 dB; n=1 by 15 dB) at exit testing in either left or right ears. Hearing thresholds demonstrated a decline from baseline to exit testing with a significant difference in PTA from baseline to exit testing in both the left and right ears (p=0.001). Males were more affected than females, but the differences were statistically insignificant. The mean PTA difference from baseline to exit testing in the left ears was 4.2 dB (SD=4.2, IQR=3.7) and 3.6 dB (SD=4.6, IQR=6.2) in the right ears.

Table 4.2: Description and outcomes of pure-tone testing for baseline and exit testing (n=32)

	Baseline testing	Exit testing	Statistical significance from baseline to exit testing
Mean threshold concern at 1000 Hz when difference ≥10 dB			-
Left ears	18.8%	9.4%	
Right ears	15.6%	12.5%	
Either left or right ears (n=64)	17.2%	10.9%	
Frequencies that exceeded MPANLs (n=64)			
Left and right ears (%)			
250 Hz	40.6%	43.8%	-
500 Hz	26.6%	28.1%	
1000 Hz	39.1%	0.0%	
10000 Hz	1.6%	1.6%	
12500 Hz	1.6%	0.0%	
Mean levels by which the MPANLs exceeded the thresholds			
Left ears (SD)			-
250 Hz	6.8 (4.2)	7.4 (4.3)	
500 Hz	6.0 (5.7)	4.5 (2.6)	
1000 Hz	3.8 (1.9)	3.1 (2.3)	
10000 Hz	9.0 (0.0)**	6.0 (2.4)	
12500 Hz	3.0 (0.0)**	0.0 (0.0)**	
Right ears (SD)			-
250 Hz	6.3 (3.6)	7.8 (5.2)	
500 Hz	4.6 (2.6)	5.7 (7.5)	
1000 Hz	5.5 (3.6)	4.0 (4.3)	
Mean PTA (SD; IQR)			
Left ears	17.8 (7.8; 10.8)	21.5 (6.9; 11.0)	0.001*
Right ears	18.5 (11.1; 7.3)	22.1 (12.4; 9.6)	
Degrees of hearing loss			
Left ears			
• *Normal*	81.2%	71.9%	-
• *Mild*	18.8%	28.1%	
Right ears			
• *Normal*	93.8%	78.7%	-
• *Mild*	3.1%	18.8%	
• *Severe*	3.1%	3.1%	

SD=standard deviation, IQR=interquartile range, Hz=Hertz, dB=decibels
Mean threshold concern at 1000 Hz when difference ≥10 dB indicating possible unreliable responses from participants
MPANLs: Maximum permissible ambient noise levels
The average of 500, 1000, 2000 and 4000 Hz was used to calculate the pure tone average (PTA).
*A p-value < 0.05 was used to indicate if there was a statistically significant difference between baseline and exit testing. *: statistically significant difference from baseline to exit testing.*
***: Standard deviation cannot be computed for one observation.*

Figure 4.1 illustrates the mean thresholds per frequency for baseline and exit audiometry. Significant deterioration was observed at 250 Hz (p=0.003), 500 Hz (p=0.001), 1000 Hz

(p<0.001), 2000 (p=0.024), 4000 Hz (p=0.011) in left ears and 500 Hz (p=0.031) and 1000 Hz (p=0.001) in right ears from baseline to exit testing. Although not always showing a significant shift due to the prevalence of high frequency hearing loss at baseline testing, the most affected frequencies according to ototoxicity monitoring criteria were in the high frequencies from 4000 to 16000 Hz, emphasising the importance of including EHF in ototoxicity surveliillance protocols.

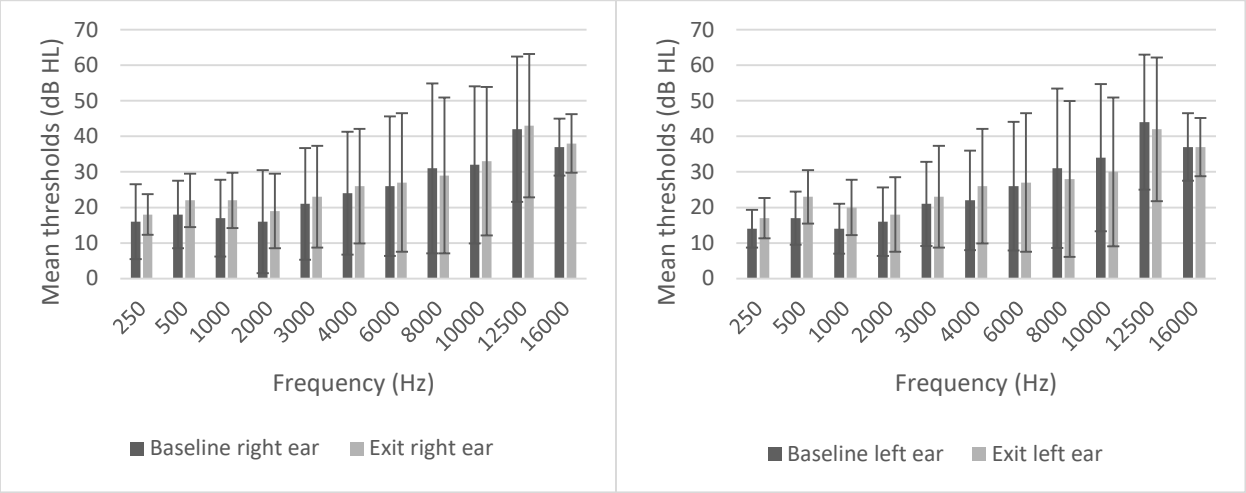

Figure 4.1: Mean frequency-specific thresholds for baseline and exit testing and error bars (standard deviation) showing difference between baseline and exit testing

Table 4.3 demonstrates the most substantial shifts from baseline to exit testing in cisplatin and carboplatin treatment cases.

Table 4.3: Mean PTA differences from baseline to exit testing for specific platinum-based compounds

Treatment and n	Baseline testing	Exit testing
Carboplatin (n=13)		
Mean PTA (dB HL) (SD, IQR)		
Left ears	18.5 (8.7; 15.5)	24.0 (7.3; 11.5)
Right ears	21.6 (16.4; 11.3)	27.2 (16.8; 7.4)
Cisplatin (n=10)		
Mean PTA (dB HL) (SD, IQR)		
Left ears	16.0 (6.9; 3.98)	18.5 (2.99; 5.9)
Right ears	15.6 (3.97; 5.3)	17.95 (4.7; 7.4)
Oxaliplatin (n=5)		
Mean PTA (dB HL) (SD, IQR)		
Left ears	18.2 (9.7; 16.3)	23.3 (9.8; 15.0)
Right ears	18.9 (5.8; 9.6)	19.7 (7.2; 11.7)

Participants (n=4) on combined treatments were excluded.
SD=standard deviation, IQR=interquartile range, PTA=pure tone average, dB HL=decibels hearing level

4.4 Discussion

As long as the best evidence-based practice for the treatment of certain cancers includes treatment with platinum-based compounds, ototoxic hearing loss will need to be considered as a likely side-effect.[4,27] For cancer patients, hearing monitoring should be performed in the patient's treatment venue.[28] The mHealth-supported device used in the current study has proved to successfully provide ototoxicity monitoring in the patient's treatment venue. Mobile audiometry applications with automated test sequences, integrated noise monitoring, data capturing and data sharing make asynchronous ototoxicity monitoring possible, and can be facilitated onsite by minimally trained persons.[13] This could minimise the impact on the already full treatment schedule of cancer patients as monitoring can take place during in- or outpatient chemotherapy treatments. This could also address the issue of neglecting to follow up, as the prolonged effect of chemotherapy on hearing requires long-term monitoring.

Half (50.0%) of the participants in the current study presented with a significant hearing threshold shift from baseline to exit testing. Studies have reported that, on average, 60% to 70% of adults treated with cisplatin present with ototoxicity[29], 20% of patients treated with carboplatin present with ototoxicity, and that ototoxicity from oxaliplatin is typically rare.[25] Using an mHealth audiometry application supported the ototoxicity monitoring conducted at baseline and exit testing within multiple oncology units and hospital wards.

Hearing testing was possible without cancer patients being required to attend audiology clinics.

EHF frequency testing was included for surveillance purposes using the mHealth audiometry application. The current study found that 4000 to 16000 Hz showed the largest average threshold shifts from baseline to exit testing according to ototoxicity monitoring criteria. EHF allows for early identification of hearing disorders before changes are seen in conventional pure-tone audiometry, and, subsequently, before speech understanding is compromised.[30] The EHF mHealth audiometry used in this study tested up to 16000 Hz at a maximum output of 40-60 dB HL.[25,28,31] A study by Singh et al.[31] demonstrated that hearing loss was much more common in the 10000 to 20000 Hz range (70.1%) than in the 250 to 8000 Hz range (29.9%) in patients receiving potentially ototoxic drugs (gentamicin, amikacin or cisplatin). In the current study, EHF hearing loss prevalence from baseline to exit testing was 71.4% for cisplatin cases compared to 28.6% in the conventional test frequency range. Using EHF for ototoxicity monitoring requires better baseline hearing (that is, responses within the normal range at EHF) in order to track ototoxicity exposure hearing changes. Although statistically significant ($p < 0.05$) changes from baseline to exit testing were not evident in this study for EHF, threshold shifts up to 4.9 dB according to ototoxicity threshold shift criteria were evident. This small threshold shift and lack of significance may be due to EHF thresholds that were affected (threshold at maximum EHF intensity for the device) at baseline testing for 59.0% of ears tested in this study. Singh et al.[31] found that most of the patients in the age range of 51 to 70 years, showed no response at the EHF, both before and after drug exposure, likely due to presbycusis. Half (50.0%) of participants in this study were above 50 years of age, and present with high-frequency hearing loss at baseline testing. This highlights a limitation of EHF testing with thresholds often absent, especially in older persons, which makes it unsuitable for monitoring purposes in this age group. Cancer patients on platinum-based compounds are often in older age groups[33] and the validity and reliability of measurements involved in hearing evaluations must be considered in effective monitoring programmes.

Frequencies that demonstrated a significant ($p < 0.05$) decline from baseline to exit testing were 250, 500, 1000, 2000 and 4000 Hz in left ears and 500 and 1000 Hz in right ears from baseline to exit testing. Surprisingly, the low frequencies in the current study showed that there was a significant difference from baseline to exit testing. Noise levels also affected the lower frequencies, which could have resulted in the significant differences from baseline to exit testing.

On average, a significant average deterioration of PTA from baseline to exit was evident in this study across left and right ears. Additionally, the frequency specific deterioration of the left ears (4.2dB) was significantly greater compared to the right ears (3.6dB). A study examining the role of EHF in ototoxicity monitoring among the 45 patients affected by ototoxicity also observed that hearing loss was unilateral in 31.1% (n=14) before bilateral hearing loss had been reported.[31] Hypothetical explanations for unilateral involvement in ototoxicity include the fact that asymmetry and the genetic difference of bilateral organs are well-known; therefore, a correlation of a genotype with unilateral ototoxicity is possible. It is assumed that two molecular mechanisms with different speeds may cause ototoxicity. Due to the asymmetry of organs and expression of enzymes, the slow toxicity becomes unilateral first and then bilateral. Another theory may be related to the unilateral noise–induced effect during treatment, as the ears are more susceptible to extreme noise during treatment. This sensitivity may also be related to some gene variants.[32] When shifts are observed in one ear, it therefore provides the opportunity to adjust the patient's drug regimen to prevent or limit progression to the other ear.[31]

Most participants in the current study had normal hearing (according to conventional PTA) at baseline testing, and degrees of hearing remained the same at exit testing. The frequencies showing the largest average threshold shift in this study were 2000, 3000, 4000 and 6000 Hz. Although not significantly different from baseline to exit testing per individual frequency, there was a significant decline of PTA in both ears. Platinum-induced hearing loss reportedly initially affects the higher frequencies (≥4000 Hz).[25] Therefore, a shift in hearing threshold is not always evident using the conventional PTA (average of 5000, 1000, 2000 and 4000 Hz). Consequently, mHealth-supported devices

should include calculations of high-frequency pure-tone average (HFPTA) (average of 2000, 4000 and 6000 Hz) and potentially extended high-frequency pure-tone average (EHFPTA) (average of 10000, 12000, 14000, and 16000 Hz) in cases where baseline EHF thresholds could be obtained.[34]

The mHealth audiometry application monitored environmental noise during threshold testing since testing was performed outside a sound-treated environment.[13] Frequencies that exceeded MPANLs were in the lower frequencies in this study. This may be attributed to testing outside a sound-treated room and the effect of environmental noise. Noise concerns were predominantly noted in this study at 250, 500 and 1000 Hz. The mean levels by which the MPANLs exceeded the thresholds was 3.0–7.8 dB, which emphasises that MPANLs were exceeded by a small margin on average. Considering the convenience, and often the only option for ototoxicity surveillance to take place at the cancer patient's treatment venue, the possible noise interference at the lower frequencies highlights the need to focus on the high frequencies to detect threshold shifts in these settings. As the most sensitive frequencies for ototoxicity are in the in high frequencies,[4] it could mitigate concerns of noise levels affecting the results when testing during chemotherapy in- and outpatient appointments as an early detection measure. Longer duration of platinum-based treatment also eventually affects the middle and lower frequencies, so this should be kept in mind when using an ototoxicity monitoring protocol that only focuses on the higher frequencies.[4,27] It also highlights the value of having real-time monitoring of allowable noise levels during audiometry testing as flexible approaches to testing can be applied when required.

Limitations of the current study include the exclusion of control conditions in a sound-treated room, due to the challenging immunocompromised nature of cancer patients. Additionally, no external sound-level measurements apart from the smartphone monitoring included in the mHealth application were employed to monitor environmental noise.

In conclusion, the current study demonstrated the usefulness of using mHealth audiometry including EHF in ototoxicity surveillance for cancer patients receiving platinum-based chemotherapy, although EHF proved to be of limited value in older individuals above 50-years. Changes in hearing ability over time could be tracked by employing baseline and exit testing. Shortened monitoring protocols focusing on high frequencies and EHF may be more efficient, and mitigate the possibility of noise interference in the lower frequencies during testing. Monitoring of hearing sensitivity can take place at chemotherapy in- and outpatient treatment venues without adding to the patient's already over-burdened treatment schedule.

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Competing interests

The authors Ehlert K, Heinze B and Graham ME have declared that no competing interest exists. The author Swanepoel DW has equity interest, consultancy and potential royalties in the *hearX Group*.

Ethical considerations

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation (Research Ethics Committee of the Faculty of Health Sciences and Faculty of Humanities of the University of Pretoria on 11 January 2019 (665/2018)) and with the Helsinki Declaration of 1975, as revised in 2008.

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CHAPTER 5

CHANGES IN VESTIBULAR AND COCHLEAR FUNCTION FOLLOWING PLATINUM-BASED CHEMOTHERAPY

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5.1 Abstract

Background

Vestibulotoxicity monitoring is rarely conducted in cancer patients receiving chemotherapy.

Objectives

This study investigated the vestibular and cochlear function in patients receiving chemotherapy.

Methods

A longitudinal study of 32 participants was conducted. Baseline and exit assessments that included video head impulse (VHIT) testing, cervical and ocular vestibular evoked myogenic potentials (VEMP), dynamic visual acuity (DVA) and pure-tone audiometry were performed at the patient's treatment venue.

Results

Half (50%) of the participants showed cochleotoxicity from baseline to exit testing, with left ears significantly more affected than right ears. There was no consistent relationship between hearing loss and vestibular dysfunction. DVA yielded normal results at baseline and exit testing in all participants. VEMP responses were absent in 28.1% of participants at baseline, reflecting the possible challenges of using VEMP for vestibulotoxicity monitoring. VEMP and VHIT results showed a statistically significant ($p < 0.05$) decline in results from baseline to exit testing; however, participants did not report symptoms related to vestibular dysfunction. VHIT showed left ears significantly ($p < 0.05$) more affected than right ears.

Conclusions

VHIT proved to be a valuable measure of changes in vestibular function secondary to ototoxicity. Vestibulotoxicity criteria and optimal protocols for monitoring vestibular function during chemotherapy treatment at the patient's treatment venue is needed.

Keywords: cochleotoxicity; monitoring; ototoxicity; platinum-based chemotherapy; vestibular dysfunction; vestibulotoxicity

5.2 Introduction

Cancer is considered one of the world's leading fatal diseases, with nearly 19.3 million new cases and 10 million deaths in 2020. It is estimated that the total number of people living within five years of a cancer diagnosis, called the five-year prevalence, is 50.6 million globally [1]. While cancer seems to be a life-altering disease, in the last two decades there has been an overall decrease (26%) in cancer deaths thanks to medical advances [2]. However, recovery results may also result in long-term physical and psychological complications for survivors [3]. More focus is therefore placed on long-term effects, health-related quality of life (HRQoL), and follow-up care after cancer treatment as a result of these improved survival rates [3].

Platinum-based chemotherapy is a key antineoplastic intervention used for a variety of human cancers, including testicular, ovarian, bladder, head and neck, and non-small cell lung cancer [3]. Ototoxicity refers to medication-induced auditory and/or vestibular system dysfunction that results in hearing loss or disequilibrium [4]. Furthermore, ototoxicity is a well-known adverse effect following platinum-based chemotherapy (especially cisplatin), which causes variable-degree permanent irreversible hearing loss in 40–80% of patients [5]. As signs of ototoxicity are poorly correlated with drug dosage, peak serum levels, and other toxicities, the only way to detect ototoxicity is by assessing auditory and vestibular function directly [3].

Since the inner ear's auditory and vestibular organs share the same blood, nerve and fluid sources, ototoxicity is possible in both the hearing and vestibular systems [4]. Yet, there are some variations in physiologic function between the cochlear and vestibular end organs, which may affect the extent of ototoxicity. A major physiological difference between the cochlear and vestibular systems is the endolymphatic potential [4]. The vestibular system demands lower endolymphatic potentials for its proper function compared to the high endolymphatic potential in the cochlea. Morphological vestibular damage was not found at early stages in ototoxicity, which suggests that functional vestibular impairment may not be associated with sensory hair cell damage, but rather with other biochemical factors such as electrolyte or electro-potential disturbances [3]. Therefore, considering this shared anatomy and physiology of the inner-ear structures, ototoxicity is not limited to alterations in cochlear functioning [3].

The monitoring of cochleotoxicity in platinum-based chemotherapy is well established; however, there are no universally accepted guidelines for vestibulotoxicity monitoring and it is rarely conducted in patients who are critically ill [3,4,6]. Furthermore, present ototoxicity testing recommendations include detailed test protocols [7]. The biggest challenge in monitoring vestibulotoxicity is the detection of symptoms that are only visible when patients are mobilised, which can also be falsely attributed to the patient’s weakened state [7]. By the time a patient complains of imbalance or dizziness, permanent vestibular system damage has more than likely already occurred. For patients undergoing

chemotherapy, the difficulties of introducing an ototoxicity monitoring protocol include fatigue, general acute illness, travel problems and priority issues [7]. Limited research has been published about the potential effects of cisplatin on the vestibular system. Furthermore, there is a large variability (0–50%) in the rates of vestibulotoxicity reported by objective tests following treatment with platinum-based chemotherapy [3]. Other limitations of published studies are small sample sizes, various methods of vestibular evaluation and criteria to determine abnormalities in the vestibular system, and outdated studies.

Since there is no single test that can identify vestibulotoxicity, tests for screening, such as dynamic visual acuity (DVA), dizziness handicap inventory (DHI) and head impulse tests are recommended to monitor patients. In addition, diagnostic vestibular procedures are also often impractical due to the compromised health status of the patient [3,7,8]. Vestibular symptoms reported by patients are often underappreciated due to the underlying cancer diagnosis and adverse effects of treatment, such as dehydration, nausea and vomiting, persistent weakness, anaemia and hypotension [3], which can be due to nonspecific symptoms of imbalance. In addition, vestibulotoxicity is typically symmetrical and progressively affects both ears, resulting in insidious imbalance, postural imbalance and oscillopsia, which are less likely to undergo clinical evaluation [8]. Additionally, due to the slow progressive nature of vestibulotoxicity, vestibular dysfunction may be hidden by central compensation, obscuring peripheral vestibular pathology [9]. Lastly, platinum-based chemotherapy agents are often prescribed with other potentially ototoxic drugs and the effect of platinum-based chemotherapy can be obscured [4].

It is important to identify the presence, severity and nature of vestibular signs in patients on chemotherapy treatment so that healthcare providers can be alerted early, to mitigate debilitating vestibular symptoms affecting the patient’s HRQoL and potential earning ability after remission [3,10]. Balance concerns such as falls and impairment in mobility are more dominant in cancer survivors than in the general population. This is of importance because falling is a leading cause of injury and death in the community [11].

Early identification and monitoring of vestibulotoxicity provide audiologists with the opportunity to perform appropriate rehabilitation during and after treatment [4].

Vestibulotoxicity confirmed by objective vestibular assessments has been associated with cochleotoxicity (either hearing impairment or tinnitus) [3]. There is some evidence of vestibulotoxicity associated with platinum-based chemotherapy, especially cisplatin, but this is not always validated with patient-reported symptoms [3]. Objective tests such as the video head impulse test (VHIT) provide quick and objective measurements of the vestibular-ocular reflex (VOR) and efficiently assess the dizzy patient to determine if the dizziness is related to a vestibular disorder [12]. A recent study based on patient self-reported symptoms revealed that vestibular signs after cisplatin treatment occurred in 17% (n=65) of adult cancer survivors [13]. Patients with peripheral neuropathy were more likely to have vestibular dysfunction. No vestibular dysfunction was detected with the VHIT (testing all semicircular canals) in cancer survivors after cisplatin therapy; however, benign paroxysmal positional vertigo (BPPV) was relatively prevalent in this group of patients [13]. On the contrary, a study by Hulse et al. [8] found that VHIT showed a significantly reduced median gain six weeks after chemoradiation and significantly more refixational saccades could be detected after therapy. A study in paediatric cancer patients revealed bilateral vestibular hypofunction (25%) following the VHIT [3].

Vestibular-evoked myogenic potentials (VEMP) assess otolith and vestibular nerve function with air conduction cervical VEMP (cVEMP) and ocular VEMP (oVEMP) [14]. VEMP amplitudes were significantly decreased after cisplatin exposure in an animal-related study [14]. Another study revealed that no consistent trend could be found amongst VEMP responses or hearing loss in patients undergoing cisplatin-based chemoradiation. Both cVEMP and oVEMP results showed extended latencies at follow-up testing; however, these were not statistically significant [8]. Dynamic visual acuity (DVA) assesses the vestibulo-ocular reflex (VOR), which is most helpful for diagnosing ototoxicity and other bilateral vestibular pathologies. DVA as a vestibular screening test showed abnormal results (28%) in paediatric head and neck cancer patients receiving platinum-based chemotherapy [15].

Evidence of clinically significant vestibular dysfunction after platinum-based chemotherapy is still not clear [13]. There is also a lack of guidelines for a vestibular assessment protocol that is appropriate to detect vestibulotoxicity in a manner that is sensitive to the over-burdened treatment schedule of cancer patients. This study investigated the changes in vestibular and cochlear function in patients receiving platinum-based chemotherapy using VHIT, VEMP and DVA testing along with pure-tone audiometry.

5.3 Materials and methods

Ethical clearance was obtained from the Research Ethics Committee of the Faculty of Health Sciences and Faculty of Humanities of the University of Pretoria on 11 January 2019 (665/2018).

5.3.1 Study design, setting and participants

A longitudinal study design was implemented. Inclusion criteria included all consenting participants (aged >10 years) treated with platinum-based compounds (cisplatin, carboplatin and/or oxaliplatin) for the first time in private and public oncology units and hospitals. Testing was conducted during chemotherapy treatment in oncology clinics or at the hospital bedside. Thirty-two participants above the age of 10 years participated in the study, taking into account that repeated measures (baseline and exit testing) were performed for each participant. Testing was performed in the oncology rooms during chemotherapy appointments or oncology visits, as well as in hospital wards. Participants were tested prior to initiation of treatment or within 24 hours of treatment initiation (baseline testing). Post-treatment follow-up occurred at three to six months post treatment (exit testing).

5.3.2 Equipment

Hearing testing was performed with the hearTest^{R} certified digital audiometer (IEC 60645-1, hearX Group, South Africa) for baseline and exit testing. Supra-aural Sennheiser HDA 300 headphones (Sennheiser, Wedemark, Germany) calibrated according to prescribed

standards (International Organisation for Standardisation, ISO 389–1, 2017), and adhering to equivalent threshold sound pressure levels determined for this headphone were connected to the smartphone. Automated protocols were used to obtain hearing thresholds and monitor cochleotoxicity.

Vestibular assessment included VHIT, VEMP and bedside DVA. The ICS impulse VHIT device (GN-Otometrics, Denmark) and ICS impulse video goggles (GN Otometrics, Taastrup, Denmark) with a camera speed of 250 frames per second, recording motion of the right eye, was used to assess semi-circular canal function. The SOCRATES Clinical Auditory Evoked Potentials (Hedera Biomedics, Italy) was used to obtain cVEMP and oVEMP measurements. SOCRATES is a computer-based medical device that can detect auditory evoked potentials by using two independent channels. A Snellen eye chart was used for bedside DVA.

5.3.3 Data-collection procedures

The *ototoxicity monitoring case history interview* [16] was used as a guideline during case history at baseline testing. The case history included questions regarding any history of hearing loss, auditory-related symptoms, previous vestibular insults or symptoms and timing of such events. Patients were also requested to report on vestibular symptoms experienced throughout the chemotherapy treatment. Testing was performed in the oncology rooms during chemotherapy appointments or oncology visits. Participants were tested prior to initiation of treatment or within 24 hours of treatment initiation (baseline testing). Post-treatment follow-up occurred at three to six months post treatment (exit testing). All assessments were completed at a single assessment. Participants with changes in vestibular function and hearing were advised to continue monitoring until vestibular function and hearing stabilised up to 12 months post treatment [12]. All participants, even those without a significant deterioration in vestibular and hearing function, were advised to continue annual monitoring of hearing and vestibular function.

In addition to the objective vestibular tests, viz. VHIT (to measure semicircular canal function) and VEMP (to measure otolith function), DVA was included to assess the

functional VOR, which is often compromised in those with bilateral vestibular loss [15]. Pure-tone audiometry was performed using an mHealth supported device.

Pure-tone audiometry

Prior to baseline testing, participants were provided with simple instructions and a demonstration of the testing procedure. An automated protocol was employed for baseline and exit audiometry (hearTest^{R}) to determine participant thresholds. Participants were expected to indicate when they heard the tone by pressing a button on the smartphone. The shortened threshold ascending method was used in the automated protocol to obtain thresholds [17].

The pure-tone average (PTA) was calculated as the better ear average for four frequencies of 500, 1000, 2000, and 4000 Hz. The WHO grades of hearing impairment were used to determine severity of hearing loss. A PTA of <25 dB indicates normal hearing, 26–40 dB HL slight hearing loss, 41–60 dB HL moderate hearing loss, 61–80 dB HL severe hearing loss and >81dB profound hearing loss [18].

Ototoxicity monitoring criteria were regarded as significant when there were threshold shifts of 20 dB decrease or greater at one frequency, a 10 dB decrease or greater at two adjacent frequencies, and loss of response at three consecutive frequencies where there was a previously recorded response [19].

Video head impulse test (VHIT)

Participants were tested in a well-lit room with an eye-level target at a distance of 1 m in front of them while seated in a chair. Spectacles were removed for this assessment. VHIT goggles were tightened on the head until movement of the goggles at the bridge of the nose was minimal to avoid goggle slippage [12].

Calibration of the eye position signal was performed with the subject successively fixating on two projected laser dots separated by a known horizontal angle. For each of the canal

planes, the researcher aimed to deliver a range of velocities in random order and direction so as to achieve at least 10 artefact-free impulses in each of the following ranges: horizontal: 10 <120°/s, 10 in the range 120–180°/s, and 10 over 180°/s in each direction. For vertical impulses, the ranges were: 10 <110°/s; 10 between 110° and 140°/s; 10 >140°/s [12].

For the horizontal VHIT stimulus, the researcher delivered small, passive, abrupt horizontal head rotations, with an unpredictable direction and magnitude. All tests were performed by the same right-handed researcher. Horizontal tests were performed with both hands on the top of the head, well away from the goggles strap and forehead skin [12].

Vertical VHIT included left anterior, right posterior (LARP) and right anterior, left posterior (RALP) semi-circular canals. For LARP, the participant's head was rotated 30°–40° to the right of the fixation point. The participant was instructed to keep fixating on the target on the wall. Thereafter, a diagonal head pitch forward (toward the fixation target) activated the left anterior canal and caused an upward eye movement, and a head pitch back (away from the fixation target) activated the right posterior canal and caused a downward eye movement. Similarly, the RALP was performed with the participant's head turned 30°–40° to the left of the target, while still fixating on the target. A head pitch forward activated the right anterior canal, and a head pitch back activated the left posterior canal [12]. The entire VHIT took 10–15 minutes to complete.

Test results were interpreted as abnormal if i) the VOR gain value <0.8 for lateral canals and <0.7 for vertical canals or ii) if overt (saccades after the head movement) or covert (saccades during the head movement) catch-up saccades were present [12].

Vestibular evoked myogenic potentials (VEMP)

Participants were seated on a standard chair for both cVEMP and oVEMP testing. Ipsilateral electromyography recordings were performed for cVEMP testing. The participants had to obtain sufficient tonicity of the sternocleidomastoid (SCM) muscle with

minimum discomfort in order for the cVEMP to be recorded [20]. The participants turned their head contralateral to the side of stimulation and neck flexion of the SCM muscle was achieved while being instructed to gaze at a target point in order to generate cVEMP with the most robust amplitudes and without premature fatigability [20]. An electromyography (EMG) monitor was used to ensure consistent and sufficient muscle contraction. Disposable wet-gel electrodes were used for recording after mild scrubbing of the electrode sites. The active (inverting) electrode was positioned on the ipsilateral mid-portion of the SCM muscle of the test ear, the reference (non-inverting) electrode was placed on the sternum, and the ground electrode was positioned on the forehead [20]. Impedances were kept below 5 kΩ. The stimulus was presented using insert earphones and an air-conduction tone burst stimulus of 500 Hz was presented at an intensity of 97 dB nHL using alternating polarity. A 2-ms rise/fall time and plateau time was used with band pass filters ranging from 10 to 1000 Hz at a repetition rate of 5.1 per second. One hundred sweeps were averaged for each cVEMP test. For the cVEMP waveform interpretation, the first positive peak on the waveform was marked as P1 and the first negative deflection was marked as N1. Normal P1 latency was ≤19 ms and for N1, ≤28 ms was considered normal [20]. The inter-peak (peak-to-peak) amplitude was the sum of the amplitudes of the repeated cVEMP responses.

Regarding oVEMP testing, electromyography recordings from the extra-ocular muscles in the infra-orbital region are recorded while the stimulus is presented in the contralateral test ear. An upward gaze during the stimulation and recording of oVEMP is required. Participants were asked to maintain their gaze on a stationary target on the ceiling. The active (inverting) electrode was positioned under the opposite eye on the inferior oblique muscle from the test ear. The reference (non-inverting) electrode was placed on the nose bridge, and the ground electrode was positioned on the forehead [20]. A 1-ms rise/fall time and 2-ms plateau time with band pass filters ranging from 2 to 500 Hz. One-hundred and fifty sweeps were averaged for each oVEMP test. For the oVEMP waveform interpretation, the first negative deflection was marked as N1 and the first positive peak was marked as P1 [20]. Normal latencies for N1 were ≤11.1, and a latency of ≤17.6 ms

was considered normal for P1. The interpeak amplitude was the sum of the amplitudes of the repeated oVEMP responses [20].

The VEMP asymmetry ratio (AR) was calculated using the Jongkees formula: (AR): [(AL - AS) / (AL+ AS)] x 100, where “AL” represents the larger P1-N1 amplitude and “AS” the smaller P1-N1 amplitude. In order to confirm the presence of VEMP responses, the responses and the peaks had to be repeated within the correct latencies to test for wave reproducibility and to disregard potential artefacts. The VEMP responses were interpreted according to the following parameters: (i) classified as normal in the presence of identifiable P1 and N1 waveforms; (ii) the presence of identifiable P1 and N1 waveforms and latencies above the upper limits of the waveform were considered present yet delayed, and recorded as abnormal; (iii) the presence of an AR of ≥40% was considered abnormal, as it confirms amplitude differences between the ears and (iii) absent VEMPS could not be interpreted and were not useful for ototoxicity monitoring [20].

Bedside dynamic visual acuity (DVA)

The participant was seated approximately 3 m from a Snellen eye chart, which was placed at eye level. Eyeglasses were permitted during this test. To determine static visual acuity, the participant was asked to read the smallest line, while reading all of the letters correctly. After verifying and recording the line of static visual acuity, the examiner stood behind the participant and rotated his/her head side to side at a speed of 2 Hz to effectively elicit a VOR response. A metronome was used to ensure that the appropriate speed was maintained throughout. To determine the DVA, the participant was again asked to read the smallest line possible in which all of the letters were read correctly, while his/her head was moving. A decline of more than two lines from static head recordings was considered abnormal [15].

5.3.4 Data analysis

SPSS was used for all data analysis (IBM SPSS Statistics 27) except for the achieved power where G*Power version 3.1.9.4 was used. Descriptive statistics (averages and

standard deviation) were used to determine the decline in vestibular function from baseline to exit testing. The Shapiro-Wilk test was used to test for normality, and since the *p*-values were less than 0.05, the data differed significantly from normality, and non-parametric tests were used. A within-subject statistical test (Wilcoxon signed-rank (WSR)) was used to determine whether there were statistically significant differences in the vestibular function from baseline to exit testing. If the *p*-value is < 0.05, then there is a statistically significant difference between baseline and exit. Non-parametric Spearman correlations were used to report on statistically significant (*p*-value < 0.05) correlations. The achieved power for a level of significance of 0.05, and sample size of 32 and an effect size of 0.573 (calculated from the data), equal 0.973. In order to show an association between cochleotoxicity and vestibulotoxicity, correlations were used between VEMP and VHIT responses and average hearing thresholds. If the $p > 0.05$, then there was no significant correlation. On the other hand, if the $p < 0.05$, the correlation was significant and could be interpreted. A positive correlation was used to conclude that as cochleotoxicity increases, so does vestibulotoxicity.

5.4 Results

The characteristics of participants with regards to gender, age, type of cancer and treatment received as well as time frame between baseline and exit testing is described in table 5.1.

Table 5.1: Characteristics of participants (n=32)

Characteristics	
Gender	**n (%)**
Male	16 (50.0%)
Female	16 (50.0%)
Mean age (Median, SD; IQR)	47 (49.5; 16.7; 22)
Age range: 11-70	**n (%)**
11-15 years	3 (9.4%)
25-29 years	3 (9.4%)
30-39 years	3 (9.4%)
41-49 years	7 (21.9%)
50-59 years	9 (28.1%)
61-69 years	4 (12.6%)
70-74 years	3 (9.4%)
Type of cancer (CA)	**n (%)**
Lymphoma	6 (18.8%)
CA Cervix	5 (15.6%)
CA Lung	4 (12.5%)
CA Breast	3 (9.4%)
CA Gastric	3 (9.4%)
CA Colon	3 (9.4%)
CA Oesophagus	2 (6.3%)
CA Breast and lymph	1 (3.1%)
CA Bladder	1 (3.1%)
CA Prostrate	1 (3.1%)
Seminoma	1 (3.1%)
Cholangiocarcinoma	1 (3.1%)
CA tongue	1 (3.1%)
Mean number of days between baseline and exit testing (SD; IQR)	217 days (105.8; 200)
Platinum-based chemotherapy compounds	**n (%)**
Cisplatin	11 (34.4%)
Carboplatin	12 (37.5%)
Oxaliplatin	5 (15.6%)
From n=32, 4 were on combination treatments:	
Combination 1 (cisplatin and oxaliplatin)	3 (9.4%)
Combination 2 (cisplatin, carboplatin and oxaliplatin)	1 (3.1%)
Mean dosages of platinum-based compounds	
Cisplatin: Mean dose (SD)	507 mg (194.8)
Dosage range	200-825 mg
Carboplatin: Mean dose (SD)	212.4 mg (1325)
Dosage range	169-4338 mg
Oxaliplatin: Mean dose (SD)	948.2 mg (438.8)
Dosage range	180-2040 mg

IQR=inter-quartile range, n= number of participants, SD=standard deviation, mg=milligrams
The average of 500, 1000, 2000 and 4000 Hz was used to calculate the pure-tone average (PTA).

Case history at baseline testing included self-reported tinnitus by 34.4% (n=11) of participants prior to chemotherapy treatment, and all of these participants also reported an increase in tinnitus during the course of treatment. All participants (100%; n=32)

reported an awareness of tinnitus during treatment, and 81.3% (n=26) reported tinnitus symptoms at exit testing. No vestibular symptoms were reported during case history at baseline testing or at exit testing. Table 5.2 describes the hearing status of participants at baseline and exit testing.

Table 5.2: Hearing status of participants at baseline and exit testing (n=32)

Hearing status (n, %)	**Baseline**	**Exit**
Left ears		
• *Normal*	26 (81.2%)	23 (71.9%)
• *Mild*	6 (18.8%)	9 (28.1%)
Right ears		
• *Normal*	30 (93.8%)	25 (78.7%)
• *Mild*	1 (3.1%)	6 (18.8%)
• *Severe*	1 (3.1%)	1 (3.1%)
Mean PTA (Median, SD; IQR)		
Left ears	17.8 (13.8; 7.8; 10.8)	21.5 (19.4; 6.9; 11.0)*
Right ears	18.5 (16.7; 11.1; 7.3)	22.1 (20.0; 12.4; 9.6)
Hearing change from baseline to exit testing according to ototoxicity criteria (n, %)		
20 dB decrease or greater at one frequency	-	10 (31.3%)
10 dB decrease or greater at two adjacent frequencies		15 (46.9%)
Loss of response at three consecutive frequencies where there was a previously recorded response		1 (3.1%)

IQR=inter-quartile range, n= number of participants, SD=standard deviation.
The average of 500, 1000, 2000 and 4000 Hz was used to calculate the pure-tone average (PTA).
A p-value < 0.05 was used to indicate if there is a statistically significant difference between baseline and exit testing
**: statistically significant difference from baseline to exit testing (p=0.001).*

Cochleotoxicity according to ototoxicity monitoring criteria was present in 50% (n=16) of participants. No vestibulotoxicity criteria exist in order to confirm the presence of early signs of vestibular damage. A significant association between cochleotoxicity and vestibulotoxicity was present in 3.1% (n=1) for left ear PTA values and oVEMP P1 results ($p < 0.05$). No further significant associations between cochleotoxicity and vestibulotoxicity were identified. Therefore, no consistent relationship between cochleotoxicity and vestibulotoxicity could be identified.

DVA yielded normal results at both baseline and exit testing (100%, n=32). cVEMP could be elicited from 65.6% (n=21) participants. cVEMP were absent in the remainder of the participants (28.1%, n=9), and cVEMP could not be performed in 6.2% (n=2) due to large

lymphoma neck masses. cVEMP were present within normal limits at baseline and exit testing for 65.6% (n=21).

oVEMP were elicited from 68.8 (n=22) participants. oVEMP were absent in 28.1% (n=9), and 3.1% (n=1) were in isolation where limited tests were permitted (only VHIT was performed). oVEMP were present within normal limits at baseline and exit testing for 68.8% (n=22). cVEMP and oVEMP at baseline, remained present with normal latencies and IP amplitudes at exit testing. Although statistically significant ($p < 0.05$) changes from baseline to exit testing were identified, no clinically relevant changes were present as patients did not report experiencing vestibular symptoms. VEMP results were absent in all participants older than 60 years of age. Table 5.3 describes the results of VEMP testing at baseline and exit assessments.

Table 5.3: VEMP testing at baseline and exit assessments (cVEMP n=21; oVEMP n=22). ***VEMP were absent in 9/32 participants***

VEMP	Baseline testing (mean, median, SD, IQR)	Exit testing (mean, median, SD, IQR)	Baseline to exit change statistical significance (WSR *p*-value)
cVEMP right ears (n=21)			
cVEMP P1 (ms)	17.2 (17.3; 1.0; 1.8)	15.7 (15.8; 1.8; 1.4)	0.001*
cVEMP N1 (ms)	25.2 (25.2; 1.7; 2.8)	23.6 (23.8; 1.8; 1.8)	0.001*
cVEMP amplitude	56.1 (44.3; 36.6; 47.3)	41.2 (35.7; 21.7; 32.2)	0.137
cVEMP left ears (n=21)			
cVEMP P1 (ms)	16.6 (17.1; 1.7; 2.3)	14.8 (15.0; 1.5; 2.6)	0.001*
cVEMP N1 (ms)	24.0 (24.7; 2.2; 3.2)	21.8 (22.3; 2.7; 5.2)	0.001*
cVEMP amplitude	31.1 (26.6; 13.7; 21.6)	28.0 (25.3; 16.9; 13.7)	0.562
cVEMP asymmetry ratio (%)	19.4 (18.7; 4.5; 6.2)	21.5 (21.8; 4.1; 3.2)	0.103
oVEMP right ears (n=22)			
oVEMP P1 (ms)	10.6 (10.8; 0.7; 3.4)	10.1 (10.1; 0.8; 2.0)	0.001*
oVEMP N1 (ms)	15.3 (15.5; 1.7; 1.0)	13.8 (13.5; 1.2; 1.4)	0.001*
oVEMP amplitude	13.9 (11.2; 10.0; 17.4)	9.7 (6.5; 8.2; 9.0)	0.045*
oVEMP left ears (n=22)			
oVEMP P1 (ms)	10.7 (10.8; 0.8; 0.8)	9.8 (9.9; 0.7; 0.8)	0.001*
oVEMP N1 (ms)	15.1 (15.1; 1.5; 2.6)	13.2 (13.2; 1.6; 2.5)	0.001*
oVEMP amplitude	12.0 (7.2; 9.7; 11.3)	10.4 (5.8; 8.8; 9.2)	0.001*
oVEMP asymmetry ratio (%)	18.1 (17.6; 6.7; 10.7)	16.7 (17.1; 5.6; 7.7)	0.229

Abbreviations: cVEMP, cervical vestibular evoked myogenic potentials; oVEMP, ocular vestibular evoked myogenic potentials; VEMP, vestibular evoked myogenic potential, ms=milliseconds
**Statistically significant results (p<0.05).*

All VHIT (lateral, LARP and RALP) assessments could be performed on 93.8% (n=30) of participants. For 3.1% (n=1), only some VHIT assessments (lateral) could be completed

due to a large neck mass that caused discomfort, and 3.1% (n=1) participants were in isolation where limited tests were permitted. VHIT gain was within normal limits at baseline and exit testing for all participants; however, there was an increase in the percentage of corrective saccades at exit testing. Furthermore, although gain values remained within normal limits, a significant decline in gain was noted at exit testing (Table 5.4).

Table 5.4: VHIT results at baseline and exit testing (lateral SCC n=31; anterior SCC n=30; posterior SCC n=31)

VHIT	Baseline testing (mean gain, median, SD, IQR)	Exit testing (mean gain, median, SD, IQR)	Baseline to exit change statistical significance (WSR *p*-value)
Lateral SCC gain			
Right ears (n=31)	1.03 (1.01; 0.10; 0.12)	0.95 (0.95; 0.09; 0.12)	0.001*
Left ears (n=31)	0.96 (0.96; 0.12; 0.15)	0.90 (0.91; 0.10; 0.15)	0.001*
Anterior SCC gain			
Right ears (n=30)	0.93 (0.94; 0.13; 0.20)	0.86 (0.86; 0.08; 0.15)	0.001*
Left ears (n=30)	0.84 (0.81; 0.12; 0.14)	0.79 (0.79; 0.07; 0.11)	0.005*
Posterior SCC gain			
Right ears (n=31)	1.02 (1.03; 0.12; 0.15)	0.94 (0.96; 0.09; 0.12)	0.001*
Left ears (n=31)	0.96 (0.94; 0.14; 0.26)	0.87 (0.89; 0.09; 0.11)	0.001*
Occurrence of overt and covert corrective saccades (lateral SCC) (n, %)	3 (9.7%)	7 (22.6%)	-

Abbreviations: VHIT, Video head impulse test; SCC, semicircular canals.
Overt saccades: saccades present after the heard movement, covert saccades: saccades present during the head movement.
**Statistically significant results (p<0.05).*

Table 5.5 depicts the comparison of VEMP and VHIT results in left and right ears. Left ears were significantly more affected than right ears for VHIT. No significant differences between ears were found for VEMP test results.

Table 5.5: Comparison of VEMP and VHIT results in left and right ears: cVEMP n=21; oVEMP n=22; lateral SCC n=31, anterior SCC n=30; posterior SCC n=31)

Vestibular assessment	Left ears (mean, median, SD, IQR)	Right ears (mean, median, SD, IQR)	Baseline to exit change statistical significance (WSR *p*-value)
VEMP			
cVEMP P1 latency (ms) (n=21)			
Baseline	16.6 (17.1; 1.7; 2.3)	17.2 (17.3; 1.0; 1.8)	0.206
Exit	14.8 (15.0; 1.5; 2.6)	15.7 (15.8; 1.8; 1.4)	0.083
cVEMP N1 latency (ms) (n=21)			
Baseline	24.0 (24.7; 2.2; 3.2)	25.2 (25.2; 1.7; 2.8)	0.017*
Exit	21.8 (22.3; 2.7; 5.2)	23.6 (23.8; 1.8; 1.8)	0.005*
CVEMP amplitude (mV) (n=21)			
Baseline	31.1 (26.6; 13.7; 21.6)	56.1 (44.3; 36.6; 47.3)	0.015*
Exit	28.0 (25.3; 16.9;13.7)	41.2 (35.7; 21.8; 32.2)	0.051
oVEMP P1 latency (ms) (n=22)			
Baseline	15.1 (15.1; 1.5; 2.6)	15.3 (15.5; 1.7; 3.4)	0.639
Exit	13.2 (13.3; 1.6; 2.5)	13.8 (13.5; 1.2; 2.0)	0.276
oVEMP N1 latency (ms)(n=22)			
Baseline	10.7 (10.8; 0.8; 0.8)	10.6 (10.8; 0.7; 1.0)	0.468
Exit	9.8 (9.9; 0.7; 0.8)	10.1 (10.0; 0.8; 1.4)	0.235
oVEMP amplitude (mV) (n=22)			
Baseline	12.0 (7.3; 9.7; 11.3)	13.9 (11.2; 10.0; 17.4)	0.358
Exit	10.4 (9.2; 8.8;9.2)	9.7 (9.0; 8.2; 9.0)	0.830
VHIT			
Lateral SCC gain (n=31)			
Baseline	0.96 (0.96; 0.12; 0.15)	1.03 (0.01; 0.10; 0.12)	0.001*
Exit	0.90 (0.91; 0.10; 0.15)	0.95 (0.95; 0.09; 0.12)	0.001*
Anterior SCC gain (n=30)			
Baseline	0.84 (0.81; 0.12; 0.14)	0.93 (0.94; 0.13; 0.20)	0.001*
Exit	0.79 (0.79; 0.07; 0.11)	0.86 (0.86; 0.08; 0.15)	0.001*
Posterior SCC gain (n=31)			
Baseline	0.96 (0.94; 0.14; 0.27)	1.02 (1.03; 0.12; 0.15)	0.010*
Exit	0.87 (0.89; 0.09; 0.11)	0.94 (0.96; 0.09; 0.12)	0.001*

Abbreviations: cVEMP, cervical vestibular evoked myogenic potentials; oVEMP, ocular vestibular evoked myogenic potentials; VHIT, Video head impulse test; SCC, semicircular canals, ms=milliseconds, mV=millivolt
**Statistically significant results (p<0.05).*

5.5 Discussion

This study investigated the vestibular and cochlear function in patients receiving chemotherapy. VHIT proved to be a valuable measure of changes in vestibular function secondary to ototoxicity, however VEMP was logistically challenging and time consuming when performed at the patient's treatment venue. Self-report did not reveal any vestibular symptoms at baseline or exit testing in the current study. Self-reported impact of the cochlear and vestibular handicap should be included in a monitoring and surveillance

programme for appropriate investigation and management [13]. Hulse et al. [8] reported that none of their patients had subjective dizziness or balance problems during vestibular monitoring and after being treated with chemoradiation. Another study based on patient self-reported symptoms indicated that dizziness was prevalent in 17% of the participants, and patients with peripheral neuropathy were more likely to have balance symptoms, as confirmed by objective vestibular tests [13]. Dizziness and light-headedness (not related to vestibular function) were reported by some participants in the current study who also suffered from hypotension and neuropathy following chemotherapy. Although balance problems can also be associated with vestibular toxicities, the participants in the current study felt that other comorbidities, such as weakness and neuropathy, were responsible for the dizziness and light-headedness [4].

Vestibular dysfunction has been reported with cochleotoxicity (either hearing impairment or tinnitus) [3], whereas no hearing loss was found in some patients with abnormal objective vestibular assessments [3]. The current study demonstrated no consistent relationship between cochleotoxicity and vestibular dysfunction. Vestibular damage may remain undetected, as patients and healthcare professionals assign imbalance symptoms to other causes and no vestubulotoxicity criteria exist to identify early damage caused by chemotherapy. Patients in the current study did not report vestibular related symptoms. Moreover, normal auditory function does not imply that vestibular function is also unimpaired [6]. Further research with larger sample sizes is required to confirm if hearing dysfunction can serve as a proxy for vestibular dysfunction during ototoxicity monitoring. Both cochleotoxicity and vestibulotoxicity (including at minimum, patient self-report of symptoms) should be included when testing patients being treated with platinum-based agents at the treatment venue or hospital ward.

Although VEMP in the current study stayed within the normal range for both cVEMP and oVEMP at baseline and exit testing, statistically significant ($p<0.05$) changes were evident. There was a definite decrease in N1 and P1 latency values, as well as amplitude from baseline to exit testing in both cVEMP and oVEMP, with oVEMP more affected. VEMP in patients receiving chemoradiation have demonstrated statistically significant

changes following treatment [8]. An important limitation of using VEMP is the fact that VEMP were absent in all participants over 60 years in the current study [21]. When VEMP are absent bilaterally in an older adult, it can be challenging to interpret. The individual may have a bilateral otolith impairment, or an impairment occurring anywhere along the VEMP reflex pathway, inability to hold the muscle contraction, possibly be due to recording and/or stimulus parameters used to elicit the responses, or just be absent due to age above 60 years [21]. Furthermore, cancer patients on platinum-based compounds are often in older age groups [22] and the validity and reliability of measurements involved in vestibular evaluations must be considered in effective monitoring programmes.

The VHIT gain results remained within normal limits from baseline to exit testing. However, there was a significant (p<0.05) decrease in gain at exit testing, suggesting signs of early vestibulotoxicity. From baseline (9.7%), there was also an increase of corrective saccades (23%) at exit testing. Research by Hulse et al. [8] reported saccades present in 39% of participants following chemoradiation treatment, and significantly reduced median gain six weeks after treatment. Increased corrective saccades can be an indicator of vestibular loss [8]. Other studies have found posterior labyrinth damage following treatment with cytostatics such as cisplatin [3]. A study by Prayuenyong et al. [13] found that no vestibular dysfunction was detected by VHIT; however, benign paroxysmal positional vertigo (BPPV) was relatively prevalent in this group of cancer patients.

Average hearing thresholds showed a statistically significant ($p < 0.05$) decline from baseline to exit testing, with left ears more affected than right ears. A study examining the role of EHF in ototoxicity monitoring demonstrated that among the 45 patients affected by ototoxicity, hearing loss was unilateral in 31.1% (n=14) before bilateral hearing loss was reported [5]. Similar to hearing threshold changes, the VHIT results in the current study showed that left ears were significantly more affected than right ears. Vestibulotoxicity may well follow a similar trajectory because of the shared blood, nerve and fluid sources [5]. Hypothetical explanations for unilateral involvement in ototoxicity include the fact that asymmetry and the genetic difference of bilateral organs are well-known; therefore, a

correlation of a genotype with unilateral ototoxicity is possible. It is assumed that two molecular mechanisms with different speeds may cause ototoxicity. Due to the asymmetry of organs and expression of enzymes, the slow toxicity becomes unilateral first and then bilateral. Another theory may be related to the unilateral noise–induced effect during treatment, as the ears are more susceptible to extreme noise during treatment. This sensitivity may also be related to some gene variants [23]. This potentially provides the opportunity to adjust the patient's drug regimen to prevent progression to bilaterality.

DVA was not sensitive in identifying vestibulotoxicity in the current study, as normal results were present at baseline and exit testing for all participants. The results of vestibular objective testing in this study (with significant changes from baseline to exit testing) did not correspond to patient symptoms, as participants did not report symptoms related to vestibular dysfunction. Studies have shown that the prevalence of vestibular dysfunction after chemotherapy administration varied from 0 to 50% [3]. Patients with vestibular dysfunction at baseline are at greater risk for vestibulotoxicity following treatment with cisplatin [3].

The limitations of the current study include a limited sample size and follow-up conducted only up to three to six months after chemotherapy. Longer follow-up is potentially needed as platinum-based compounds remain in the bloodstream for an extended period, and the effects of possible central compensation could therefore be monitored. Long-term follow up could identify the possible development of other vestibular disorders such as BPPV, and ensure early management of those disorders.

5.6 Conclusion

This study suggests that both VHIT and VEMP testing showed significant changes from baseline to exit testing, and may prove to be effective measures of changes in vestibular function secondary to ototoxicity. VHIT can easily be performed at the patient's bedside or treatment venue during an ototoxicity monitoring programme. However, VEMP at the patient's treatment venue has proved to be logistically challenging and time-consuming

when performed as part of a cochleotoxicity and vestibulotoxicity monitoring programme. Furthermore, considering that VEMP responses are absent in patients >60 years and the prevalence of cancer is higher in this age group, VEMP may not be practical as part of a vestibulotoxicity monitoring tool for older cancer patients. Criteria for vestibulotoxicity and optimal protocols for monitoring vestibular function during chemotherapy treatment, and preferably in the patient's treatment venue or hospital ward, should be explored. By the time a patient complains of imbalance or dizziness, permanent vestibular system damage has more than likely already occurred. The opportunity for early identification and possible prevention of further damage may be missed if only self-report symptoms or handicap scales are used. The practicality and ease of providing vestibular assessment protocols must, however, be considered, especially for those patients receiving medical care, who may already be weak or debilitated in hospital, or may merely not have access to more comprehensive testing facilities. Where objective testing is possible, the VHIT proved to be fast to perform in a patient treatment venue and sensitive in identifying vestibulotoxicity. This study showed statistically significant ($p < 0.05$) changes in vestibular function from baseline to exit testing, however, patients did not report vestibular symptoms that had a functional impact on daily life. These significant changes may be due to central compensation that occurs, as well as possibly an early indicator of vestibular dysfunction, before subjective symptoms are reported, motivating the need for vestibular monitoring during ototoxicity surveillance. Therefore, patient self-report of symptoms may be sufficient to monitor vestibulotoxicity in the treatment venue for patients who are ill and incapacitated, and referrals can be made for further in-depth vestibular assessments when symptoms are reported.

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Declaration of competing interest

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Ethical statement

This study was approved by the University of Pretoria Faculty of Health Sciences and Faculty of Humanities (ethics reference number: 665/2018). All study procedures adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the participants after all study procedures had been explained in detail.

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CHAPTER 6

DISCUSSION, CLINICAL IMPLICATIONS AND CONCLUSIONS

This research project aimed to survey current ototoxicity monitoring performed for patients receiving platinum-based chemotherapy in South Africa and to investigate the associated cochleotoxicity and vestibulotoxicity. An mHealth hearing assessment approach to monitoring ototoxicity, including extended high-frequency audiometry, was also investigated.

The aim of this chapter is to summarise and contextualise the results of this research project and to critically evaluate the strengths and limitations of the study. Implications for clinical practice and recommendations for further research are also included. Recommendations for implementing an improved ototoxicity monitoring protocol considering the research findings are proposed.

6.1 Summary of findings and clinical implications

This project included three studies.

Study I: National survey of ototoxicity monitoring in South African cancer facilities

Study I surveyed ototoxicity monitoring nationally in South African cancer facilities. This survey is the first to report the national status of ototoxicity monitoring in cancer patients in the public and private healthcare sector in South Africa. A descriptive quantitative survey was conducted in public and private oncology units and audiology referral clinics where healthcare professionals completed the survey on behalf of the oncology units and audiology referral clinics.

Ototoxicity monitoring protocols were not followed in either the private or the public oncology units. In the public sector, systematic referrals were not considered as standard practice, as all (100%) hearing tests were performed according to clinician referrals.

Clinicians refer if patients complain about hearing-related problems. Systematic referrals for ototoxicity monitoring did also not take place in the private oncology units. In the private sector, patients mostly refer themselves. Often, by this time, a hearing loss is already noticeable and likely irreversible. Feedback from the open-ended questions in the survey indicated that private sector oncology units did not give as much attention to hearing loss as they should. Private oncology units reported that it was not a lack of awareness of ototoxicity that resulted in the absence of systematic ototoxicity monitoring, but rather the cancer diagnosis, advanced disease, other oncologic emergencies, and emotional, financial and physical constraints that were prioritised (Carrera, et al., 2018; Oun et al., 2018). The private oncology units believed identifying a patient who had a high risk was more valuable than identifying just anyone on platinum-based treatments, as hearing loss did not seem to be a main complaint in patients seen (Paken, et al., 2020).

Poor awareness of ototoxicity monitoring best practice guidelines was reported by all oncology units and 14% of audiology referral clinics. This study indicated a comprehensive understanding of ototoxicity across all disciplines; however, there is limited familiarity with implementing ototoxicity monitoring and referral pathways, and greater awareness amongst healthcare professionals is needed. Various ototoxicity monitoring protocols were applied when testing cancer patients. Practices ranged from no baseline testing and routine monitoring to some form of testing in some patients. Audiology referral clinics could identify ototoxicity monitoring protocols proposed by ASHA (1994), AAA (2009) and HPCSA (2018); however, they were not widely implemented as only 43% followed best practice guidelines. Pure-tone audiometry (PT), extended high-frequency audiometry (EHF), audiometry and distortion product otoacoustic emissions (DPOAEs) were cited as the most crucial tests, as suggested in ototoxicity monitoring guidelines. Although audiology referral clinics reported that vestibular problems may be caused by platinum-based chemotherapy, vestibular assessments were not typically included in monitoring protocols. When ototoxic testing was performed, monitoring continued for 6–12 months post-treatment, with some suggesting follow-up for a person’s entire lifespan (Pearson, et al., 2019). Monitoring outcomes were believed to influence dosage and treatment choices, result in

otoprotective agents being prescribed, and it ensured follow-up appointments and frequent visits to the audiologist.

The most prominent challenges reported by oncology units and audiology referral clinics were referral system (67% oncology units; 57% audiology referral clinics), environmental noise (83% oncology units; 86% audiology referral clinics) and the compromised status of cancer patients (67% oncology units; 57% audiology referral clinics) (Konrad-Martin, et al., 2018). More than half of audiology referral clinics in this study were in favour of a novel approach to ototoxicity monitoring. Considering the challenges identified in ototoxicity monitoring, the integration of mobile health (mHealth) tools such as smartphone audiometry is a novel approach, which can improve the effectiveness and efficiency of ototoxicity monitoring in cancer patients. This approach allows for testing to take place in the patient treatment venue and centralised surveillance of ototoxicity using data uploaded in the cloud.

The clinical implications of Study I highlighted the need for effective scheduling and test location as key aspects for successful monitoring in oncology units. There is a need to consider simplified approaches to ototoxic monitoring of hearing and vestibular function to reduce test time and make it less stressful and tiresome to the patient. Testing at the patient's chemotherapy treatment venue may alleviate the over-burdened treatment schedule for the patients. To test in the treatment venue, mHealth testing devices such as smartphone audiometry and shortened monitoring protocols are required due to their mobility and also potentially because they can incorporate quality control metrics such as noise monitoring. At minimum, the inclusion of vestibular self-report of symptoms should be included, and where vestibular symptoms are reported, the use of bedside and objective tests can be considered.

It is clear from the results of this survey that systematic monitoring for ototoxicity is not performed in either the private or the public oncology units. Ototoxic monitoring programmes need to become standard of care for all patients receiving treatment with ototoxic medications. For cancer patients who are transitioning to a life with and beyond

cancer, there is a need to assess how ototoxicity affects their HRQoL (Pearson, et al., 2019), which will provide opportunities for early identification and intervention of hearing and vestibular dysfunction.

Study II: Surveillance for ototoxicity in platinum-based chemotherapy using mHealth audiometry with extended high frequencies

Study II investigated mHealth-enabled surveillance for ototoxicity. A longitudinal study of 32 participants (10–70 years) receiving chemotherapy participated in the study. Baseline and exit audiograms that included conventional and extended high-frequency audiometry were recorded within the patient's treatment venue using a validated mHealth audiometer. The mHealth-supported device used in the current study proved to be successful in facilitating ototoxicity monitoring at the patient's treatment venue and identifying changes in hearing.

Half of participants (50%, n=16) presented with a threshold shift according to ototoxicity monitoring criteria. EHF audiometry was included for surveillance purposes using the mHealth audiometry application. Frequencies affected most were between 4000 and 16000 Hz, with left ears significantly more affected than right ears. The current study found that the most sensitive individual frequencies were 4000 to 16000 Hz, with the largest average threshold shifts (up to 4.9 dB) from baseline to exit testing. A limitation of EHF testing was identified with thresholds often absent at baseline testing, especially in persons older than 65 years (16% of participants in this study had absent EHF baseline thresholds, n=5), which makes it unavailable for monitoring purposes and possibly influencing the lack of statistically significant changes from baseline to exit testing in the high frequencies.

Results also showed that a shift in hearing threshold is not always evident using the conventional PTA (average of 5000, 1000, 2000 and 4000 Hz). Consequently, ototoxicity monitoring protocols in mHealth-supported devices should include calculations of HFPTA (average of 2000, 4000 and 6000 Hz) and potentially EHFPTA (average of 10000, 12000, 14000, and 16000 Hz) in cases where baseline EHF thresholds could be obtained.

Noise concerns during pure-tone audiometry were predominantly noted in this study at 250, 500 and 1000 Hz as measured by the mHealth audiometer during testing. The mean levels by which the MPANLs exceeded the thresholds varied between 3.0 and 7.8 dB across frequencies, indicating minimal potential effects of these instances. Considering the convenience of doing ototoxicity surveillance at the cancer patient's treatment venue, which is often also the only option, there is a need to consider approaches that target high frequencies that are least affected by environmental noise. High frequencies are also the most sensitive for ototoxicity (Landier, 2016), mitigating concerns of noise levels affecting the results when testing during chemotherapy in- and outpatient appointments as an early detection measure.

The ototoxicity monitoring survey showed that systematic monitoring did not take place in oncology units. A novel approach to monitoring using mHealth audiometry was demonstrated to overcome some of the challenges in implementing an ototoxicity monitoring protocol, by testing at the patient's treatment venue. The clinical implications of Study II demonstrated the usefulness of using mHealth audiometry including EHF in ototoxicity surveillance for cancer patients receiving platinum-based chemotherapy. Changes in hearing ability over time could be tracked by employing baseline and exit testing. Shortened monitoring protocols focusing on high frequencies and EHF should be considered in future studies and protocols. High-sensitivity monitoring may be more efficient and address the possibility of noise interference in the environment during testing. Monitoring can take place at chemotherapy in- and outpatient treatment venues and without adding to the patient's already over-burdened treatment schedule.

Study III: Changes in vestibular and cochlear function following platinum-based chemotherapy

Study III investigated the changes in vestibular and cochlear function following platinum-based chemotherapy. A longitudinal study of 32 participants (10–70 years) receiving chemotherapy participated in the study. Baseline and exit vestibular and hearing assessments that included video head impulse (VHIT) testing, vestibular evoked

myogenic potentials (VEMP), bedside dynamic visual acuity (DVA) and pure-tone audiometry were performed at the patient's treatment venue.

Half (50%) of the participants showed cochleotoxicity from baseline to exit testing according to ototoxicity criteria, with left ears significantly more affected than right ears. The current study demonstrated no consistent relationship between cochleotoxicity and vestibular dysfunction. Patient self-report did not reveal any vestibular symptoms at baseline or exit testing. DVA yielded normal results at baseline and exit testing in all participants (100%). VEMP responses were absent in 28.1% of participants at baseline due to increased age or cancer tumours affecting muscle contraction (Piker et al., 2013). This reflects the possible challenges of using VEMP for vestibulotoxicity monitoring. VEMP and VHIT results showed a statistically significant (p<0.05) decline in results from baseline to exit testing; however, participants did not report symptoms related to vestibular dysfunction. As in cocheotoxicity, VHIT showed left ears affected significantly (p<0.05) more than right ears. VEMP results did not show significant differences between the ears.

This study suggests that both VHIT and VEMP testing showed significant (p < 0.05) changes from baseline to exit testing and may prove to be effective measures of changes in vestibular function resulting from ototoxicity. These significant changes may be dues to central compensation that occurs in vestibular dysfunction, as well as an early indicator of vestibular dysfunction, before subjective symptoms are reported, motivating the need for vestibular monitoring during ototoxicity surveillance. The clinical implications of Study III suggested that VHIT can easily be performed at the patient's bedside or treatment venue during an ototoxicity monitoring programme; however, VEMP at the patient's treatment venue has proved to be logistically challenging and time-consuming when performed as part of a cochleotoxicity and vestibulotoxicity monitoring programme. Furthermore, considering that VEMP responses were absent in patients >60 years in this study, VEMP were ineffective as part of a vestibulotoxicity monitoring tool for older cancer patients. The practicality and ease of providing vestibular assessment protocols must be considered, especially for those patients receiving medical care, who may already be

weak or debilitated in hospital, or may merely not have access to more comprehensive testing facilities.

Criteria for vestibulotoxicity and optimal protocols for monitoring vestibular function during chemotherapy treatment, and preferably in the patient's treatment venue or hospital ward, should be explored. Where objective testing is possible, the VHIT proved to be quick to perform in a patient treatment venue and could potentially serve as a sensitive measure of vestibulotoxicity. As patients did not report vestibular symptoms that had a functional impact on daily life (Prayuenyong, et al., 2018), patient self-report of symptoms may be sufficient to monitor vestibulotoxicity in the treatment venue for patients who are ill and incapacitated.

6.2 Recommendations for ototoxicity monitoring in cancer patients receiving platinum-based chemotherapy

For cancer patients who are transitioning to a life with and beyond cancer, there is a need to consider how hearing loss and vestibular dysfunction affect their HRQoL (Horta, et al., 2020). Audiologists must prioritise programmes that are thorough, efficient and accurate, and based on patient-centred care. Audiologists need to be proactive and develop exceptional working relationships with oncologists and nursing staff in the oncology units, ensuring that an appropriate referral system is identified and implemented. A referral system is more than likely unique to each oncology unit, and a uniform approach may not be appropriate.

Ototoxicity surveillance is not an integrated routine part of the oncology treatment package and is dependent on individual initiatives. Oncology units should prioritize ototoxicity monitoring as part of the standard oncology treatment programme, as opposed to it being an optional extra. Ototoxicity monitoring costs should therefore be included in oncology treatment programmes offered by private medical schemes as well as in public oncology care.

A proposed cochleotoxicity and vestibulotoxicity protocol that can be used in the patient's treatment venue was developed based on the results of this project. These proposed protocols could be more cost effective, practical and sensitive in identifying ototoxicity. As cancer patients face unique health problems and side effects throughout the course of platinum-based chemotherapy treatment, a flexible approach to ototoxicity monitoring is required. Ototoxicity monitoring programmes should be responsive to the unique needs and health-related state of each cancer patient. Results obtained at baseline testing should guide the battery of assessments that will be appropriate for further monitoring. Figure 6.1 illustrates a novel approach to ototoxicity monitoring, using an mHealth approach for identification of cochleotoxicity. Vestibular assessments that are appropriate and can be implemented at the patient's chemotherapy treatment venue, and that consider the patient's compromised health-related state, are described in Figure 6.2.

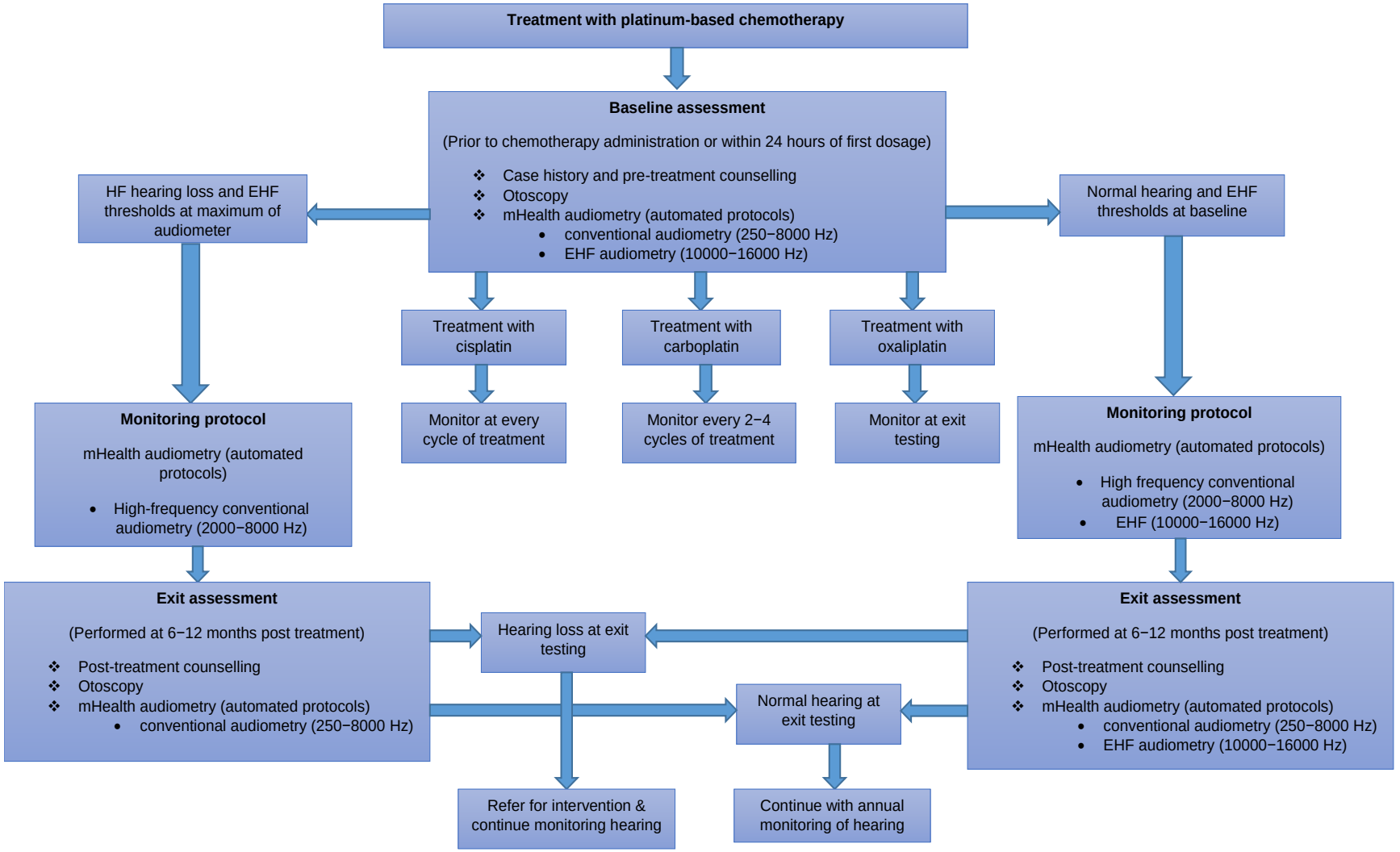

Figure 6.1 Proposed conceptual mHealth cochleotoxicity monitoring guideline

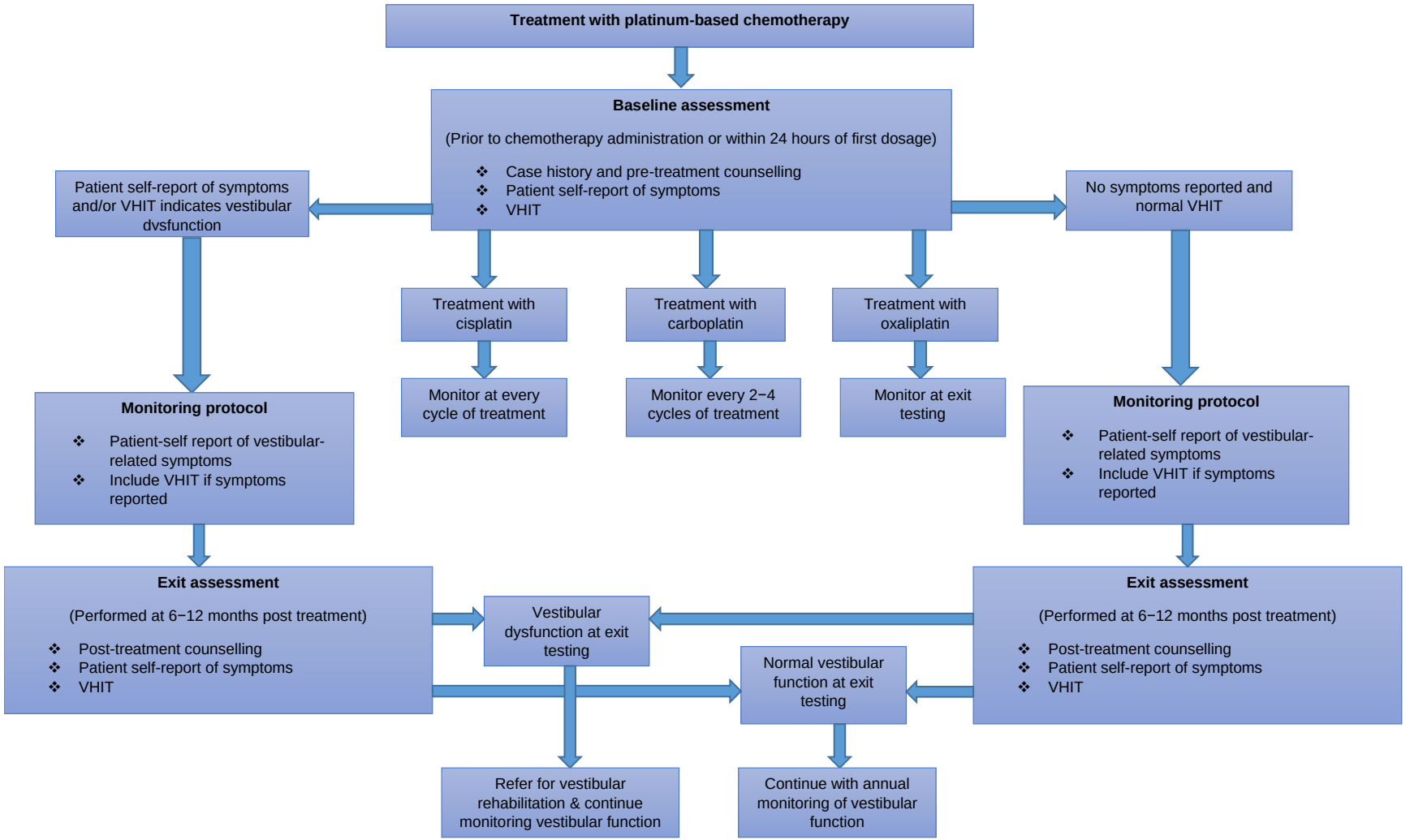

Figure 6.2 Proposed conceptual vestibulotoxicity monitoring guideline

A final consideration is that data collection for this project took place during the COVID-19 pandemic. In March 2020 the WHO announced a world-wide pandemic after a wave of COVID-19 hit the world. Mobility restrictions were present in South Africa as various levels of lockdown were implemented. Physical distancing was one of the most effective methods of limiting virus transmission and this had a major impact on the provision of healthcare (Gunjawatea, Ravia, Yerraguntlab, Rajashekharb, & Vermac, 2021). Cancer patients are also identified as vulnerable and additional restrictions were required (Russell, Moss, Shah, Ko Ko, Palmer, Sylva, et al., 2021). The pandemic highlighted the critical role of telehealth and the use of connected technologies to ensure the continuation of services. mHealth-supported audiometers allow for asynchronous services as automated protocols are used and data is automatically uploaded into centralised cloud-based services that are accessible to the treating audiologists for interpretation. As patients did not report vestibular symptoms that had a functional impact on daily life, patient self-report of symptoms via communication devices may be sufficient to monitor vestibulotoxicity for patients who are ill and incapacitated, or where physical distancing is required. Thus, a hybrid approach to ototoxicity monitoring should be considered when access to patients is limited due to the pandemic or the patient's often debilitated state during chemotherapy treatment.

6.3 Research strengths and limitations

This section critically evaluates the strengths and limitations of the research project. The critical evaluation aided in identifying recommendations for future research.

Study strengths

This research was the first to investigate the status of ototoxicity monitoring nationally in South Africa. Previous studies were limited to certain geographical areas and Study I of this project provided country-wide data. Furthermore, ototoxicity monitoring was provided to real cancer patients throughout their cancer journey, demonstrating ecological validity as test performances were representative of real-world settings.

The longitudinal within-subject research design allowed for the assessment of variables over time. The most powerful type of research designs is a within-subject

design because each participant serves as their own control. Individual participants bring into the test their own history, background knowledge, and context. Multiple observations were taken to understand longitudinal effects. Furthermore, smaller sample sizes are acceptable when using within-subject designs (Mouton, 2000). Additionally, the researcher performed all the baseline and exit hearing and vestibular assessments for all participants. This limited method-related variances, as the same person conducted all the assessments. Test-retest reliability was confirmed, as the same tests were used at baseline and exit testing.

Lastly, this project included both hearing and vestibular function monitoring. The majority of ototoxicity monitoring programmes focus on hearing monitoring only. This project also investigated novel monitoring approaches to implement ototoxicity monitoring at the patient's chemotherapy treatment venue, to minimise the already over-burdened treatment schedules of cancer patients.

Study limitations

For Study I, not all participants who participated in the telephonic survey consented to complete the questionnaire. Therefore, a certain amount of non-responder bias may have occurred as participants who completed the questionnaires may have been systematically different from those who did not. Reasons for not completing the questionnaire were that some of the units did not perform ototoxicity monitoring, and thereby did not consent to completing the questionnaire as they felt that they had no more value to add to the study. Furthermore, some oncology units also had several branches, and responses were only obtained from one branch, as similar ototoxicity monitoring practices were followed at the branches. Therefore, a higher questionnaire completion rate may have decreased the likelihood of bias.

For studies II and III, a limited sample size participated in the study, and follow-up was conducted only up to six months after chemotherapy. Longer follow-up is potentially needed because platinum-based compounds remain in the bloodstream for an extended period, and the effects of possible central compensation (Lacour, et al., 2016) can be monitored in vestibular function. Long-term follow up (for the patient's

lifespan) can identify hearing difficulties and the possible development of other vestibular disorders such as BPPV (Prayuenyong et al., 2021), and be managed early.

Another limitation for Study II was the exclusion of control conditions in a sound-treated room, due to the challenging immuno-compromised nature of cancer patients. Additionally, no external sound-level measurements apart from the smartphone monitoring included in the mHealth application were employed to monitor environmental noise. Criterion validity may have been compromised as another instrument that measures the same variables (such as noise concerns) was not included.

Furthermore, the use of EHF testing in an ototoxicity monitoring protocol is only useful when thresholds are within the normal range at baseline testing. EHF thresholds results that were affected (absent threshold at maximum EHF intensity for the device) at baseline testing were 16% of ears tested in Study II, as the largest group of participants were aged between 51 and 70 years. Similarly, VEMP results were typically absent at baseline for participants older than 60 years (cVEMP: 38%; oVEMP, 36%). Cancer patients on platinum-based compounds are often in older age groups (Yancik, 2005) and the validity and reliability of measurements involved in hearing evaluations must be considered in effective monitoring programmes. A “one size fits all” approach is not appropriate. Furthermore, there was a lack of subjective correlation of vestibulotoxicity with significant changes in objective measures, which may be related to central compensation that occurs in vestibular dysfunction.

Lastly, in studies II and III, age- and sex-matched control participants who were not on chemotherapy were not involved. The inclusion of control subjects minimises bias and strengthens the conclusion drawn from the study sample.

6.4 Recommendations for future research

Future research in ototoxicity monitoring should include a larger sample size, and longer-term follow-up (> one year) after treatment, as platinum-based chemotherapy can remain in the body for an extended period (Langer et al., 2013). Exploration of using synchronous versus asynchrounous telehealth methods of monitoring is

important, in addition to involving other healthcare professionals using mHealth-supported devices with automated protocols. Task-shifting with minimally trained health workers, which facilitates ototoxicity monitoring in cancer treatment venues with audiologists overseeing training, programme management and surveillance, should be investigated further. This would be in line with the World Report on Hearing recommendations for task shifting and could reduce costs, making it more widely available. Mobile technologies have shown to be reliably used by community health workers (Bright et al. 2019; Dawood, Mahomed Asmail, Louw & Swanepoel, 2021). Therefore, task shifting could be very appropriate and should be investigated further as a reliable and cost-effective model for ototoxicity monitoring.

Research into the inclusion of control conditions in a sound-treated room or addition of external sound-level measurements apart from the smartphone monitoring included in the mHealth application could be conducted. Frequency-specific MPANLs should not be exceeded when performing audiometric testing outside of a sound-treated room (Behar, 2021). The HearTest^{R} includes noise monitoring control metrics and this study showed that the low frequencies were affected by noise; however, no external noise monitoring device was used to confirm this phenomenon.

More research is required to confirm if cochleotoxicity can be used as a predictor for vestibulotoxicity. This study showed no consistent relationship between cochleotoxicity and vestibular dysfunction, but a larger sample size is required to confirm this. It is necessary to explore alternative reduced cochleotoxicity protocols such as shortened high-frequency protocols in noisy environments. Additionally, it seems viable to investigate the use of self-report of vestibular symptoms during an ototoxicity monitoring programme, as vestibulotoxicity confirmed by objective tests is often not validated with patient-reported symptoms (Prayuenyong, et al., 2018). The DizzyGuide is certified as a medical device according to the Medical Device Directive 93/42 EEC. Further investigation into the use of the DizzyGuide in vestibulotoxicity monitoring during the course of chemotherapy treatment may be useful, as this can be completed in the comfort of the patient's home. The DizzyGuide is an electronic balance questionnaire that aims to ask all relevant questions about the patient's dizziness and aims to suggest further testing procedures required to make a diagnosis and implement treatment. If objective tests are used for vestibular assessment in the

patient treatment venue, more research is required to determine the ideal battery of tests that are valid, reliable and quick to perform at the chemotherapy treatment venue or hospital ward, taking into consideration the already over-burdened treatment schedule and debilitated state of cancer patients.

6.5 Conclusions

This project found that ototoxicity monitoring was not routinely implemented across oncology units in South Africa. Multidisciplinary teamwork and a simplified national ototoxicity monitoring protocol may improve hearing outcomes for patients. A novel ototoxicity monitoring approach that could be performed in the patient treatment venue was investigated. mHealth-supported audiometry proved to be an efficacious tool for ototoxicity monitoring at the treatment venue. Changes in hearing ability over time could be tracked, improving surveillance in patients with full treatment schedules. A limitation of EHF testing was identified with thresholds often absent at baseline testing, especially in persons older than 65 years, which makes it unavailable for monitoring purposes.

VHIT and VEMP testing showed significant changes from baseline to exit testing and proved to be effective measures of changes in vestibular function secondary to ototoxicity. VEMP at the patient's treatment venue has proved to be logistically challenging and time-consuming when performed as part of a cochleotoxicity and vestibulotoxicity monitoring programme. Furthermore, VEMP results were absent in patients older than 60 years, limiting its value for monitoring. Where objective testing was possible, the VHIT proved to be fast to perform in a patient treatment venue and sensitive in identifying vestibulotoxicity. As patients did not report vestibular symptoms that had a functional impact on daily life, patient self-report of symptoms may be sufficient to monitor vestibulotoxicity in the treatment venue for patients who are ill and incapacitated.

If ototoxicity monitoring could be done as standard practice at the patient's treatment venue, it would relieve the over-burdened treatment schedule of cancer patients. This would ensure that HRQoL is preserved and an opportunity for early intervention and aural rehabilitation is provided. Rehabilitation is cost-effective and may reduce both

direct and indirect healthcare costs, thereby reducing the immense financial burden of cancer and ensuring that cancer survivors can remain gainfully employed. An impairment-driven cancer rehabilitation model that includes ototoxicity monitoring along the continuum of care would maximise HRQoL and minimise disability.

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APPENDICES

APPENDIX A: ETHICAL CLEARANCE CERTIFICATES

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

29 May 2018

Dear Mrs Ehlert

Project: Cochleotoxicity and vestibulotoxicity in patients receiving chemotherapy in South Africa
Researcher: K Ehlert
Supervisors: Prof D Swanepoel, Dr B Heinze
Department: Speech-Language Pathology & Audiology

The Research Ethics Committee of the Department Speech-Language Pathology and Audiology considered your proposed research project for postgraduate (PhD) purpose. In general, the committee agreed that the research topic is relevant to the South African context and novel. The research design is appropriate to the aims of the study.

As Department we therefore grant approval to continue with developing and finalizing your research proposal that will be submitted for approval by the Faculty of Health Sciences and Faculty of Humanities.

We wish you success with this project.

Kind regards

Dr Lidia Pottas, PhD
Chair: Departmental Research Ethics Committee

Dr Jeannie van der Linde, PhD
Acting head of Department

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Kgoro ya Phatholotši ya Polelo-Maleme le Go kwa

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UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Exoires 03/14/2020.

11 January 2019

Approval Certificate
New Application

Ethics Reference No.: 665/2018
Title: Cochleotoxicity and vestibulotoxicity in patients receiving chemotherapy in South Africa

Dear Mrs K Ehlert

The **New Application** as supported by documents received between 2019-01-07 and 2018-11-21 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 2018-11-21.

Please note the following about your ethics approval:

- Ethics Approval is valid for 1 year and needs to be renewed annually by 2020-01-11.
- Please remember to use your protocol number (665/2018) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers
MBChB MMed (Int) MPharmMed PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health)

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Lefapha la Disaense tša Maphelo

UNIVERSITEIT VAN PRETORIA
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YUNIBESITHI YA PRETORIA

Humanities 100
1919 - 2019

Research Ethics Committee

5 February 2019

Dear Ms Ehlert

Project:	**Cochleotoxicity and vestibulotoxicity in patients receiving chemotherapy in South Africa**
Researcher:	**K Ehlert**
Supervisor:	**Prof DCD Swanepoela nd Dr B Heinz**
Department:	**Speech-Language Pathology and Audiology**
Reference number:	**98001800 (HUM20190201)**

Thank you for your application for ethical consideration.

The Committee notes that your application was **approved** by the Faculty of Health Science's **Research Ethics Committee** on 21 November 2018. Your application was thus further **approved** by the Faculty of Humanities **Research Ethics Committee** on 6 February 2019. Further data collection may therefore commence.

Please note that this approval is based on the assumption that the research will be carried out along the lines laid out in the proposal. Should your actual research depart significantly from the proposed research, it will be necessary to apply for a new research approval and ethical clearance.

We wish you success with the project.

Sincerely

Prof Maxi Schoeman
Deputy Dean: Postgraduate and Research Ethics
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail: PGHumanities@up.ac.za

cc: Prof DCD Swanepoel and Dr B Heinz (Supervisors) Dr J van der Linde (HoD)

Life Healthcare Head Office
Oxford Manor, 21 Chaplin Road, Illovo 2196
Private Bag X13, Northlands 2116, South Africa
Telephone: +27 11 219 9000
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National Health Research Ethics Committee registration: **REC 251015-048**

REF: 04052019/2

05 April 2019

Dear Katerina Ehlert

RE: APPLICATION TO CONDUCT RESEARCH:

Title of study: Cochleotoxicity and vestibulotoxicity in patients receiving chemotherapy in South Africa

The Research & Scientific Committee of Life Healthcare Group hereby grants permission with no conditions for your study to be conducted at **Life Groenkloof Hospital.**

1. If patient or institutional confidentiality is breached, Life Healthcare is entitled to withdraw this permission immediately. The Higher Education institution under which the research is taking place will be notified, and Life Healthcare reserves the right to take legal action against you, should the company feel that this is warranted.

2. An electronic copy of the research report must be submitted to the Life Healthcare Research Ethics Committee prior to publication. Failure to do this may result in permission to continue to examination being withdrawn. The Higher Learning institution will be notified of this withdrawal.

3. No direct reference may be made to Life Healthcare, its subsidiaries or any of its facilities or institutions in the research report or any publications thereafter. The Company and its facilities, patients and staff must be de-identified in the study, and remain so for any other studies which may utilise this information.

4. The research must be completed within the time allotted by the Higher Learning institution. If the research is being done in an individual capacity by an employee of the life Group, the research must be conducted within one year of permission being given by the Company, OR the proposed time period must be specified in the proposal, and approved. Permission may be withdrawn if the research extends beyond the approved time period.

5. Life Healthcare will not take responsibility for any unforeseen circumstances within its institutions which may materially change the context and potential outcomes of a student's research. Should this occur, the student will be required to approach their Higher Learning institution for guidance around alternatives.

6. Placement of the electronic research report and any publications on the Company's research register after approval by the associated Higher Education Institution.

7. Life Healthcare will not be liable for any costs incurred during or related to this study.

Yours sincerely,

On behalf of the Research & Scientific Committee

Life Healthcare Group Proprietary Limited
Reg. no. 2003/024367/07 Registered address Oxford Manor, 21 Chaplin Road, Illovo 2196, Private Bag X13, Northlands 2116
Directors: CI Koekemoer, AM Pyle, PF Theron, PP van der Westhuizen, SB Viranna, KA Wylie

APPENDIX B: INFORMED CONSENT AND SELF-ADMINISTERED QUESTIONNAIRE

Study 1: A national survey of ototoxicity monitoring in South African cancer facilities

PATIENT OR PARTICIPANT'S INFORMATION & INFORMED CONSENT DOCUMENT

Researcher's name Katerina Ehlert

Student Number 98001800

Department of Speech-Language Pathology and Audiology

University of Pretoria

Dear Participant

Cochleotoxicity and vestibulotoxicity in patients receiving chemotherapy in South Africa

I am a **PhD** student in **Audiology** in the Department of Speech-Language Pathology and Audiology**,** University of Pretoria. You are invited to volunteer to participate in our research project on **Cochleotoxicity and vestibulotoxicity monitoring in patients receiving chemotherapy: characteristics and a novel monitoring approach**.

This letter gives information to help you to decide if you want to take part in this study. Before you agree you should fully understand what is involved. If you do not understand the information or have any other questions, do not hesitate to ask us. You should not agree to take part unless you are completely happy about what we expect of you.

The purpose of the study is to determine current practices regarding ototoxicity monitoring for cancer patients in South Africa – A national survey

We would like you to complete a questionnaire. This may take about **20** minutes. The questionnaire will be administered through survey monkey where completed questionnaires will be stored automatically. Questionnaires will be kept in a safe place to ensure confidentiality. Please do not write your name on the questionnaire. This will ensure confidentiality. I Katerina Ehlert (katerina.ehlert@gmail.com, 0834920204) will be available to help you with the questionnaire or to fill it in on your behalf.

No sensitive questions are included and only refer to current ototoxicity monitoring practices within your environment.

The Research Ethics Committee of the University of Pretoria, Faculty of Health Sciences, telephone numbers 012 356 3084 / 012 356 3085 granted written approval for this study.

Your participation in this study is voluntary. You can refuse to participate or stop at any time without giving any reason. As you do not write your name on the questionnaire, you give us the information anonymously. Once you have given the questionnaire back to us, you cannot recall your consent. We will not be able to trace your information. Therefore, you will also not be identified as a participant in any publication that comes from this study.

In the event of questions asked, which will cause emotional distress, then the researcher is able to refer you to a competent counselling.

Note: The implication of completing the questionnaire is that informed consent has been obtained from you. Thus any information derived from your form (which will be totally anonymous) may be used for e.g. publication, by the researchers. Data will be stored for 15 years.

We sincerely appreciate your help.

Yours truly,

Katerina Ehlert

Please tick the appropriate box or give the necessary information in the space provided.

1. Demographics:

1.1. Race:

Black ☐ White ☐ Indian ☐ Coloured ☐ Other ☐

1.2. Gender:

Male ☐ Female ☐

1.3. Age:

20 – 25 ☐ 26 – 30 ☐ 31 – 35 ☐ 36 – 40 ☐ 41+ ☐

1.4. Years' experience working in cancer units:

0-5 years ☐ 6-10 years ☐ 11-15 years ☐ 16-20 years ☐ 21+ years ☐

1.5. Current workplace:

Public Hospital ☐ Private ☐ Other: ☐ Specify_____

1.6. Profession:

General Practitioner ☐ Nurse ☐ Audiologists ☐ Oncologist ☐ Pharmacist ☐

Other: ☐ Specify_____

1.7. Where did you obtain your degree and when?

_____

1.8. Does the cancer unit where you work provide ototoxicity monitoring?

Yes ☐ No ☐

1.9. Where did you learn about ototoxicity monitoring (tick all that apply)?

University programme ☐ On the job ☐ Own reading ☐

Conferences & workshops ☐

2. General perceptions towards ototoxicity monitoring

2.1. Ototoxicity is
- (A) A side effect of medicine resulting in auditory and/or vestibular dysfunction resulting hearing loss and disequilibrium
- (B) A toxic reaction resulting from an interaction between two or more drugs
- (C) Renal impairment due to medicine overdose
- (D) A side effect of medicine resulting in severe skin rash
- (E) Don't know

2.2. Signs of ototoxicity include
- (A) Hearing loss
- (B) Disequilibrium
- (C) Renal impairment
- (D) A and B
- (E) A, B and C

2.3. Which of the following medicines used for cancer is likely to cause hearing loss:
- (A) Ifosfamide
- (B) Cisplatin
- (C) Methotrexate
- (D) A and B
- (E) B and C

2.4. What proportion of patients receiving cisplatin chemotherapy would develop hearing lc
- (A) 0%
- (B) 25%
- (C) 50%
- (D) 75%
- (E) 100%

2.5. What hearing loss configuration would ototoxicity likely cause?
- (A) Flat
- (B) High frequency
- (C) Low frequency

2.6. How severe is the hearing loss likely to be?
- (A) Mild
- (B) Moderate
- (C) Severe
- (D) Profound

2.7. What impact do you think this hearing loss would have on their daily life?
- (A) None
- (B) Slight
- (C) Moderate
- (D) Severe

2.8. How likely is it that these patients will also develop tinnitus (ringing in ears)?
(A) unlikely
(B) slight
(C) moderate
(D) very

2.9. What impact do you think this tinnitus would have on their daily life?
(A) none
(B) slight
(C) moderate
(D) severe

2.10. Are these patients also likely to develop balance/vestibular problems?
(A) unlikely
(B) slight
(C) moderate
(D) very

2.11. What impact do you think these balance/vestibular problems would have on their daily life?
(A) None
(B) Slight
(C) Moderate
(D) Severe

2.12. What is the purpose of ototoxicity monitoring (select all that apply)?
(A) Early identification of hearing loss
(B) To terminate ototoxic treatment
(C) To adjust treatment dosages
(D) Improve quality of life post-treatment
(E) Provide appropriate and timely intervention

2.13. What benefits are there for the patient in ototoxicity monitoring (select all that apply)?
(A) Knowledge about ototoxic hearing loss
(B) Early identification of hearing loss
(C) Early intervention
(D) Other, please specify_____

2.14. Are you aware of any South African ototoxicity protocols or best practice guidelines regarding monitoring?
(A) Yes
(B) No
If yes, please specify protocols known _____

3. Challenges

3.1. Is the referral process that leads to a patient receiving potentially ototoxic treatments being seen by Audiology a challenge?
(A) Yes
(B) No

3.2. How important is a baseline audiogram?
(A) not important
(B) somewhat important
(C) moderately important
(D) very important

3.3. Waiting lists vary. Are there any assurances or checks that are made to make sure the patient is seen before their first ototoxic treatments (e.g. chemotherapy/radiation/aminoglycosides), or do they just get the first available appointment?
(A) All oncology patients receive baseline assessments
(B) Only patients referred receive baseline assessments
(C) Patients do not receive baseline assessments
(D) Other, please specify_____

3.4. When these patients arrive at the audiology clinic, how informed do you think they are about the risk to their hearing from their treatment?
(A) uninformed
(B) slight
(C) moderately
(D) well

3.5. Where do you think most patients get this information?
(A) General practitioner
(B) Oncologist
(C) Nursing staff
(D) Pharmacists
(E) Other, please specify _____

3.6. Whose responsibility should it be to inform the patient about the potential risk to their hearing?
(A) General practitioners
(B) Oncologists
(C) Nursing staff
(D) Audiologists
(E) Pharmacists
(F) Other, please specify _____

3.7. What patient challenges are experienced?
(A) Patients too ill to attend the audiology clinic
(B) Patients tested in the wards due to poor immunity and isolation
(C) Environmental noise challenging when testing in ward environment
(D) Other, please specify

4. Monitoring Protocols (To be completed by Audiologists)

4.1. Does your Audiology department have ototoxicity monitoring protocols?
(A) Yes
(B) No
(C) Unsure

4.2. Are the protocols written down?
(A) Yes
(B) No
(C) Unsure

4.3. Is it compulsory to follow the protocols or are they just guidelines?
(A) Compulsory
(B) Guideline
(C) Unsure

4.4. How often are the protocols followed?
(A) never
(B) sometimes
(C) most of the time
(D) always

4.5. How much time is typically allocated for a first appointment with this type of patient?
(A) 0-30 minutes
(B) 30-60 minutes
(C) 60 -90 minutes
(D) 90-120 minutes
(E) 120 minutes+

4.6. What baseline audiometric data is typically collected (select all that apply)?
(A) Pure tone air conduction
(B) High frequency audiometry
(C) Distortion Product Oto-acoustic emissions
(D) Vestibular assessments, please specify
_____

4.7. Where did this list or practice come from?
(A) Just what's done here/hospital protocol of unknown origin
(B) Hospital protocol of known origin, please specify _____
(C) Existing published protocol, please specify _____
(D) Protocol followed exactly
(E) Protocol is modified
(F) What is asked for by referring clinician

4.8. What factors influence what you measure?
(A) Clinical necessity
(B) Best practice
(C) Equipment owned by hospital/practice
(D) Equipment owned but not always available (e.g. being used).
(E) Available time for appointment
(F) Audiologist training or knowledge
(G) Other, please specify_____

4.9. After the first set of results is obtained, are reports sent to anyone? If so, who (select al relevant answers)?
(A) Oncologist
(B) Nursing staff
(C) Pharmacists
(D) Patient
(E) Other, please specify _____

4.10. How do you think this audiometric information is used by the referring clinician (select al relevant aspects)?
(A) Influences treatment choices
(B) Influences dosage choices
(C) Ensures oto-protective agents (e.g. N-acetylcysteine (ACC-200®) are prescribed
(D) Ensures follow-up appointment/referral with audiologist
(E) Ensures frequent visits to the audiologist

4.11. What serial monitoring audiometric data is typically collected (select all that apply)?
(A) Pure tone air conduction
(B) High frequency audiometry
(C) Distortion Product Oto-acoustic emissions
(D) Vestibular assessments, please specify
_____

4.12. Who decides when the ototoxicity monitoring appointments stop?
(A) Oncologist
(B) Audiologist
(C) Pharmacist
(D) Other, please specify_____

4.13. How long after treatment should ototoxicity monitoring appointments stop?
(A) 3 months
(B) 6 months
(C) 12 months
(D) Immediate

5. Suggested improvements in ototoxicity monitoring

5.1. Do you think anything needs to be done at your DHB to improve ototoxicity monitoring practice or hearing and balance outcomes for patients receiving potentially ototoxic treatments?
(A) Yes, please specify_____
(B) No
(C) Unsure

5.2. Is there a need for greater instruction/awareness among health professionals?
(A) Yes
(B) No
(C) Unsure

5.3. Is there a need for greater instruction/awareness among oncologists?
(A) Yes
(B) No
(C) Unsure

5.4. Would you be in favour of a national ototoxicity monitoring protocol to be used by all hospitals?
(A) Yes
(B) No
(C) Unsure

5.5. If there was a national ototoxicity programme, would you follow it?
(A) Yes
(B) No
(C) Don't know
(D) Would modify to suit my setting

5.6. Would having a national protocol make it easier for you to get that equipment (in terms of lobbying for it)?
(A) Yes
(B) No
(C) Unsure

5.7. Would a novel monitoring approach (i.e. using mobile phone devices for monitoring) at the patient's bedside be beneficial?
(A) Yes
(B) No
(C) Unsure

Thank you for taking the time to complete this questionnaire.

APPENDIX C: CASE HISTORY

(Adapted from Campbell, 2007; Venter, 2011)

Study 2: Surveillance for ototoxicity in platinum-based chemotherapy using mHealth audiometry with extended high frequencies

Study 3: Changes in vestibular and cochlear function following platinum-based chemotherapy

1. *[Clinician at the first visit]*
   Did you have hearing loss before the start of treatment?
   □Yes
   □No

   If yes, how long have you had hearing loss?
   □Less than 1 year
   □1-2 years
   □3-5 years
   □6-10 years
   □11-20 years
   □More than 20 years
   □Not sure

   If yes, do you know the cause of the hearing loss?
   □Middle ear infections
   □Noise-induced
   □Old age
   □Family history of hearing loss
   □Congenital
   □Other, please specify: _____
   □Not sure

2. *[Clinician at the first visit]*
   Did you have persistent tinnitus before the start of treatment?
   □Yes
   □No

   If yes, how long have you had tinnitus?
   □Less than 1 year
   □1-2 years
   □3-5 years
   □6-10 years

□11-20 years
□More than 20 years
□Not sure

[Clinician at follow-up visit]

3. Have you noticed any hearing loss since you started the treatment?
   □Yes
   □No

If yes, how is it different?

_____

4. Have you noticed any speech discrimination difficulties since you started the treatment?
   □Yes
   □No

If yes, how is it different?

_____

5. Have you noticed any persistent tinnitus since you started the treatment?
   □Yes
   □No

   If no, interview is complete and no further questions are required. If yes, continue to question 6.

6. What does your tinnitus sound like? (Mark all that apply)
   □Ringing
   □Hissing
   □Buzzing
   □Sizzling
   □Crickets
   □Whistle
   □Hum
   □Other: _____

7. Does your tinnitus have a pulsing quality to it?
   □Yes
   □No

8. Where is your tinnitus located?
   - Left ear only
   - Right ear only
   - Both ears
   - Inside head
   - Other: _____

9. Is your tinnitus louder on one side of your head than the other?
   - Right is louder than left
   - Left is louder than right
   - Equal

10. How loud is your tinnitus on average?
   - Not loud at all
   - Slightly loud
   - Moderately loud
   - Very loud
   - Extremely loud

11. How much of the time do you think your tinnitus is present?
   - Occasionally
   - Some of the time
   - Most of the time
   - Always

12. On average, how much of a problem is your tinnitus?
   - Not a problem
   - Slight problem
   - Moderate problem
   - Big problem
   - Very big problem

[Clinician: Ask the following questions only if the patient (1) had tinnitus before the start of treatment, or (2) reported tinnitus previously with this ototoxicity monitoring case history interview. The objective is to determine if the patient's tinnitus is being affected by the drug treatment. If the patient has previously responded to this interview, each response should reflect the period of time since the last interview. Otherwise, each response reflects the period of time since before the start of treatment].

13. Has the sound of your tinnitus changed?
    - Yes
    - No
    - Unsure

If yes, how is it different?

_____

14. Has the location of your tinnitus changed?
    - Yes
    - No
    - Unsure

    If yes, how is it different?

    _____

15. Has the loudness of your tinnitus changed?
    - No
    - Yes, louder now
    - Yes, quieter now
    - Not sure

16. Has the amount of time your tinnitus is present changed?
    - No
    - Yes, more often
    - Yes, less often
    - Not sure

APPENDIX D: INFORMED CONSENT

Study 2: Surveillance for ototoxicity in platinum-based chemotherapy using mHealth audiometry with extended high frequencies

Study 3: Changes in vestibular and cochlear function following platinum-based chemotherapy

PARTICIPANT'S INFORMATION & INFORMED CONSENT/ASSENT DOCUMENT (ADULT)

STUDY TITLE: Cochleotoxicity and vestibulotoxicity monitoring in patients receiving chemotherapy in South Africa

Principal Investigators: Katerina Ehlert (supervised by Prof D Swanepoel and Dr B Heinze)

Institution: University of Pretoria

DAYTIME AND AFTER HOURS TELEPHONE NUMBER(S):
Daytime numbers: 0834920204 / 012 521 3844
Afterhours: 012 664 1661/ 0834920204

DATE AND TIME OF FIRST INFORMED CONSENT DISCUSSION:

			:
dd	**mm**	**year**	**Time**

Dear Prospective participant

Dear Mr. / Mrs. .....

1) INTRODUCTION

You are invited to volunteer for a research study. This information document is to help you to decide if you would like to participate. Before you agree to take part in this study you should fully understand what is involved. If you have any questions, which are not fully explained in this document, do not hesitate to ask the investigator. You should not agree to take part unless you are completely happy about all the procedures involved.

2) THE NATURE AND PURPOSE OF THIS STUDY

This study aims to determine if the chemotherapy has any effect on the hearing and balance organs of the inner ear. Testing will be done at regular intervals, including before chemotherapy (or immediately after), during treatment and 6 months after treatment.

By doing so we wish to learn more about the progression of hearing and balance function caused by chemotherapy treatment. Some problems could be serious and if identified early could save you from having problems later on.

All the research data and/or documents referring to the above mentioned study will be stored for 15 years and will be available for future research.

3) EXPLANATION OF PROCEDURES TO BE FOLLOWED

This study involves answering some questions with regard to your illness. Participants will be expected to undergo hearing and balance testing before initiation of chemotherapy, as well as at each subsequent chemotherapy treatment and six months after treatment.

The following hearing tests will be done:
1. Otoscopy:
For this test, you will be required to be seated upright while I visually inspect your ear canal and your eardrum by using an otoscope (ear light).

2. Hearing test:
For this test, you will wear earphones on your ears. You will be required to respond to a soft sound by pushing a button. Your hearing sensitivity will be measured.

The following vestibular (balance) tests will be done:
1. Vestibular Evoked Myogenic Potentials:
You will be required to be lying down on the bed with a soft probe placed in your ear canal while a sound stimulus is presented to you. Four different electrodes will be placed on your eyes, neck and chest. When the sound is presented, you will be required to lift your head and to look upwards towards the marked “X” on the roof for the duration of the sound.
2. Video Head Impulse Test:
You will be required to be seated upright while I move your head sideways and up-and-down while I measure your eye movements with a camera.

3. Dynamic Visual Acuity:
You will be required to identify characters on the screen with your head still and while shaking your head from side to side.

4) RISK AND DISCOMFORT INVOLVED

There are no medical risks or discomforts associated with this study. The benefit for the participants will be hearing and balance monitoring provided throughout the treatment in order to preserve hearing, balance and quality of life. If you do not want to take part any more you may decide at any time during the study, not to carry on. No one will force you to carry on. No one will be cross or upset with you if you don't want to, and your doctor will still look after you. The University of Pretoria has limited insurance for research related injuries.

5) POSSIBLE BENEFITS OF THIS STUDY

Many of these tests are done routinely on patients. It will enable us to intervene if you should have hearing and balance problems.

6) I understand that if I do not want to participate in this study, I will still receive standard treatment for my illness.

7) I may at any time withdraw from this study.

8) HAS THE STUDY RECEIVED ETHICAL APPROVAL?

This Protocol was submitted to the Faculty of Health Sciences Research Ethics Committee, University of Pretoria, telephone numbers 012 356 3084 / 012 356 3085 and written approval has been granted by that committee. The study has been structured in accordance with the Declaration of Helsinki (last update: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human/subjects. A copy of the Declaration may be obtained from the investigator should you wish to review it.

9) INFORMATION

If I have any questions concerning this study, I should contact:
Mrs Katerina Ehlert, Tel: 012 6641661or cell: 0834920204.

10) CONFIDENTIALITY

All records obtained whilst in this study will be regarded as confidential. Each participant that undergoes testing will be provided with an alphanumeric coded number e.g. KE001, thus ensuring confidentiality. The identity of the participant represented by this code will be known only to the researcher. Results will be published or presented in such a fashion that participants remain unidentifiable.

11) CONSENT/ASSENT TO PARTICIPATE IN THIS STUDY

I have read or had read to me in a language that I understand the above information before signing this consent form. The content and meaning of this information have been explained to me. I have been given opportunity to ask questions and am satisfied that they have been answered satisfactorily. I understand that if I do not participate it will not alter my management in any way. I hereby volunteer to take part in this study.

I have received a signed copy of this informed consent/assent agreement.

.....	.....
Participant name	Date
.....	.....
Participant signature	Date
.....	.....
Investigator's name	Date
.....	.....
Investigator's signature	Date
.....	.....
Witness name and signature	Date

VERBAL PARTICIPANT INFORMED CONSENT (applicable when participants cannot read or write)

I, the undersigned, Mrs Katerina Ehlert (researcher) / research assistant, have read and have explained fully to the participant, named ……..and/or his/her relative, the participant's information & informed consent/assent document, which has indicated the nature and purpose of the study in which I have asked the participant to partake. The explanation I have given has mentioned both the possible risks and benefits of the study and the alternative treatments available for his/her illness. The participant indicated that he/she understands that he/she will be free to withdraw from the study at any time for any reason and without jeopardizing his/her treatment.

I hereby certify that the participant has agreed to participate in this study.

Participant's Name _____
(Please print)

Participant's Signature _____ Date _____

Investigator's Name _____
(Please print)

Investigator's Signature _____ Date _____

Witness's Name _____ Witness's Signature _____ Date _____
(Please print)

(Witness - sign that he/she has witnessed the process of informed consent)

ASSENT FORM FOR 7-18 YEARS

Assent form for Protocol Title: Cochleotoxicity and vestibulotoxicity monitoring in patients receiving chemotherapy in South Africa

We wish to know if you would like to volunteer to be part of a research study in which you will undergo hearing and balance tests at regular intervals, including before chemotherapy (or immediately after), during treatment and 6 months after treatment. The study will help us to learn more about the progression of hearing and balance function caused by chemotherapy treatment. Some problems could be serious and if identified early could save you from having problems later on.
Your parents (or legal guardian) and Dr..... think that early identification and management of hearing and balance problems could improve your quality of life later on.

About 30 participants are going to take part in this study, and it will last 6 months.

During the study they will do different kinds of tests on you. This study involves answering some questions with regard to your illness. Participants will be expected to undergo hearing and balance testing before initiation of chemotherapy, as well as at each subsequent chemotherapy treatment and six months after treatment.

The following hearing tests will be done:
1. Otoscopy:
For this test, you will be required to be seated upright while I visually inspect your ear canal and your eardrum by using an otoscope (ear light).

2. Hearing test:
For this test, you will wear earphones on your ears. You will be required to respond to a soft sound by pushing a button. Your hearing sensitivity will be measured.

The following vestibular (balance) tests will be done:
1. Vestibular Evoked Myogenic Potentials:
You will be required to be lying down on the bed with a soft probe placed in your ear canal while a sound stimulus is presented to you. Four different electrodes will be placed on your eyes, neck and chest. When the sound is presented, you will be required to lift your head and to look upwards towards the marked “X” on the roof for the duration of the sound.
2. Video Head Impulse Test:
You will be required to be seated upright while I move your head sideways and up-and-down while I measure your eye movements with a camera.

3. Dynamic Visual Acuity:
You will be required to identify characters on the screen with your head still and while shaking your head from side to side.

These tests will last for about 1 hour but will only take place 4 times during the whole study.

There are no medical risks or discomforts associated with this study. The benefit for the participants will be hearing and balance monitoring provided throughout the treatment in order to preserve hearing, balance and quality of life. If you do not want to take part any more you may decide at any time during the study, not to carry on. No-one will force you to carry on. No-one will be cross or upset with you if you don't want to, and your doctor will still look after you. You don't have to give us your answer now, take your time and read the rest of this form before you decide.

If you sign at the bottom it will mean that you have read this document, and that you would like to be in this study.

	Your Name	**Person Obtaining Consent**	**Parent / Guardian / Nurse As Witness**
Name Please Print			
Signature			
Date			

PARENT OR GUARDIAN INFORMATION & INFORMED CONSENT DOCUMENT

TITLE OF STUDY: Cochleotoxicity and vestibulotoxicity monitoring in patients receiving chemotherapy in South Africa

Dear Parent

1) INTRODUCTION

We invite your child to participate in a research study. This information document will help you to decide if you want your child to participate. Before you agree to take part you should fully understand what is involved. If you have any questions that this document does not fully explain, please do not hesitate to ask the researcher Katerina Ehlert.

2) THE NATURE AND PURPOSE OF THIS STUDY

This study aims to determine if the chemotherapy has any effect on the hearing and balance organs of the inner ear. Testing will be done at regular intervals, including before chemotherapy (or immediately after), during treatment and 6 months after treatment.

By doing so we wish to learn more about the progression of hearing and balance function caused by chemotherapy treatment. Some problems could be serious and if identified early could save your child from having problems later on.

All the research data and/or documents referring to the above mentioned study will be stored for 15 years and will be available for future research.

You as a parent are a very important source of information on your child's condition.

3) EXPLANATION OF PROCEDURES TO BE FOLLOWED

This study involves answering some questions with regard to your child's illness. Participants will be expected to undergo hearing and balance testing before initiation of chemotherapy, as well as at each subsequent chemotherapy treatment and six months after treatment.

The following hearing tests will be done:
1. Otoscopy:
For this test, your child will be required to be seated upright while I visually inspect your child's ear canal and eardrum by using an otoscope (ear light).

2. Hearing test:
For this test, your child will wear earphones on his/her ears. Your child will be required to respond to a soft sound by pushing a button. Your child's hearing sensitivity will be measured.

The following vestibular (balance) tests will be done:

1. Vestibular Evoked Myogenic Potentials:
Your child will be required to be lying down on the bed with a soft probe placed in his/her ear canal while a sound stimulus is presented to your child. Four different electrodes will be placed on your child's eyes, neck and chest. When the sound is presented, your child will be required to lift his/her head and to look upwards towards the marked "X" on the roof for the duration of the sound.

2. Video Head Impulse Test:
Your child will be required to be seated upright while I move his/her head sideways and up-and-down while I measure your child's eye movements with a camera.

3. Dynamic Visual Acuity:
Your child will be required to identify characters on the screen with his/her head still and while shaking his/her head from side to side.

4) RISK AND DISCOMFORT INVOLVED

There are no medical risks or discomforts associated with this study. The benefit for the participants will be hearing and balance monitoring provided throughout the treatment in order to preserve hearing, balance and quality of life. If you or your child does not want to take part any more you may decide at any time during the study, not to carry on. No one will force your child to carry on. No one will be cross or upset with your child if you don't want to, and your doctor will still look after your child.

The interview / measuring session will take about an hour of your child's time during oncological treatments.

5) POSSIBLE BENEFITS OF THIS STUDY

Your child will benefit directly by the study because many of these tests are done routinely on patients. It will enable us to intervene if your child should have hearing and balance problems.

6) WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

Your child's participation in this study is entirely voluntary. Your child can refuse to participate or stop at any time during the study without giving any reason. Your child's withdrawal will not affect you or your child's treatment / access to treatment in any way.

7) HAS THE STUDY RECEIVED ETHICAL APPROVAL?

This Protocol was submitted to the Faculty of Health Sciences Research Ethics Committee, University of Pretoria, telephone numbers 012 356 3084 / 012 356 3085 and written approval has been granted by that committee. The study has been structured in accordance with the Declaration of Helsinki (last update: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human/subjects. A copy of the Declaration may be obtained from the investigator should you wish to review it.

8) INFORMATION AND CONTACT PERSON

If you or your child have any questions concerning this study, you should contact: Mrs Katerina Ehlert, Tel: 012 6641661or cell: 0834920204. Alternatively you may contact my supervisor at the following telephone number: 012420 5358.

9) COMPENSATION

Your child's participation is voluntary. No compensation will be provided as testing takes place during other oncological treatments in the oncology ward.

10 CONFIDENTIALITY

All information that your child gives will be kept strictly confidential. Once we have analysed the information no one will be able to identify your child. Research reports and articles in scientific journals will not include any information that may identify your child.

CONSENT TO PARTICIPATE IN THIS STUDY

I confirm that the person asking my consent to take part in this study has told me about nature, process, risks, discomforts and benefits of the study. I have also received, read and understood the above written information (Information document and Informed consent) regarding the study. I am aware that the results of the study, including personal details, will be anonymously processed into research reports. My child is participating willingly. I have had time to ask questions and have no objection for my child to participate in the study. I understand that there is no penalty should I /my child wish to discontinue with the study and my child's withdrawal will not affect any treatment / access to treatment in any way.

I have received a signed copy of this informed consent agreement.

Parent's name …….....(Please print)

Parent's signature: .....…… Date.....

Investigator's name .....……...(Please print)

Investigator's signature .....…… Date.….....

Witness's Name .....(Please print)

Witness's signature ..... Date….....

VERBAL INFORMED CONSENT

I, the undersigned, have read and have fully explained the participant information document, which explains the nature, process, risks, discomforts and benefits of the study to the participant whom I have asked to participate in the study.

The child indicates that s/he understands that the results of the study, including personal details regarding the interview will be anonymously processed into a research report. The child indicates that s/he has had time to ask questions and has no objection to participate in the study. S/he understands that there is no penalty should s/he wish to discontinue with the study and his/her withdrawal will not affect any treatment / access to treatment in any way. I hereby certify that the participant has agreed to partake in this study.

Participant's Name .....(Please print)

Person seeking consent .....(Please print)

Signature .....Date.....

Witness's name .....(Please print)

Signature .....Date….....

APPENDIX E: HOSPITAL AND ONCOLOGY DEPARTMENT CONSENT LETTERS

Study 2: Surveillance for ototoxicity in platinum-based chemotherapy using mHealth audiometry with extended high frequencies

Study 3: Changes in vestibular and cochlear function following platinum-based chemotherapy

Permission to access Records / Files / Data base at Doctor George Mukhari Academic Hospital (DGMAH) / Life Healthcare / Mediclinic / Netcare

TO:
The [CEO] Chief Executive Officer of_____Hospital

Re: Permission to do research at _____ Hospital

TITLE OF STUDY: Cochleotoxicity and vestibulotoxicity monitoring in patients receiving chemotherapy in South Africa

This study is approved by the relevant Head of Department [HOD]: …[Print Name and Surname]…Signature……..

This request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No. 2 of 2000.

I am a researcher / student at the Department of Speech-Language Pathology and Audiology at the University of Pretoria /Hospital. I am working with adult and adolescent cancer patients. I herewith request permission on behalf of all of us to conduct a study on the above topic on the hospital / clinic grounds. This study involves access to patient records. This study involves clinical research.

The researchers request access to the following information: clinical files, record books and data bases.

We intend to publish the findings of the study in a professional journal and/ or to present them at professional meetings like
symposia, congresses, or other meetings of such a nature.

We intend to protect the personal identity of the patients by assigning each individual a random code number.

We undertake not to proceed with the study until we have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

Yours sincerely

Print Name Katerina Ehlert **Signature**
Principal Investigator

Permission to do the research study at this hospital / clinic and to access the information as requested, is hereby approved, on condition that there will be no cost to the hospital.

Title and name of Chief Executive Officer: _____

Name of hospital / clinic: _____

Signature: _____ Date: _____

Oncology Department: Doctor George Mukhari Hospital, Groenkloof Life Healthcare

Project information

I am a researcher / student at the Department of Speech-Language Pathology and Audiology at the University of Pretoria /Hospital. I am working with adult and adolescent cancer patients. I herewith request permission on behalf of all of us to conduct a study on the above topic on the hospital / clinic grounds. This study involves access to patient records. This study involves clinical research.

The researchers request access to the following information: clinical files, record books and data bases.

We intend to publish the findings of the study in a professional journal and/ or to present them at professional meetings like
symposia, congresses, or other meetings of such a nature.

We intend to protect the personal identity of the patients by assigning each individual a random code number.

We undertake not to proceed with the study until we have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

1.1 Title of research project: Cochleotoxicity and vestibulotoxicity monitoring in patients receiving chemotherapy in South Africa

1.2 Researcher details: Katerina Ehlert, Department Speech-Language Pathology and Audiology, contact no: 0834920204

1.3 Research study description. The study will describe the characteristics of cochleotoxicity and vestibulotoxicity in patients receiving chemotherapy and develop a novel ototoxicity monitoring approach. There will be four related studies, each designed for submission to ISI accredited peer-reviewed journals are proposed upon completion of the studies. The four aims will be as follows:

1. To describe ototoxicity monitoring protocols used in South African cancer facilities – A national survey
2. To determine the incidence and characteristics of hearing loss longitudinally in adolescents and adults receiving platinum-based chemotherapy
3. To determine alterations in vestibular function longitudinally in adolescents and adults receiving platinum-based chemotherapy
4. Ototoxicity surveillance in patients undergoing chemotherapy using smartphone audiometry

Based on the fact that chemotherapy can cause hearing loss and balance problems, participants will be expected to undergo hearing and vestibular testing before initiation of chemotherapy, as well as at each subsequent chemotherapy treatment and six months after treatment. There are no medical risks or discomforts associated with this study. The benefit for the participants will be hearing and vestibular monitoring provided throughout the treatment in order to preserve hearing, balance and quality of life. If participants do not want to take part any more they may decide at any time during the study not to carry on.

Yours sincerely

Print Name Katerina Ehlert **Signature**
Principal Investigator

Title and name of Head of Oncology Unit: _____

Name of hospital / clinic: _____

Signature: _____ Date: _____

APPENDIX F: RESEARCH SITES APPROVAL LETTERS

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Gauteng Department of Health
Helen Joseph Hospital
Enquiries: Dr. F.G Benson
Acting Chief Executive Officer
Tel :(011) 489-0306/1087
Fax :(011) 726-5425
E mail:Frew.Benson@gauteng.gov.za
Date: 18 February 2019

Dr. F.G. Benson
Acting Chief Executive Officer
Helen Joseph Hospital

Dear Dr. F. G. Benson

STUDY: Cochleotoxicity and Vestibulotoxicity in Patients receiving chemotherapy in South Africa.

RESEARCHERS: Mrs K Ehlert

Ethics: 665/2018

Above the study was discussed at the Research Committee meeting. We recommend that permission be granted for Helen Joseph Hospital to be used as a site for the above research, However , since this is individual /Patients.

Upon completion of the study, copy thereof should be submitted to Helen Joseph Hospital. It is duty of the researcher to collect the data to the relevant department after the Research Committee approved the study.

Thank you

Dr. Murimisi Mukansi
CHAIRPERSON
DATE:

Approved

Dr. F.G.Benson
Acting CHIEF EXECUTIVE OFFICER
DATE: 2019/3/6

Province of the
EASTERN CAPE
HEALTH

Enquiries: Zonwabele Merile Tel no: 083 378 1202

Email: zonwabele.merile@echealth.gov.za Fax no: 043 642 1409

Date: 30 January 2019

RE: Cochleotoxicity and vestibulotoxicity in patients receiving chemotherapy in South Africa. (EC_201901_008)

Dear Katerina Ehlert

The department would like to inform you that your application for the abovementioned research topic has been approved based on the following conditions:

1. During your study, you will follow the submitted protocol with ethical approval and can only deviate from it after having a written approval from the Department of Health in writing.

2. You are advised to ensure, observe and respect the rights and culture of your research participants and maintain confidentiality of their identities and shall remove or not collect any information which can be used to link the participants.

3. The Department of Health expects you to provide a progress update on your study every 3 months (from date you received this letter) in writing.

4. At the end of your study, you will be expected to send a full written report with your findings and implementable recommendations to the Eastern Cape Health Research Committee secretariat. You may also be invited to the department to come and present your research findings with your implementable recommendations.

5. Your results on the Eastern Cape will not be presented anywhere unless you have shared them with the Department of Health as indicated above.

Your compliance in this regard will be highly appreciated.

SECRETARIAT: EASTERN CAPE HEALTH RESEARCH COMMITTEE

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF HEALTH

Ref: LP 201901_009
Enquiries: Stander SS
Tel: 015 293 6650
Email: research.limpopo@gmail.com

Ehlert K
University of Pretoria
Private Bag X 323
Arcadia
0007

Greetings,

RE: COCHLEOTOXICITY AND VESTIBULOTOXICITY IN PATIENTS RECEIVING CHEMOTHERAPY IN SOUTH AFRICA

1. Permission to conduct the above mentioned study is hereby granted.
2. Kindly be informed that:-
   - Research must be loaded on the NHRD site (http://nhrd.hst.org.za) by the researcher.
   - Further arrangement should be made with the targeted institutions, after consultation with the District Executive Manager.
   - In the course of your study there should be no action that disrupts the services, or incur any cost on the Department.
   - After completion of the study, it is mandatory that the findings should be submitted to the Department to serve as a resource.
   - The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
   - The above approval is valid for a 1 year period.
   - If the proposal has been amended, a new approval should be sought from the Department of Health.
   - Kindly note, that the Department can withdraw the approval at any time.

Your cooperation will be highly appreciated.

Head of Department

19.02.2019.
Date

Private Bag X9302 Polokwane
Fidel Castro Ruz House, 18 College Street. Polokwane 0700. Tel: 015 293 6000/12. Fax: 015 293 6211.
Website: http/www.limpopo.gov.za

The heartland of Southern Africa – Development is about people!

Western Cape Government
Health

TYGERBERG HOSPITAL
REFERENCE:
Research Projects
ENQUIRIES: **Dr GG Marinus**
TELEPHONE:**021 938 5752**

Ethics Reference: 665/2018

TITLE: **Cochleotoxicity and vestibulotoxity in patients receiving chemotherapy in South Africa.**

Dear Mrs K Ehlert

PERMISSION TO CONDUCT YOUR RESEARCH AT TYGERBERG HOSPITAL.

1. In accordance with the Provincial Research Policy and Tygerberg Hospital Notice No 40/2009, permission is hereby granted for you to conduct the above-mentioned research here at Tygerberg Hospital.

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

DR GG MARINUS
MANAGER: MEDICAL SERVICES

DR D ERASMUS
CHIEF EXECUTIVE OFFICER
Date: 11 March 2019

Administration Building, Francie van Zijl Avenue, Parow, 7500
tel: +27 21 938-6267 fax: +27 21 938-4890
Private Bag X3, Tygerberg, 7505
www.capegateway.go.v.za

Ethics Reference: 665/2018

TITLE: **Cochleotoxicity and vestibulotoxity in patients receiving chemotherapy in South Africa.**

BY 

An authorized representative of Tygerberg Hospital

NAME Dr DS Erasmus

TITLE CEO

DATE 11 March 2019

DEPARTMENT OF HEALTH
LEFAPHA LA BOPHELO BO BOTLE
DEPARTEMENT VAN GESONDHEID
ISEBE LEZEMPILO

Research and Development Unit
Executive Offices
Northern Cape Department of Health
Du Toit Span Road, Belgravia
P/Bag X5049, Kimberley, 8300
Tel: 053 830 2134
Fax: 086 485 3243
Email: BMashute@ncpg.gov.za/
EWorku@ncpg.gov.za

Enquiries:
Dipatlisiso:
Imibuzo:
Navrae :

Dr. E Worku

Date:
Leshupelo:
Umhla:
Datum:

25 March 2019

Reference:
Tshupelo:
Isalathiso:
Verwysing:

NC_201901_002

Mrs. Katerina Ehlert
PO Box 22129
Lyttelton, Centurion
0140

Dear Mrs. Ehlert

Project Title: ***Cochleotoxicity and vestibulotoxicity in patients receiving chemotherapy in South Africa***

The application requesting permission to conduct the above-mentioned research study was reviewed at a meeting of the Provincial Health Research and Ethics Committee (PHREC) for gate-keepers' permission on Wednesday 06 March 2019 and permission was also requested from Robert Mangaliso Sobukwe Hospital (Kimberley Hospital).

PHREC's Decision: Approval granted to conduct this research project at Robert Mangaliso Sobukwe Hospital (Kimberley Hospital).

Your Provincial Ethics Reference Number is ***NC_201901_002,*** kindly use that reference number in correspondence with the PHREC administration

Please note the following:

1) This approval is valid for a period of one (1) year from the date of approval.
2) The researcher is hereby requested to make all the necessary arrangement with the facility CEO to ensure that the provision of healthcare services is not compromised when this project is being conducted.

Please note the following conditions:

1) This project must be conducted at no cost to the Northern cape Department of Health
2) This approval is limited to the research proposal as submitted in the application
3) No variation or modification on the research project
4) PHREC may monitor the research progress at anytime
5) At the completion of this study, a copy of the final report must be submitted to the Research and Development Unit
6) The Northern Cape Department of Health Senior Management Committee shall be briefed on the outcome of the study prior publishing

The committee wishes you success on your research study

Kind regards

Dr. E Worku
Chairperson of PHREC
Tel: 053 830 2134
Cell: 072 703 8037
Email: EWorku@ncpg.gov.za

25/03/2019
Date

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Dr. George Mukhari Academic Hospital

Office *of the Director Clinical Services*
Enquiries : Dr. C Holm
Tel : (012) 529 3691
Fax : (012) 560 0099
Email:Christene.Holm @gauteng.go.za
keitumetse.mongale@gauteng.gov.za

To Mrs K Ehlert
Department of Health Sciences
University of Pretoria
Private Bag X 323
ARCADIA
0007

Date : 01 February 2019

PERMISSION TO CONDUCT RESEARCH

The Dr George Mukhari Academic Hospital hereby grants you permission to conduct research on "Cochleotoxicity and vestibulotoxicity in patients receiving chemotherapy in South Africa" at Dr George Mukhari Academic Hospital

This permission is granted subject to the following conditions:

- ☑ That you obtain Ethical Clearance from the Human Research Ethics Committee of the relevant University
- ☑ That the Hospital incurs no cost in the course of your research
- ☑ That access to the staff and patients at the Dr George Mukhari Hospital will not interrupt the daily provision of services.
- ☑ That prior to conducting the research you will liaise with the supervisors of the relevant sections to introduce yourself (with this letter) and to make arrangements with them in a manner that is convenient to the sections.
- ☑ Formal written feedback on research outcomes must be given to the Director: Clinical Services
- ☑ Permission for publication of research must be obtained from the Chief Executive Officer

Yours sincerely

DR. C. HOLM
ACTING DIRECTOR CLINICAL SERVICES
DATE: 1/2/19

health
Department of
Health
North West Province
REPUBLIC OF SOUTH AFRICA

3801 First Street
New Office Park
MAHIKENG, 2735

Enq Nthabiseng Mapogo
Tel 018 391 4504
NMapogo@nwpg.gov.za
www.nwhealth.gov.za

POLICY, PLANNING, RESEARCH, MONITORING AND EVALUATION

Name of researcher : **Ms. K. Ehlert**
University of Pretoria

Physical Address Room 3-11, Level 3 Communication Pathology Building
(Work/ Institution) Lynnwood Rd, Hatfield, Pretoria 0002.

LEPAPHA LA BOITEKANELO
DEPARTMENT OF HEALTH
Kgetsana Poso /Private Bag X2068
Mmabatho,2735
04 FEB 2019
NORTH WEST PROVINCE
REPUBLIC OF SOUTH AFRICA

Subject : **Research Approval Letter- Cochleotoxicity and vestibulotoxicity in patients receiving chemotherapy in South Africa.**

This letter serves to inform the Researcher that permission to undertake the above mentioned study has been granted by the North West Department of Health. The Researcher is expected to arrange in advance with the chosen facilities, and issue this letter as proof that permission has been granted by the Provincial office.

This letter of permission should be signed and a copy returned to the department. By signing, the Researcher agrees, binds him/herself and undertakes to furnish the Department with an electronic copy of the final research report. Alternatively, the Researcher can also provide the Department with electronic summary highlighting recommendations that will assist the department in its planning to improve some of its services where possible. Through this the Researcher will not only contribute to the academic body of knowledge but also contributes towards the bettering of health care services and thus the overall health of citizens in the North West Province.

Kindest regards

Dr. F.R.M. Reichel
Director: PPRM&E

LEPAPHA LA BOITEKANELO
DEPARTMENT OF HEALTH
Kgetsana Poso /Private Bag X2068
Mmabatho,2735
04 -8 2019
NORTH WEST PROVINCE
REPUBLIC OF SOUTH AFRICA

03/02/2019
Date

Researcher

04/02/2019
Date

Healthy Living for All

DEPARTMENT OF HEALTH
LEFAPHA LA BOPHELO BO BOTLE
DEPARTEMENT VAN GESONDHEID
ISEBE LENKONZO ZENTLALONTLE

Robert Mangaliso
Sobukwe Hospital

Head Clinical Management: Medical

Du Toitspan Road
Private Bag X5021
Kimberley

Tel: 053 802 2147
Fax: 053 832 9413
086 617 4089

Date: 7th February 2019 Dr H Saeed

TO: Mrs K Ehlert

RE: Permission to do research

Permission is hereby granted to conduct a medical research project at Kimberley Hospital complex, title proposed: "Cochleotoxicity and vestibulotoxicity in patients receiving chemotherapy in South Africa"

Please submit proof of ethics clearance, before commencing with the research.
Kindly submit research protocol to the Northern Cape Provincial Health Research and Ethics Committee for approval.

Contact Details:
Dr E Worku
Email address: eworku@ncpg.gov.za
Tel: (053) 8302134

Dr H Saeed
MBBS,H.Dip.Int.Med.(CMSA),M.Fam.Med.(UFS).
Specialist Family Physician
Acting Head Clinical Management: Medical

Date: 07/02/19

APPENDIX G: RESEARCH GRANT APPROVAL

SEFAKO MAKGATHO
HEALTH SCIENCES UNIVERSITY

Office of the DVC: Research, Postgraduate Studies and Innovation

28 August 2018

Enquiry: Mohlatlego Sebola
+27 12 521 4611
Email: mohlatlego.sebola@smu.ac.za

Dear **Ms E Ehler**

RE: Application for PhD

I am pleased to inform you that after reviewing your application and related budget in support of the above said purpose, the Research Support Review Committee has conditionally approved your application for **R 244 360.00**. This award is subject to the following conditions.

1. That a revised signed budget be submitted within 5 working days of receipt of this letter in order to effect transfer of the approved amount.
2. That you accept and sign the Memorandum of Agreement (MoA).
3. The release of any funds and / or procurement of goods and services from this grants is subject to financial, procurement and all other relevant policies and procedures of the university.

You are wished well in your studies.

Yours Sincerely,

PROF OA AYO-YUSUF, BDS, MSc, DHSM, MPH, PhD (Maastricht)
DVC: RESEARCH, POSTGRADUATE STUDIES AND INNOVATION

Molotlegi Street, Ga-Rankuwa
Pretoria, Gauteng
PO Box 201, Medunsa, 0204
www.smu.ac.za

Telephone: +27 12 521 4340/4961
Facsimile: +27 12 12 560 0018

Email: lekan.ayo-yusuf@smu.ac.za

APPENDIX H: PROOF OF ACCEPTANCE AND SUBMISSION OF ARTICLES

Study 1: A national survey of ototoxicity monitoring in South African cancer facilities

From: aosis@sajcd.org.za
To: katerina.ehlert@smu.ac.za; barbara.heinze@up.ac.za; dewet.swanepoel@up.ac.za
Subject: SAJCD 846: Manuscript Accepted for Publication, Sent to Editing
Date: Tuesday, 28 September 2021 10:02:49

****
Ref. No.: 846
Manuscript title: Ototoxicity monitoring in South African cancer facilities – A national survey
Journal: South African Journal of Communication Disorders
****
Dear Katerina Ehlert, Barbara Heinze, Dewet Swanepoel

We are pleased to confirm your manuscript's acceptance for publication on 27-Sep-21.

We can also confirm that the Submission and Review Department released your manuscript to our Finalisation Department to commence the various editing processes to secure online publication within the next 90 days (if not sooner).

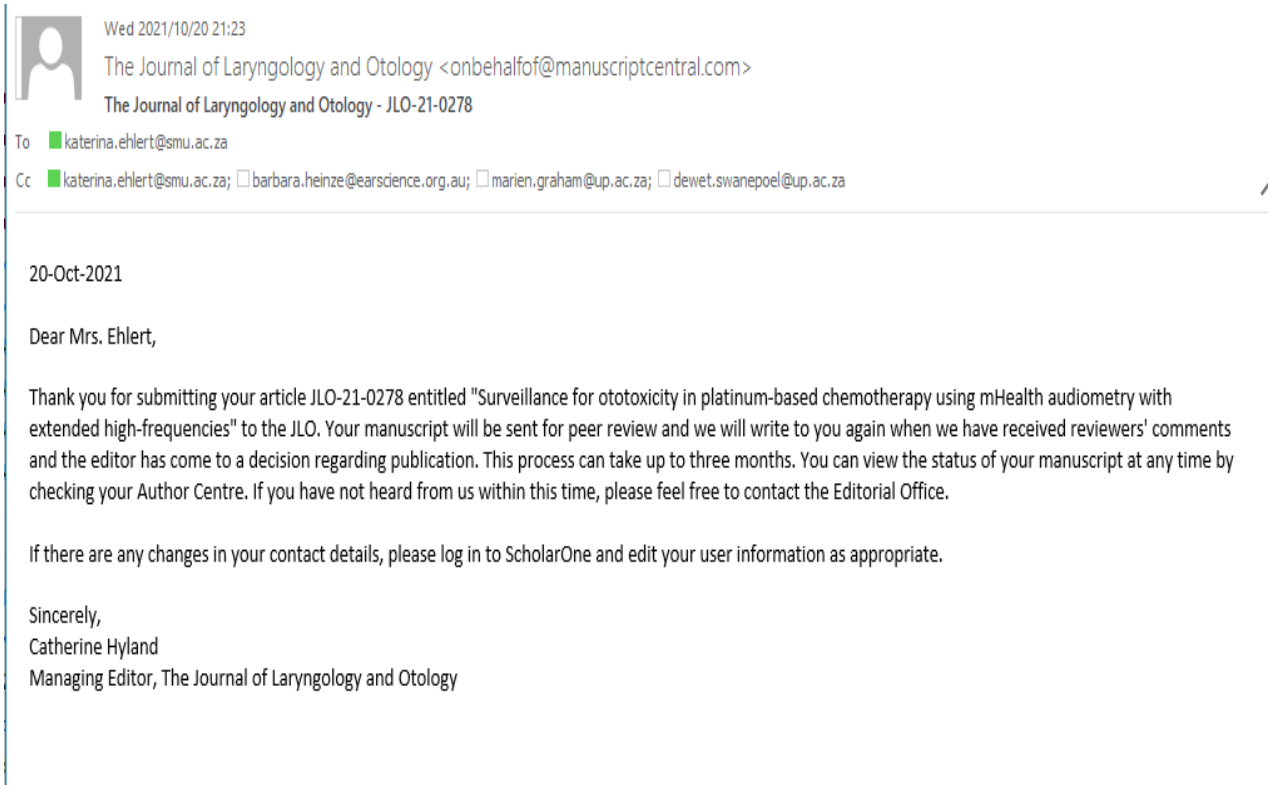
Kindly note:
1. If you need to make contact with AOSIS Publishing during the finalisation stage of your manuscript, kindly contact us per email or phone.
2. The finalisation procedure works as follows: (a) The first stage is the language editing that is returned to the corresponding Author for review. This will be the final opportunity for the corresponding Author to make text changes to the manuscript. (b) At a later stage, the editorial staff will send the corresponding author one set of galley proofs, at which time the Author will have two working days to mark any typographical errors.
3. Manuscript tracking is available on the submitting authors' journal profile. The submitting Author could visit their home page frequently to assess the stage of the manuscript.

Thank you for your continued patience and support, and we hope you have joined our online community by signing up to our RSS alerts and Twitter page.

Kind regards,
Ms Adams
AOSIS
Editorial Coordinator
Submissions and Review Unit
Scholarly Journals Department
AOSIS Publishing, Empowering Africa through access to knowledge

South African Journal of Communication Disorders | https://sajcd.org.za | ISSN: 0379-8046 (PRINT) | ISSN: 2225-4765 (ONLINE)

Study 2: Surveillance for ototoxicity in platinum-based chemotherapy using mHealth audiometry with extended high frequencies



Wed 2021/10/20 21:23

The Journal of Laryngology and Otology <onbehalfof@manuscriptcentral.com>

The Journal of Laryngology and Otology - JLO-21-0278

To katerina.ehlert@smu.ac.za

Cc katerina.ehlert@smu.ac.za; barbara.heinze@earscience.org.au; marien.graham@up.ac.za; dewet.swanepoel@up.ac.za

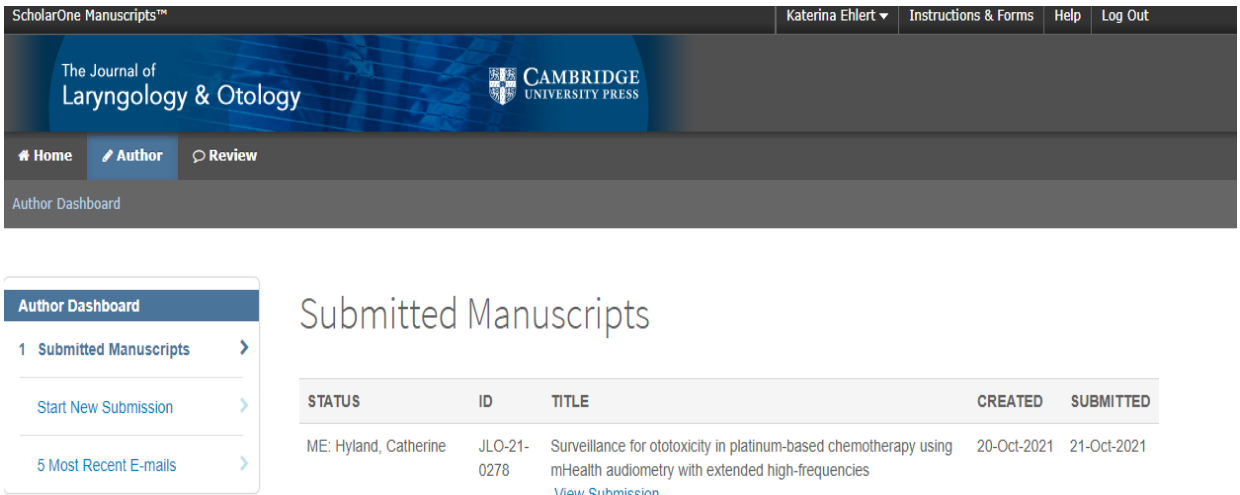
20-Oct-2021

Dear Mrs. Ehlert,

Thank you for submitting your article JLO-21-0278 entitled "Surveillance for ototoxicity in platinum-based chemotherapy using mHealth audiometry with extended high-frequencies" to the JLO. Your manuscript will be sent for peer review and we will write to you again when we have received reviewers' comments and the editor has come to a decision regarding publication. This process can take up to three months. You can view the status of your manuscript at any time by checking your Author Centre. If you have not heard from us within this time, please feel free to contact the Editorial Office.

If there are any changes in your contact details, please log in to ScholarOne and edit your user information as appropriate.

Sincerely,
Catherine Hyland
Managing Editor, The Journal of Laryngology and Otology



Study 3: Changes in vestibular and cochlear function following platinum-based chemotherapy

Jan 17, 2022

Dear Mrs Ehlert,

Your submission entitled "Changes in vestibular and cochlear function following platinum-based chemotherapy" has been received by journal Hearing, Balance and Communication

You will be able to check on the progress of your paper by logging on to Editorial Manager as an author. The URL is https://www.editorialmanager.com/ihbc/.

Thank you for submitting your work to this journal.

Kind regards,

Hearing, Balance and Communication

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Remove my information/details). Please contact the publication office if you have any questions.