THE AUDIOLOGICAL PROFILE OF PAEDIATRIC PATIENTS TREATED WITH CISPLATIN AT A TERTIARY HOSPITAL IN SOUTH AFRICA

By

MUKOVHE PHANGUPHANGU

Student Number: PHNMUK001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree:

MSc Audiology (Master of Sciences in Audiology)

Faculty of Health Sciences,

UNIVERSITY OF CAPE TOWN

Date of submission: 19 February 2018

Supervisor:

Associate Professor Lebogang Ramma,

Head of Department: School of Health and Rehabilitation Sciences,

Faculty of Health Sciences, University of Cape Town
The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.
Plagiarism Declaration

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

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: [Signed by candidate]

Date: February 14, 2018
“Arise and shine;

for thy light is come, and the glory of the LORD is risen upon thee... and His glory shall be seen upon thee”

(Isaiah 60:1-2 KJV)
Acknowledgements

First, to The God of Mount Zion, the Omnipresent and Supreme Deity who always shows mercy, stability and love, and He who has given me the strength and courage throughout this project, le ge ke hlælwâ ke mantšu a ditebogo, ke leboga go menegane.

To my academic advisor Professor Lebogang Ramma, for your guidance and ever-present assurance for this project from beginning to end, I feel short of words to say thank you, but nevertheless, thank you for your encouragement and belief that together we can do it.

To the Management and Clinicians at Red Cross War Memorial Children’s Hospital and all involved in allowing me access to patient’s records, many a thanks.

To Mohlatlelo Nakedi, for assisting with the statistical analysis for this project without hesitation and free of charge, ke o leboga go menegane.

My former colleague and endeared friend Maserole Montjane, biggest of thanks for your support. Andronica Masipa, I could never thank you enough for the editorial revisions for this thesis. Kulani Kwinika, your words of encouragement have made this a success. Special mentions to my best friend, fellow researcher and “editor-in-chief” in everything research, Vera-Genevey Hlayisi, without your motivation, pushing me when I wanted to give up, this project would not have made it to fruition, we have made it, yet again!

To my family: The Queen Mother, Mutshinyani Gladys Phanguphangu, for your undying support, prayers and love that never falls short, your calm and understanding, your pioneering spirit and belief in my work, I can never thank you enough. My older brother, Carter Phanguphangu, your prayers and encouragement delivered at the right time made it possible.

Special mentions to my late grandpa William, and the Matriarch, Tshinakaho, your grandson has made it. This is dedicated to the pair of you. Last but not least, the fallen heroes and heroines of the Black Consciousness, here’s to one for the sons and daughters of the soil. Aluta continua
# Table of Contents

**Abstract** ........................................................................................................................................... 6

**List of Tables** .................................................................................................................................... 6

**List of Figures** .................................................................................................................................... 8

**List of Appendices** .............................................................................................................................. 9

**Key Abbreviations:** ............................................................................................................................. 10

**Definitions of Terms** ......................................................................................................................... 12

**CHAPTER 1: INTRODUCTION AND BACKGROUND FOR THE STUDY** ................. 13

  - Global and regional cancer statistics .............................................................................................. 13
  - Global and regional paediatric cancer statistics .............................................................................. 14
  - Short-term and long-term effects of cancer treatments .................................................................. 15
  - Chemotherapy ..................................................................................................................................... 20

**CHAPTER 2: LITERATURE REVIEW** ................................................................................................. 20

  - Pathophysiology of cisplatin-induced ototoxicity .......................................................................... 22
  - Prevalence of cisplatin-induced ototoxicity in paediatrics ............................................................ 23
  - Risk-factors for cisplatin-induced ototoxicity in paediatric patients ............................................. 25
  - Ototoxicity grading scales in paediatrics ........................................................................................ 29
  - Study rationale .................................................................................................................................... 33

**CHAPTER 3: METHODOLOGY** ........................................................................................................ 35

  - Aims and objectives .......................................................................................................................... 35
  - Research design ............................................................................................................................... 36
  - Participants ........................................................................................................................................ 37
CHAPTER 4: RESULTS .......................................................... 52

Participants ........................................................................ 52
Prevalence of hearing loss .................................................. 54
Nature of hearing loss .......................................................... 54
Degree of the hearing loss ..................................................... 54
Otoacoustic emissions results ................................................. 56
Correlation between cPTA and DPOAE findings, and HF-PTA and DPOAEs .... 56
Other auditory pathologies .................................................... 57
Factors associated with developing hearing loss during cisplatin chemotherapy .... 58
Grading of ototoxic hearing loss ............................................. 59
Chapter summary ............................................................... 61

CHAPTER 5: DISCUSSION .......................................................... 62

Limitations of the study ....................................................... 71

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS .............. 71

Conclusion ........................................................................... 71

Clinical implications and recommendations for future research .................... 72

REFERENCES ........................................................................ 74

APPENDICES ......................................................................... 96
Abstract

**Background:** Fourteen million new cancer cases are reported annually and up to 10% of those involve children below 15 years. Cisplatin, a commonly used anti-cancer drug for its high success rate, is associated with ototoxicity. Cisplatin-induced ototoxicity is characterised by permanent bilateral severe-to-profound hearing loss and hearing loss, when occurring during childhood, can impact negatively on communication development, scholastic performance and quality-of-life.

**Aims:** To determine the prevalence of cisplatin-induced ototoxicity in paediatric oncology patients as well as determining the best paediatric ototoxicity grading scale with regards to early identification and making treatment recommendations in line with the set standards.

**Study Design:** Retrospective records review of paediatric oncology patients who underwent cisplatin-based chemotherapy from January 2016 to December 2017. Data collected included demographic, cisplatin treatment, audiometric and distortion products otoacoustic emissions [DPOAEs] information. The IBM SPSS was used for data analysis.

**Results:** A total of 49 medical records of patients were reviewed for this study. Ototoxic hearing loss was found in 39 (80%) of the patients and a majority (65%) presented with a bilateral moderate-to-severe sensorineural hearing loss. DPOAEs were absent in 32 (67%) patients. Younger age (<10 years), black ethnicity, female gender and higher cumulative dose (>200mg/m²) were all associated with higher incidences of ototoxicity ($p<0.05$). The SIOP scale identified more subjects with hearing loss early (at 1 month testing) and made recommendations about hearing amplification more consistent with the American Academy of Audiology (AAA) Protocol.

**Conclusion(s):** This study found a high prevalence (80%) of cisplatin-induced ototoxicity, which may leave long-term negative impacts on development and quality-of-life. The SIOP scale performed better in early identification of ototoxicity and making treatment recommendations more consistent with the AAA Protocol. Consequently, this study recommends the development of paediatric-specific monitoring protocols including the use of extended high-frequency audiometry. Additionally, these findings highlight the need for experimental studies in oto-protection; to prevent the negative impacts of hearing loss in this vulnerable population group.

**Keywords:** Cisplatin; Hearing Loss, Sensorineural; Paediatrics; Ototoxicity; Tinnitus
List of Tables

Table 1: Testing Protocol Used for Ototoxicity Monitoring at RCWMCH .................. 40

Table 2: Descriptive and Inferential Statistics Used for Data Analysis .................... 46

Table 3: Measures to Ensure Reliability .................................................................... 48

Table 4: Participant Demographic Characteristics (n =58) ..................................... 53

Table 5: Hearing Loss Severity Utilizing cPTA and HF-PTA ................................. 55

Table 6: Associations Age, Gender, Ethnicity and Cancer Type with Hearing Loss ...... 58

Table 7: Comparison of Audiometric Findings Using Ototoxicity Scales ................. 60

Table 8: The Clark (1981) Hearing Loss Classification System ............................. 105

Table 9: International Society of Paediatric Oncology ototoxicity grading scale ....... 106
List of Figures

Figure 1: Tympanometry Norms................................................................. 41

Figure 2: Ototoxicity Monitoring Protocol at RCWMC ................................ 42

Figure 3: Participant Selection Process......................................................... 52

Figure 4: Otoacoustic Emissions Findings.................................................... 56

Figure 5: Prevalence of Cerumen Impaction................................................. 57
List of Appendices

Appendix 1: Ethics Approval, University of Cape Town

Appendix 2: Permission Request Letter for Study at RCWMCH

Appendix 3: Permission to Conduct Study at Red Cross War Memorial Children’s Hospital

Appendix 4: Data Abstraction Sheet

Appendix 5: The Clark (1981) Hearing Loss Classification Table

Appendix 6: International Society of Paediatric Oncology Boston ototoxicity Grading Scale
Key Abbreviations:

AAA: American Academy of Audiology

ASHA: American Speech-Language-Hearing Association

CHL: Conductive hearing loss

CNS: Central nervous system

cPTA: Conventional pure tone average

dB: Decibel

DoH: Department of Health

DPOAE: Distortion-product otoacoustic emissions

EHF: Extended high-frequency

HF-PTA: High-frequency PTA

HL: Hearing loss

NCD: Non-communicable diseases

OHC: Outer hair cells

PTA: Pure tone average

RCWMCH: Red Cross War Memorial Children’s Hospital

SANCR: South African National Cancer Registry

SAPTR: South African Paediatric Tumour Registry
SNHL: Sensorineural Hearing Loss

StatsSA: Statistics South Africa

WHO: World Health Organization

WMA: World Medical Association
Definitions of Terms

**Ototoxicity:** A chemical or drug-induced damage to the sensory structures of the inner ear, which may result in hearing loss, tinnitus, otalgia, and sometimes balance dysfunction (Li, Womer & Silber, 2003).

**Otalgia:** Any form of ear pain (Li, 2018).

**Tinnitus:** A ringing or buzzing sound perceived with or without an external sound source, usually due to inner ear pathology (Hlayisi, 2017).

**Disabling hearing loss:** A hearing loss greater than 40 decibels (dB) in the better hearing ear in adults and greater than 30 dB in the better hearing ear in children (World Health Organization, 2018).

**Cancer:** A class of diseases characterized by rapid and uncontrollable division of abnormal cells which ends up invading and destroying normal body cells. The term cancer can be used interchangeably with malignancy or carcinoma (World Health Organization, 2018).
CHAPTER 1: INTRODUCTION AND BACKGROUND

Introduction: This chapter sets the scene for the study by presenting global and regional cancer statistics, including South Africa. The chapter also gives insight into the connections between cancer, its treatment, and its contribution to the burden of hearing loss.

Global and regional cancer statistics

Cancer, or malignant tumour resulting from an uncontrolled rapid division of cells, is one of the leading non-communicable diseases (NCD) globally (Torre, Siegel, Ward, & Jemal, 2016). Approximately $1.16 trillion is spent on cancer-related costs annually (World Health Organization [WHO] 2018). It is also the second leading cause of death worldwide and resulted in approximately 8.8 million deaths in 2016 (Alleyne, Binagwaho, Haines, Jahan, Nugent, Rojhani, & Stuckler, 2013; WHO, 2018). Annually, as much as 14 million new cases of cancer are reported to the Global Cancer Registry and if the current trends continue, these statistics are projected to rise to 16 million new cancer cases and 10 million cancer-related deaths in 2020, and 27 million new cases with 17 million deaths by 2030 (WHO, 2018). Prevalence CANSA (n.d.) also estimates that by 2030, 75 million people will be diagnosed with cancer globally. More than half (57%) of cancer cases reported worldwide are from low to middle-income countries (Zubizarreta, Fidorova, Healy, & Rosenblatt, 2014).

In terms of gender distribution, there appears to be an even distribution with 52% of the cases affecting males and the remaining 48% affecting females (Fernlay, Soerjomataram, Ervik, Dikshit, Eser, Mathers, Rebelo, Parkin, Forman, & Bray, 2012). Lung, breast (female), bowel and prostate cancers are among the four leading cancers and account for over 40% of the cancer-related mortalities globally (CANSA, n.d.). Lung cancer is also the most commonly diagnosed cancer in males and accounted for 13% of cancers reported globally in 2012, while cancer of the breast is the most common in females with an estimated 1.7 million new cases in
WHO (2018) also reports that among both genders, colorectal cancer is the second most common cancer with nearly 1.4 million new cases annually.

In South Africa, cancer statistics are underreported mainly due to the limited number of cancer registers available (Stefan, Stones, Wainwright, Kruger, Davidson, Poole, Hadley, & Steliarova-Foucher, 2015). One of the cancer statistics, the South African National Cancer Registry (SANCR), indicates that 1.5 million people may have cancer and approximately 100,000 new cases are added to this register annually (CANSA, n.d.; Stefan et al., 2015). These statistics are projected to rise, with an estimated 120,000 new cases anticipated in 2030 when compared to 77,440 cases reported in 2012 (Stefan et al., 2015). The Statistics South Africa (StatsSA) report (2017) indicates that 12,000 mortalities (8%) in South Africa are due to cancer, mainly those affecting the digestive system in males and reproductive organs in females in adults aged 45 years and above.

**Global and regional paediatric cancer statistics**

According to WHO (2018), more than 10% of the reported global cancer statistics affect children below the age of 15 years. Furthermore, more than 160,000 new paediatric cancer cases are reported annually (Miller, Siegel, Lin, Mariotto, Kramer, & Rowland, 2016; WHO, 2017). In 2015, approximately 90,000 global paediatric mortalities were attributed to cancer (WHO, 2017). In South Africa, as much as 9 per 100,000 children below the age of 18 years have cancer, while more than 1,551 children lost their lives due to cancer and its related toxicities in South Africa in 2015 (Stefan et al., 2015; WHO, 2017).

Paediatric cancers tend to be different from those found in adults and most often occur in the developing cells like bone marrow, blood, kidneys and nervous system tissue whereas in adults, cancer targets viscera such as lungs and reproductive organs. As a result, the leading types of cancers in children are different to those affecting adults. A recent study by Miller and
colleagues (2016) to determine the commonly diagnosed cancers in American children below the age of 14 years found that leukaemia was the most commonly diagnosed cancer in children and accounted for more than 30% of cancers diagnosed in this age group. This finding was similar to rates in other countries. In the same study by Miller et al. (2016), brain and central nervous system (CNS) tumours came second at 26% (including benign tumours), while soft tissue sarcomas (7%) were the third commonly diagnosed cancers in children in this age group. However, in children aged 15-19, the most commonly diagnosed cancers were CNS tumours (20%) followed by leukaemia (14%) and Hodgkin’s lymphoma (13%). In South African children of the same age group, leukaemia, lymphoma, nephroblastoma, and retinoblastoma are the most commonly diagnosed cancers.

While survival rates for childhood cancer have been reported to be lower in the past, current studies indicate that timeous diagnosis, evidence-based practice through clinical trials and proper treatment regimens have led to an increase in the survival rates (Landier, Knight, & Wong, 2014). This statement is supported by Stefan et al., (2015) who also reported that with early diagnosis and timeous referrals for treatment, lymphomas and nephroblastoma have the highest survival rates, at 64% and 63% respectively. Brain tumours, however, have been reported to have the worst prognosis with a survival rate of 46.4%. Overall, the survival rate of cancer is somewhat higher in South Africa, estimated to be around 6 in every 10 patients diagnosed (Cansa, 2017).

**Short-term and long-term effects of cancer treatment**

Childhood cancer like any other cancer is treated with a range of treatments which include chemotherapy, surgery and radiation. Chemotherapy can result in a number of both short-term and long-term health effects. A recent study by Armstrong and colleagues (2013) found that more than half of paediatric patients who undergo chemotherapy develop a life-
threatening chronic health condition by the time they turn 50 years old. These chronic health conditions include but are not limited to second malignancies, cardiovascular and CNS diseases, pulmonary dysfunction, and kidney disorders. A study by Goulios and Patuzzi (2015) found that these conditions affect survivors of childhood cancers more than they affect their siblings who never had cancer. In the Childhood Cancer Survivor Study (CCSS), the collective incidence of self-reported fatal health conditions by age 20 years was reported to be 16% amongst childhood cancer survivors and by age 50 years, this incidence increased to 53.6%.

Cognitive impairment, which varies in severity, has been reported in about 33% of cancer survivors who undergo either chemotherapy or radiation (Castellino, Ulrich, Whelen, & Beverly, 2014). Radiation, surgeries and some chemotherapy for the treatment of cancers affecting the reproductive organs have been implicated in infertility among both female and male patients (Barton, Najita, Ginsburg, Leisenring, Stovall, & Weathers et al, 2013; Wasilewski-Masker, Seidel, Leisenring, Mertens, Shnorhavorian, & Ritenour et al 2014). In addition, permanent sensorineural hearing loss, tinnitus and ear pain have also been reported widely following platinum-based chemotherapeutics such as cisplatin and carboplatin (Knight, Chen, Freyer, Aplenc, Bancroft, & Bliss 2017; Mudd, 2014; Whitehorn, Sibanda, Lacerda, Sparcklen, Ramma, Dalvie, & Ramesar 2014).

Platinum-based chemotherapeutics, in particular, cisplatin, have been implicated in the development of sensorineural hearing loss among patients treated with them. Literature indicates this prevalence to range from 10-94% of those patients treated for cancer (Coradini, Cigana, Selistre, Rosito, & Brunetto, 2007; Knight et al., 2007; Whitehorn et al., 2014; Yancey, Harris, Egbelakin, Gilbert, Pisoni, & Renbarger, 2012).

The sensory nature of the hearing loss means that it is one of the few chronic and permanent conditions for which, in the majority of the cases, there are limited medico-surgical treatments. Although audiological intervention with hearing aids may improve the situation,
sensorineural hearing loss can have a negative impact on communication between the individual and those around them. Hearing loss that can result from cisplatin can have devastating consequences, especially when it occurs during childhood. According to Butler (2012), a hearing loss during childhood can have devastating impacts on a child’s development such as poor communication and socio-emotional development, poor scholastic performance, poor reading and writing abilities, and poor quality of life for the child and society at large (Butler, 2012; Humes & Bess, 2008; Phanguphangu, 2017; Theunissen, Rieffe, Kouwenberg, De Raeve, Soede, Briaire, & Frinjs, 2014).

A study by Tomblin, Harrison Ambrose, Walker, Oleson, and Moeller (2015) among 290 children aged 2-6 years found that children with a mild to moderate hearing loss had poor language development and depressed language levels when compared to their normal-hearing counterparts. The impact of hearing loss on these children manifested as poor phonological awareness, articulation and phonological disorders and language delay, which in turn resulted in poor speech-language abilities. This impact was directly related to the degree of the hearing loss, where the severe the degree of the hearing loss, the severe the communication outcomes were observed. These findings are supported by Lieu, Tye-Murray, Karzon and Piccirillo (2010) who, in their study among 148 children (6-12 years), also found that children with hearing loss had poor comprehension, grammatical skills, numeracy, and spoken language. Additionally, Lieu and colleagues (2010) also found that children with hearing loss presented with more spelling mistakes and poor reading and writing skills when they were compared to their normal-hearing peers.

Hearing loss may also have a negative impact on the development of effective social encounters with peers and friends (Preisler, Tvingstedt, & Ahlstrom, 2002). Because hearing loss impacts the effective use of spoken language as stated above, children with hearing loss may also have difficulties in forming positive relationships with normal hearing children.
A study by Bat-Chava and Deignan (2001) which investigated social skills among school-age children with hearing loss found that positive and friendly relationships among hearing-impaired children and normal hearing children are somewhat different when compared to relationships between normal hearing children and their hearing friends. Bat-Chava and Deignan (2010) theorized that this could be due to the fact that children with hearing loss may have trouble understanding spoken language, and by virtue, feel isolated and intimidated by those with normal hearing and thus their relationships are less friendly. Bat-Chava and Deignan (2010) also indicated that those children with hearing loss felt isolated because the hearing loss makes it difficult for them to engage in social interactions as their communication skills, which are mostly delayed in these children, are a prerequisite for communication between two parties.

Wauters and Knoors (2007) conducted a study on social media usage in children and adolescents and found that those with hearing loss were more active on social media; however, the relationships they had were not as concrete when compared to those with normal hearing. This finding was attributed to the fact that social media is more a written form of language than spoken language and thus, those with hearing loss could interact with others without using spoken language. Wauters and Knoors (2007) reported that more children with hearing loss resorted to social media as they had a higher sense of isolation, not fitting in with friends, and feeling lonely. Additionally, children with hearing loss were reported to have fewer friends because they felt rejected or neglected more often than their hearing peers, leading them to feel isolated and lonely.

It is clear from the studies reviewed above that the negative consequences of hearing loss on communication and socio-emotional development and language use, in general, can have a negative impact on scholastic performance and academic achievement. Similar observations were made by Daud and colleagues (2010) who found that 88% of students who
performed poorly at school had mild to moderate hearing loss. Poor scholastic performance and academic achievement has been directly linked to poor employment opportunities later in life, and thus poor economic status and quality of life. A study by Punch, Creed, and Hyde (2006) assessing employment opportunities on 65 adolescents who developed childhood hearing loss found that the functional effects of hearing loss and the negative attitudes of those around them created barriers for employment opportunities. Punch and colleagues (2006) assert that this is because a majority of the public, including potential employers, see hearing loss as a limitation to the accessibility of many occupations. Furthermore, Szymanski, Hershenson, Enright and Ettinger (1996) also argue that although modifications can be done in the workplace to accommodate those with hearing loss, ignorance of the possibility of such job accommodations may lead to these patients not getting employed. Consequently, these patients do not become economically active; they avoid social interactions with their hearing counterparts and also feel isolated and depressed (Bat-Chava & Deinan, 2001; Punch, Creed & Hyde, 2006; Szymanski et al., 1996; Zubizarreta et al., 2014). Additionally, families of those with hearing loss and society may also suffer third party disability as they may struggle to adjust to the communication needs for the hearing impaired. This is most evident where caregivers may have to learn sign language, master communication skills required to communicate with a hearing impaired or deaf patient as well as having to plan social activities that would also include someone with a hearing impairment (Bat-chava and Deignan, 2010; Lieu et al., 2010; Martin et al., 2010; Preisler et al., 2002; Wauters & Knoors, 2007). As can be seen, early identification of hearing loss in children who are being treated for cancer is, therefore, of paramount importance where timeous management is concerned.
CHAPTER 2: LITERATURE REVIEW

Introduction: In this chapter, literature linking cisplatin chemotherapy with hearing loss is critically reviewed. Existing gaps in literature specific to cisplatin-induced ototoxicity in the paediatric population in South Africa are highlighted to provide a rationale for this study.

Chemotherapy

Chemotherapy is the first line of treatment for cancer for a few soft tissue tumours which dates back to the 1940s when nitrogen was used in clinical practice (Knight et al., 2017; Waissbluth, Pitaro, & Daniel, 2012; Whitehorn et al., 2014). Additionally, it is also used as an augmentative treatment to other treatment modalities such as surgery or radiation. In many instances, a combination of drugs is used to achieve successful treatment (Reavis, McMillan, Austin, Gallun, Fausti, Gordon, & Konrad-Martin, 2011). This is because the majority of chemotherapy drugs have dose-limiting factors such as ototoxicity and nephrotoxicity amongst others (Knight, et al., 2017; Waissbluth et al., 2012; Whitehorn, et al., 2014). Chemotherapy for childhood cancer is mainly through platinum-based chemotherapeutics such as carboplatin and cisplatin (Reavis et al, 2011; Waissbluth et al., 2012; Whitehorn, et al., 2014).

Connection between cancer and hearing loss

The connection between cancer and hearing loss is due to the fact that cisplatin, one of the main drugs for cancer chemotherapy treatment, can lead to a permanent hearing loss (Knight et al., 2017; Mudd, 2016; Whitehorn et al., 2014). Chemotherapy for childhood cancer is mainly through platinum-based chemotherapeutics such as cisplatin, oxiplatin and carboplatin (Knight et al., 2017; Waissbluth et al., 2012; Whitehorn et al., 2014). Cis-diamminedichloroplatinum (II), commonly referred to as cisplatin, is the first platinum-based chemotherapeutic to be approved for cancer treatment by the United States’ Federal Drug
Agency in 1978 (Dasari & Tchounwou, 2015). Although only approved for cancer treatment in 1978, the origin of cisplatin dates back to the 1840s (Dickey, Wu, Muldoon, & Neuwelt, 2005). To date, it is the most widely prescribed anticancer drug used in the treatment of various solid and soft tissue cancers, including cancers of the testes, ovary, lungs, lymphomas, sarcomas, CNS tumours and cancers of the head and neck amongst others (Dickey et al., 2005; Rybak, Whitworth, Mukherjea, & Ramkumar, 2007).

**Cisplatin**

Currently, nine analogues in clinical trials exist aimed at enhancing the therapeutic index of cisplatin which includes carboplatin, oxaliplatin and enloplatin amongst others (Dasari & Tchounwou, 2014). Carboplatin is the only analogue that has shown comparable efficacy to cisplatin, and it is used for the treatment of cancers of the ovaries, lung cancer and cancers of the head and neck (Dasari & Tchounwou, 2014). However, it exhibits a slower reactivity and binding properties when compared to cisplatin, and its effectiveness is 45 times less than cisplatin. And for every single dose of cisplatin required, about four doses of carboplatin are required to reach the desired effect equitable to that of cisplatin (Dickey et al., 2005). As a result, cisplatin is the drug of choice due to its relative availability, the success rate in cancer treatment and its cheaper price (Dickey et al., 2005; Paken, Govender, Pillay, & Sewram, 2016).

In children, cisplatin is mostly used for soft tissue and solid malignancies such as neuroblastomas and osteosarcomas (Knight et al., 2017; Konrad-Martin, Reavis, McMillan, Helt, & Dille, 2014). Its mode of action has been linked to its ability to bind with the purine bases on the deoxyribonucleic acid (DNA) of cancer cells, blocking the cell division process and consequently apoptotic cell death of these cancer cells (Dasari & Tchounwou, 2015). High doses of cisplatin may cause neurotoxicity, nephrotoxicity and ototoxicity (Amptoulach &
Tsavaris, 2011; Mudd, 2014; Whitehorn et al., 2014). Ototoxicity is considered and has been widely reported, to be the most notable dose-limiting factor of cisplatin, even in the current era of a wide variety of oto-protection (Knight et al., 2017).

**Pathophysiology of cisplatin-induced ototoxicity**

Literature on the pathophysiology of cisplatin-induced ototoxicity is not extensive, however, current reports indicate that cisplatin, along with the two other platinum-based agents oxiplatin and carboplatin, causes four main changes in the cochlea namely mechanical, biochemical, functional and morphological (Callejo, Sedó-Cabezón, Juan, & Llorens, 2015; Rybak et al., 2007). Cisplatin acts on the deoxyribonucleic acid (DNA) structures of the cells to inhibit cell division of the cancer cells, causing cell death by apoptosis (Florea & Büsserlberg, 2011). In the cochlea, cisplatin is absorbed into the endolymphatic fluid and thus enters the cochlear duct where it results in the formation of reactive oxygen species (ROS) due to its oxidative effects (Dasari & Tchounwou, 2015). These ROS eventually cause cell death by apoptosis, which is evidenced by the sensory nature of the hearing loss observed in these patients (Knight et al., 2017; Whitehorn, et al., 2014). Whitehorn and colleagues (2014) observed and reported that the hearing loss observed in this population begins at the higher frequencies and later progresses to the lower frequencies. This is supported by Knight et al (2017) who also documented that the hearing loss is topographic in nature, beginning in the higher frequencies to later affect the lower frequency range. Rybak and colleagues (2007) also state that the damage is topographic and thus affects the cochlea from the base to the apex, which results in hearing loss which begins at the high-frequency range and later progresses to the lower frequencies.

A study by Callejo, Sedó-Cabezón, Juan and Llorens (2015) found that cisplatin alters the endocochlear action potential, and elevates the cochlear microphonic and compound action
potential thresholds. These changes in the biochemical composition result in a misfiring of the outer hair cells within the cochlea, which is manifested by reduced or DPOAEs. Choe, Chinosornvatana and Chang (2004) also reported that cisplatin may result in damage to the cochlear outer hair cells by oxidation stemming from the formation of the ROS. The latter is also evidenced by the affected cochlear microphonic and diminished otoacoustic emissions and eventually hearing loss. Findings from animal studies by Rybak, Mukherjea, Jajoo and Ramkumar (2009) also found that not only the outer hair cells in the cochlea are affected but other structures – the organ of Corti, spiral ganglia and the cochlear lateral wall may be affected as well (Rybak, et al., 2009).

**Incidence of cisplatin-induced ototoxicity in paediatrics**

Several studies have been conducted to determine the incidence of cisplatin-induced ototoxicity in paediatric patients. Findings of these studies are variable, with a reported incidence of cisplatin-induced ototoxicity ranging from 13% to 94% (Coradini et al., 2007; Knight, Kraemer, Winter, & Neuwelt, 2007; Landier et al., 2014; Yancey et al., 2012). This variability might be explained by the heterogeneity of populations studied, sample size, variability in treatment protocols, norms used to classify hearing loss and the use of different ototoxicity grading scales (Landier, et al., 2014). For example, in a retrospective study by Yancey et al (2012) on 102 participants, cisplatin-induced ototoxicity was documented in 42% (43/102) when utilizing conventional audiometry while Li, Womer and Silber (2004) on 153 participants which utilized conventional audiometry, found an incidence of 53%. Another recent prospective study by Nitz et al (2012) on 108 paediatric participants also found that 49.1% (53/108) presented with hearing loss when evaluated using conventional pure tone audiometry.
In comparison, a prospective study by Knight, et al. (2007) utilizing conventional audiometry, EHF audiometry and otoacoustic emissions testing found higher incidence rates. In this Knight et al (2007) study with 32 participants, 63% (20/32) of the participants were diagnosed with ototoxicity using conventional audiometry, while 94% (30/32) were diagnosed with ototoxicity when utilizing EHF audiometry. Additionally, DPOAEs testing yielded an 81% incidence of ototoxicity. A similar study by Coradini et al (2007) on 23 paediatric patients utilizing EHF audiometry and DPOAEs in addition to conventional audiometry also documented higher incidence rates. In this study 94% of their participants were diagnosed with ototoxicity with extended audiometry, while DPOAEs were absent in 84% of the participants. However, when utilizing conventional audiometry, only 52% of the participants were diagnosed with ototoxicity in this study. Findings from these studies indicate that conventional audiometry may not be as sensitive in detecting ototoxic hearing loss following cisplatin, particularly in the higher frequency range where this hearing loss begins prior to its progression to the lower frequencies. Therefore, this may negatively affect early identification (i.e. through serial ototoxicity monitoring) and intervention (hearing amplification).

According to Knight et al (2017), norms used to diagnose and classify hearing loss have also been reported to result in different incidence rates. This is due to a general disagreement when it comes to diagnosis of hearing loss, specifically in paediatrics where other authors indicate that any thresholds above 16 dB HL constitute a hearing loss (Clark, 1981) while other scholars only consider thresholds above 25 dB HL to indicate a hearing loss (Stach, 2010). A study by Knight et al (2017) found that 69/101 (68%) patients seen presented with ototoxicity when the more sensitive (15 dB HL) norms were used when compared to a 28% when the less sensitive norms (25 dB HL) were used.
As can be seen from the studies reviewed thus far, there is variability in terms of incidence reported, mainly arising from the difference in sample sizes, methods used to diagnose ototoxicity and the norms used to classify hearing impairment. For example, variability in sample size can affect incidence rates. Although sample sizes are determined by the expected outcome of the measurements and the population at hand, in epidemiological studies such as the ones reviewed for this study, sample size calculations and agreements are important as they play an important role in the ability to detect the effects or outcomes being measured (Hajian-Tilaki, 2011). Smaller sample sizes do not provide a precise estimate and reliable answers to study aims and objectives. Additionally, studies with smaller sample sizes cannot reach valid and generalizable conclusions (Hajian-Tilaki, 2011). Additionally, studies with smaller sample sizes may under or over report the findings since the sample size may not be a statistically significant representation of the general population being studied. This appears to be true in the studies reviewed above, as can be seen on the variability of the incidence of ototoxic hearing loss reported by these studies.

**Risk-factors for cisplatin-induced ototoxicity in paediatric patients**

Risk factors for cisplatin-induced hearing loss in paediatrics are well documented. The available studies report two categories of risk factors, namely genetic and non-genetic risk factors. These are described in detail below.

Genetic predisposition for hearing loss: Several studies have been conducted to determine the roles of genetics in the development of sensorineural hearing loss following cisplatin chemotherapy. For example, Maagdenburg and colleagues (2016) reported that the genes *TPMT, COMT, ABCC3, SOD2* are known to increase the risk for cisplatin ototoxicity. Maagdenburg et al (2016) however, cautions that many of the studies documenting genetics and their associations to ototoxicity could not be replicated. One South African study by
Whitehorn et al (2014) on 68 adults found the alleles COMT and TPMT in high proportion among adults who developed cisplatin-induced hearing loss when compared to those who did not, although this finding was not statistically significant. Another study by Theissen et al (2017) on 149 children found that the allele ACYP2 was associated with higher (75.8%) incidences of ototoxicity in children treated with cisplatin when compared to TPMT and COMT which were not associated with sensorineural hearing loss.

✔ Established non-genetic risk factors that increase the susceptibility to ototoxic side effects and hearing loss associated with cisplatin are summarized below:

➢ Co-treatment with other potentially ototoxic drugs, particularly amino-glycoside antibiotics, has also been reported to increase the risk for developing cisplatin-induced hearing loss in paediatrics (Whitehorn et al., 2014; Yancey et al., 2012).

➢ Dose and dosing schedule: Higher cumulative doses of cisplatin are linked to greater incidences of cisplatin-induced hearing loss whereas single doses are not associated with higher incidences of ototoxicity, although the latter depends on the dose received by the patient (Li et al., 2004; Yancey et al., 2012). A study by Choeyprasert, Sawangpanich, Lertsukprasert, Udomsubpayakul, Songdej, Unurathapan, Pakasama and Hongeng (2013) among 68 paediatric participants found that cumulative doses of 400 mg/m² or more were associated with higher incidences of ototoxicity when compared to lower cumulative doses (<400 mg/m²). These findings are similar to those reported in literature, supporting that cumulative cisplatin doses of 400 mg/m² increases the chances of developing ototoxic hearing loss (Dean et al., 2008; Gupta et al., 2006; Landier et al., 2016; Nitz et al., 2013; Whitehorn et al., 2014).

➢ Cranial radiation is reported to result in a hearing loss and when coupled with cisplatin, the risk for developing cisplatin-induced hearing loss is reported to be debilitating (Khoza-Shangase, 2007). This hearing loss is attributed to the damage of
the auditory structures located within the temporal bone due to radiation. Radiation therapy-induced SNHL varies from 0% to 54% across studies (Hua, Bass, Khan, Kun, & Merchant, 2008; Jereczek-Fossa, Zarowski, Milani, & Orecchia, 2003). Although cranial radiation is less ototoxic when compared to platinum-based chemotherapy (i.e., cisplatin), it is still associated with high risk for SNHL and even more so when combined with cisplatin (Low, Toh, Wee, Fook-Chong, & Wang, 2006).

- **Age:** It is reported that children younger than 5 years are at greater risk of developing significant hearing loss when compared to those between the ages of 15–20 years (Li et al., 2004). A report by Yancey et al (2012) found that patients with a mean age of 4.5 years were reported to have acquired Brock grade 3 ototoxicity as compared to those who were 11 years and 7 years who suffered only grades 1 and 2 ototoxicity respectively. This could be attributed to their body’s ability to regulate drugs and the susceptibility of their cochlea to damage when compared to older patients.

- **Gender:** Associations between gender and ototoxicity are inconclusive. Some studies cite that gender does not play a role, while others cite males are at a higher risk, and others, on the contrary, state that females are at a higher risk (Li et al., 2004; Yancey et al., 2012). For example, similar to studies by Li et al (2004), Gupta et al (2006) and Dean et al (2008) found no associations between gender and hearing loss, reporting a fairly even distribution of gender among those with hearing loss in their studies. In contrast, studies by Yancey et al (2012) and Low et al (2006) found males to be 4 more times likely to develop hearing loss following cisplatin chemotherapy.
Preventing cisplatin-induced hearing loss

Due to advancements in cancer treatments, there has been a decline in cancer related mortalities. However, these advanced treatments, cisplatin in particular, are associated with high incidences of ototoxicity, evidenced by high-frequency sensorineural hearing loss accompanied by tinnitus and ear pain (Gurney et al., 2007). Unfortunately, ototoxic hearing loss often goes unnoticed until speech discrimination becomes affected leading to communication difficulties (Fausti et al., 2005; Konrad-Martin et al., 2005). This hearing loss is even more devastating when it occurs in children who have yet to develop communication skills, have to attend school and also acquire socio-emotional skills. Early identification of this hearing loss is therefore very important (Fausti et al., 2005). For this purpose, ototoxicity monitoring can be used to identify those who are at risk to prevent the negative impact of this hearing loss as early identification can lead to timeous and proper audiological care.

Jacob et al (2005) reports that ototoxicity monitoring is currently the only reliable means which can enable early identification and early intervention before the hearing loss advances to affect communication. As such, a cancer treatment team should, therefore, include audiologists who will provide the ototoxicity monitoring, with the patient being the central focus (Yancey et al., 2012). According to Yancey et al (2012), the role of the audiologist in the cancer treatment team is (i) early identification, (ii) informing the treating clinician of significant change in hearing thresholds, (iii) providing counselling to the patient and their family, and (iv) provision of rehabilitation services to the patient. Additionally, early identification of ototoxic hearing loss also allows oncologists with an opportunity to adjust the treatment regimen in order to reduce or prevent further deterioration of hearing (Schellack, Wium, Ehlert, van Aswegen, & Gous 2015).
Fausti and colleagues (2007), in agreement with the American Speech-Language-Hearing Association (ASHA, 1994), indicate that ototoxicity monitoring should include a detailed case history to gather information regarding previous hearing history, treatment with any other ototoxic drugs, family history of hearing loss and concomitant treatment with ototoxic drugs among others. Additionally, it should include an otoscopic examination to rule out any pathologies that could result in hearing loss and refer the patients for further management. Immittance audiometry should also be performed to assess the functioning of the middle ear status. Furthermore, pure tone and speech audiometry should also be performed to assess hearing thresholds and speech intelligibility and DPOAEs to assess the functioning of the cochlear hair cells. In addition, EHF audiometry (i.e., 8000 to 20 000 Hz) should also form part of the ototoxicity monitoring protocol, for early identification of hearing loss in the EHF range where ototoxic hearing loss typically begins prior to progression to the lower speech frequency range. These tests should be conducted prior to treatment followed by monthly assessments, and an exit audiogram at the end of therapy followed by follow-up assessments yearly for at least three years as cisplatin can result in delayed and late-onset hearing loss as reported by Campbell et al (2003). If the patient is identified with hearing loss at any of the screenings as detailed above, notification to the oncologist should be immediate for effective management, which may include altering the dosage or changing the regimen altogether (Campbell et al, 2003; Fausti et al., 2007; Yancey et al., 2012).

**Ototoxicity grading scales in paediatrics**

Hearing loss is classified and graded in severity using pure tone average (PTA) calculations (Clark, 1981). Specific to ototoxicity-induced hearing loss, there are several scales that could be used to classify and grade the severity of hearing loss. The most commonly used scales include the Common Terminology Criteria for Adverse Events (CTCAE), the Brock
grading scale and the Chang grading scales (Brock, Knight, Freyer, Campbell, Steyger, Blakley, Rassekh, Chang, Fligor, Rajput, Sullivan, & Neuwelt, 2012). There seems, however, to be a lack of consensus regarding the best grading scales due to the limitations associated with the different grading scales. For example, although, the Brock scale was developed to detect the effects of ototoxicity as well as guide treatment options, it fails to detect a slight to mild (16-40 dB HL) hearing loss. A hearing loss of this degree (16-40 dB HL) can have debilitating effects on speech and language acquisition, speech discrimination as well as phonological awareness, particularly in this study as it is mainly based on paediatric patients who are still in their language acquisition age (Butler, 2012; Phanguphangu, 2017). Thus, it fails to highlight the needs of paediatric patients who may require amplification even when they have a mild hearing loss which may result in negative impact on the speech-language acquisition.

A modified version of the Brock grading scale is the Chang grading scale, implemented to incorporate functional deficits caused by a hearing loss below 40 dB HL in children (Chang & Chinosornvatana, 2010). The Chang scale not only incorporates and highlights the importance of recommending treatment for functional and sensory deficits in patients with a slight to mild hearing loss in the normal frequency response. It also highlights the importance of incorporating higher frequencies and EHF testing, an important aspect in ototoxicity, as cisplatin-induced ototoxicity usually affects the higher frequencies first before effecting the more protected apical ends of the cochlea. As such, the Chang scale advocates for the use of the high frequencies and is more sensitive in determining the possible deficits children who are developing language and other skills required to function effectively in the classroom (Chang & Chinosornvatana, 2010).

Although the Chang scale is recommended for use in paediatrics, there is currently an argument that due to the existence of several ototoxicity grading scales, there is no common
grading scale that could be used to facilitate communication of ototoxicity across different contexts. Therefore, another ototoxicity grading scale was proposed, for use specifically in oncology patients, the International Society of Paediatric Oncology Boston (SIOP) scale (Bass et al., 2014; Brock et al., 2012).

The SIOP scale is a modified version of the Chang scale which was proposed to improve the consistency of data in multi-centred studies and allow grading when only two to three frequencies can be measured, particularly in paediatrics where hearing evaluations can prove difficult (Lewis et al., 2009). It, however, does not give information regarding hearing loss in the EHFIs where cisplatin-induced ototoxicity typically begins and where the high frequencies are topographically represented, which when damaged, can result in poor speech discrimination.

Defining and grading the severity of hearing loss following the platinum-based chemotherapy is essential for assessing the impact of treatment, and for determining appropriate clinical interventions for the different attending members of the multi-disciplinary team. However, there are various ototoxicity grading scales that are used by different professionals who manage patients who are being treated with ototoxic drugs (Schultz, Goffi-Gomez, & Liberman, 2009). Grading scales are important for grading medication’s side effects and providing guidelines for subsequent medication and therapy (Waissbluth et al., 2016). A good ototoxicity grading scale should enable early identification of hearing loss following treatment with ototoxic medications and specify the severity of the hearing loss that the patient acquired as a result of treatment; grades of severity of hearing loss specified should correlate well with functional activities and be applied by different professionals (Chang & Chinosornvatana, 2010). Furthermore, a good ototoxicity grading scale should also accurately identify patients who should be considered for further audiological management via hearing
aids or other forms of assistive listening devices when speech frequencies have been impacted (Crundwell, Gomersall & Baguley, 2016).

However, currently there is no ototoxicity grading scale that is considered a ‘gold standard’ with respect for grading treatment-induced hearing loss that is universally adopted or accepted for use across different contexts and by different professionals (Rybak, 2007). This means that different professionals use their preferred grading criteria when communicating severity of ototoxicity-induced hearing loss and this can potentially lead to a communication gap between different professionals who manage patients who are treated with ototoxic medications (Chang & Chinosornvatana, 2010).

Therefore, given the above review regarding variation in grading scales used to classify ototoxicity-induced hearing loss, there is a need to work towards identifying a common scale for grading ototoxicity which will facilitate communication across different settings and between different professionals. A major drawback of the existing criteria is that none of them elaborately evaluate and consider the patients’ complaints (Schultz et al., 2009). This information is often asked from the attending physicians to get a clear picture of the implication which hearing loss has on the patients’ quality of life (Schultz et al., 2009).


**Study rationale**

It can be concluded based on the literature reviewed thus far that cancer, one of the major leading NCDs globally, affects a significant number of children. This can potentially lead to a significant number of paediatric patients being treated with cisplatin as part of chemotherapy treatment for cancer. However, while cisplatin is highly effective for the treatment of malignancies, it is also associated with high incidence of ototoxicity. Children are especially at a higher risk to acquire cisplatin-induced hearing loss when compared to adults.

Acquiring treatment-induced hearing loss can have debilitating effects on communication and psycho-social development, scholastic performance, employment opportunities at a later stage, and quality of life, not only does it affect the patient, but the society as a whole. Thus, early detection of hearing loss becomes necessary, especially if the provision of individualised aural rehabilitation programmes is to be effected timeously. However, currently, South Africa has limited locally generated literature on the prevalence of cisplatin-induced ototoxicity in the paediatric population, which results in a lack of a reference point for audiologists, oncologists and other treating clinicians (Whitehorn et al., 2014). Also, because of the existence of various grading scales for ototoxic hearing loss, there is no consensus on the best grading scale for use in the paediatric population. Therefore, use of different grading scales may result in different audiological treatment recommendations (Bass et al., 2014). This could result in some patients not receiving the best possible audiological care. For example, the Brock scale does not incorporate deficits following slight to a mild hearing loss even though the patient may require amplification even with this kind of hearing loss.

This study aimed to address these gaps in the literature by determining the prevalence, type, degree and laterality of hearing loss observed in paediatric patients following cisplatin-
based chemotherapy in South Africa as the prevalence in other settings is readily available. This study also documented other otological abnormalities observed in the study population such as otalgia, tinnitus, aural fullness, as well as any other external and middle ear pathologies. Additionally, this study also compared different criteria used for grading ototoxic hearing loss and thus give a recommended grading criteria that may be more appropriate in a South African context. It is also envisioned that this study’s results will guide the development of a protocol for audiological and medical management of paediatric patients with cisplatin-induced ototoxicity. Furthermore, this study’s results will be used to raise an awareness to clinicians, parents, and the community at large regarding the possible side-effects of cisplatin chemotherapy.
CHAPTER 3: METHODOLOGY

Introduction: This chapter presents the study aims, objectives, study design and data collection procedures that were followed. It further outlines the data analysis procedures and concludes with a discussion of ethical considerations in this study.

Aims and objectives

This study had two main aims.

The first aim was to describe the audiological profile of paediatric oncology patients treated with cisplatin and had the following objectives:

(i) To determine the prevalence of cisplatin-induced ototoxicity in paediatric patients following cisplatin chemotherapy through:

a. Determining the proportion of patients who developed hearing loss following cisplatin chemotherapy
b. Describing the type, degree and symmetry of hearing loss in paediatric patients treated with cisplatin
c. Documenting the prevalence of other otological pathologies associated with ototoxicity following treatment with cisplatin:
   i. Tinnitus
   ii. Aural fullness
   iii. Otalgia

(ii) To determine the associations between patient and treatment factors and the likelihood of developing cisplatin-induced hearing loss such as:

a. Age
b. Gender
c. Ethnicity
d. Cancer type

e. Duration of treatment

f. Cumulative dose

The second aim of this study was to compare different criteria commonly used to grade ototoxicity-induced hearing loss with respect to:

(i) Responsiveness to changes in hearing thresholds following cisplatin chemotherapy

(ii) Ability to guide decision-making regarding the patient’s rehabilitation needs following cisplatin-induced hearing loss

**Research design**

A retrospective record review study design was used. This type of study design relies on already collected and stored information pre-recorded and patient-centred from health records in order to explore and answer research questions (Worster & Haines, 2004). In this study, medical records of all paediatric patients who underwent cisplatin-based chemotherapy at the RCWMCH whilst receiving periodic ototoxicity monitoring services at the Audiology Outpatient Department in the same hospital during January 2016 to December 2017 were reviewed. The advantages of this study design are cost-efficiency when it comes to the resources and logistics required for data collection. However, the disadvantages are that they rely on data that is already available, and as a result, certain information may be missing (for example, cumulative dose and number of treatment cycles). Therefore, the researchers have to rely on the accuracy of the data recorded by others, both of which may have an implication on reliability and validity of the study.

The present study had only one cohort group comprising patients who were treated with cisplatin for cancer. To minimize these disadvantages, and strengthen the reliability and validity of the study results, the researcher drafted a selection criteria to include only
participants who met the inclusion criteria, and all the participants not meeting the selection criteria were not included in the study.

**Participants**

The present study did not involve direct contact with patients, instead, medical records of patients who were treated for cancer with cisplatin and underwent ototoxicity monitoring at the Audiology Unit at RCWMCH.

**Sampling method**

A non-probability convenience sampling method was used to select medical folders used for data collection. In this type of sampling strategy, participants are selected based on their convenient proximity and accessibility to the researcher (Levin, 2006). This sampling method was chosen for this study as it enabled the researcher an opportunity to access data that was already available. Additionally, this sampling method was selected as it allowed the researcher an opportunity to access data in a fast, inexpensive manner (Babbie & Mouton, 2001). However, this sampling strategy is prone to selection bias which may present an over or underrepresentation of the sample, a high level of sampling error and an inability to generalize the results into the larger population (Berk & Fredman, 2003). To improve these disadvantages, only participants who met the selection criteria were included in the study.

**Sample size**

The sampling frame in this study was an estimated 100 paediatric cancer patients (50 patients per year) who undergo cisplatin-based chemotherapy at RCWMCH. As a result, the size of the sample was directly linked to the number of eligible participants who would be available at the data collection site and medical folders of all patients who met the criteria were, therefore, included for review in this study.
While a power analysis typically guides the sample size, the sample size in this study would have been constrained by the size of the sampling frame reflected by the number of patients seen at the data collection site as reported by the Head Audiologist at the data collection site. Additionally, this sample size is relatively higher than several published studies which used a sample size of 40 participants or less (Bass & Bhagat, 2014; Chen et al., 2006; Greene, Standring, Siddiqui, & Ahsan 2015; Gurney et al., 2007;). In the current study, medical folders of 122 paediatric patients treated with cisplatin from January 2016 to December 2017 at RCWMH were available for review. Of those records, 34 were not referred for ototoxicity monitoring and therefore could not be selected. A total of 88 records were therefore eligible to be selected for the study. However, 30 records were excluded; 20 records had incomplete data and 10 records were lost to follow up. In the end, 58 met the inclusion criteria to be included for review in this study and were therefore selected.

**Recruitment**

As there was no direct interaction with the participants, the researcher sought permission to conduct the study from the Management of the Hospital, the Manager of the Audiology Unit and the Manager of Medical Records. After permission was granted, the researcher asked the Manager of Audiology to provide a list of all the paediatric oncology patients who underwent cisplatin-based chemotherapy and were seen for ototoxicity monitoring. The list was then taken to the Medical Records personnel to retrieve medical records which were selected for this study.

The following inclusion and exclusion criteria were used:

**Inclusion criteria:**

Medical records of patients who met the following criteria were selected to be reviewed in this study:
✓ Aged between 5 and 18 years
✓ Confirmed diagnosis of cancer and undergoing cisplatin chemotherapy at RCWMCH between January 2016 and December 2017.
✓ Underwent ototoxicity monitoring while being treated for cancer, and have a baseline and at least 1 follow up screening (monitoring) and an exit audiogram.
✓ Normal hearing thresholds at baseline audiometric assessment

**Exclusion criteria:**
Medical records of patients with the following information were excluded from the study:
✓ Records with unreliable results – those records noted as “unreliable results” or “poor reliability” on the audiogram
✓ Previous history of radiation therapy in the head and neck region to avoid patients with sensorineural hearing loss following irradiation (Bass & Bhagat, 2014).
✓ Prior treatment with other ototoxic medications (e.g. ototoxic aminoglycosides antibiotics) during treatment.

**Data collection site & study context**

The current study was conducted in Cape Town, the capital city of the Western Cape Province. The data collection site was RCWMCH built in 1956, and currently the largest, stand-alone tertiary hospital dedicated entirely to child health care in South Africa. It is a public tertiary academic hospital which also serves as a teaching hospital for the University of Cape Town. The hospital admits approximately 260 000 children per year (about 50-60 of those are paediatric cancer patients). Serving as the main referral centre for paediatric patients, paediatric cancer patients from other hospitals and clinics across the Western Cape are therefore referred to, and managed at this hospital.
The hospital protocol requires that all paediatric patients who undergo cisplatin-based chemotherapy at the hospital have their hearing thresholds monitored during the course of their chemotherapy treatment. Cisplatin ototoxicity monitoring protocol at the hospital is outlined in Table 1 below.

### Table 1: Testing Protocol Used for Ototoxicity Monitoring at RCWMCH

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Tests</th>
<th>Equipment utilized</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>Otoscopic examination</td>
<td>Heine 3000 FO Handheld Otoscope</td>
</tr>
<tr>
<td></td>
<td>Tympanometry</td>
<td>GSI Tympstar</td>
</tr>
<tr>
<td>above 5 years</td>
<td>Conventional pure ton audiometry</td>
<td>GSI 61 Clinical Audiometer</td>
</tr>
<tr>
<td></td>
<td>Extended high-frequency audiometry</td>
<td>GSI 61 Clinical Audiometer</td>
</tr>
<tr>
<td></td>
<td>DPOAEs</td>
<td>GSI70/Audioscreener</td>
</tr>
</tbody>
</table>

**Testing protocol employed for ototoxicity monitoring at RCWMCH**

Ototoxic monitoring assessments at RCWMCH are conducted by experienced audiologists who are also registered with the Health Professions Council of South Africa. The following tests are conducted for the purpose of ototoxicity monitoring on all patients who undergo cisplatin chemotherapy treatment. For the monitoring protocol see Figure 2 below

**Otoscopic examination:** To determine any abnormalities of the outer and middle ear such as cerumen impaction and ear infections that could result in hearing loss. All patients who presented with abnormalities are referred to the relevant medical professionals for further management.

**Tympanometry:** To rule out any middle ear pathologies that could result in conductive hearing loss when assessing patients during ototoxicity monitoring. A type A tympanogram (see Figure 1 below for norms) was considered normal and any other tympanometry findings were referred to the relevant medical departments for further management.
**Figure 1: Tympanometry Norms**

**DPOAE:** examine the functioning of the outer hair cells within the cochlea which normally indicates a pass or refer result on a screening DPOAE machine. A Pass result across all 4 test frequencies (500, 1000, 2000 and 4000 Hz) is consistent with normal cochlear function whereas a Refer result may have indicate abnormal cochlear function or middle ear pathology that would result in a conductive hearing loss greater than 30 dB HL.

**Conventional and Extended High Frequency Audiometry:** This assessment is done to determine the patient’s hearing thresholds prior to, during, and post-treatment, to determine any threshold shifts following treatment with cisplatin. Conventional audiometry assesses hearing acuity between 250 and 8,000 Hz, while EHF audiometry assesses 10,000-16,000 Hz. The Clark (1981) classification of hearing loss table (see Table 8) was used to determine the severity of hearing loss and the SIOP ototoxicity grading scale (see Appendix 6: SIOP Ototoxicity Grading Scale) was used for grading ototoxicity observed. The ASHA (1994) Significant Threshold Shift guideline was used to determine the prevalence of hearing loss and the American Academy of Audiology Paediatric Amplification Protocol (AAA, 2003) was used to guide the recommendations for hearing amplification.
Figure 2: Ototoxicity Monitoring Protocol at RCWMC

Cancer dx: Pt for cisplatin-based chemotherapy  
Refer to Audiology Department for baseline  
Audiology: Baseline assessments  
• Otoscopy  
• Immittance  
• cPTA  
• EHF  
• Audiometry  
• DPOAEs  
Audiology: Monthly Screening  
• Otoscopy  
• Immittance  
• cPTA  
• EHF  
• Audiometry  
• DPOAEs  
Assess for Ototoxicity: If threshold shift:  
• Inform treating Physician and Pt,  
• Discuss future plans for pt:  
  • Assess dosage  
  • Consider altering dosage/regimen  
  • Continue/discard drug after informing patient  
End of Chemo tx:  
• Exit audiogram with all tests  
• Assess results  
• Check for threshold shifts  
• If ototoxicity present, audiological tx: Hearing aids  
  • Cochlear implant  
  • Sign Language  
  • Speech-Lang Tx  
Continue to monitor hearing annually for 5 years post-chemo
**Data Collection**

**Data collection tool**

A primary data collection tool in this study was a data abstraction sheet developed by the researcher which included the following section(s):

a) Section A: Patient demographic information; age, gender, ethnicity etc.
b) Section B: Clinical information; cancer type, number of chemo cycles, cumulative dose
c) Section C: Audiological information; otoscopy, immittance, audiometry, OAEs.
d) Section D: Other; tinnitus, otalgia, etc., (see Appendix A: Data Collection Tool).

**Data collection procedure**

1. Ethics approval was sought and obtained from the University of Cape Town’s Faculty of Health Sciences Human Research Ethics Committee prior to the commencement of the study (see Appendix 1: Ethics Approval, University of Cape Town).

2. Permission to conduct the study was sought (see Appendix 2: Letter to Request Permission to Access Records at RCWMCH) and granted by management at RCWMCH prior to commencement of data collection (see Appendix 3: Permission Letter to Conduct Study at RCWMCH).

3. A list of all the paediatric patients who were diagnosed with cancer and underwent cisplatin chemotherapy and seen for ototoxicity monitoring between January 2016 and December 2017 was sought and obtained from the head of audiology at RCWMCH. The study only focused on patients seen during this period as the Audiology Department only started seeing patients for ototoxicity monitoring and keeping such records after January 2016.

4. The list with all the patients who underwent ototoxicity monitoring between January 2016 and December 2017 was taken to the hospital’s Medical Records department to
request access to those files. All the requested files were retrieved and assigned study numbers to ensure confidentiality of patients’ records.

5. Audiological findings were recorded on the charted audiogram and data abstraction sheet (See Appendix 4: Data Abstraction Sheet). All the data collected was entered by the researcher into a Microsoft Excel spreadsheet.

Data Management

Data collection was managed by the researcher who is also a qualified audiologist. The researcher copied all the patient demographic information, clinical information, audiological, and other related characteristics for all the participating medical records including type of cancer, treatment cycles, duration of treatment and cumulative dose received onto a Microsoft Excel spreadsheet. The data was then stored in the researcher’s Personal Computer. To ensure that no other people had access to the data, the file containing all the data was encrypted with a password known only to the researcher.

Data Analysis

Both descriptive and inferential statistics were used for analysis in this study. Microsoft Excel was used to provide descriptive statistics in the form of percentages, frequency tables and means, which were used to provide a quantitative analysis and thus the prevalence of the pathologies observed. A spreadsheet was created on Microsoft Excel to enter data that was then exported to the IBM Statistical Package for Social Sciences (SPSS) version 24, which was used for inferential statistics. Graphical presentations using figures and tables were used for data presentation.

For inferential statistics, generalized linear regression models were used for data analysis. Generalized linear models are used to determine associations between one dependent variable and other independent variables (Szumilas, 2015). Logistic regression analysis was
done to determine the associations between cumulative dose and hearing loss, and treatment duration and hearing loss observed. In addition, the Pearson chi-square, which is a test to determine how likely it is that an observed distribution is due to chance (Gaunt, Pickett & Reinert, 2017) was used to determine the associations between age, gender, ethnicity and cancer type with the hearing loss observed. Analysis was done for the onset of sensorineural hearing loss during the course of treatment until the end of treatment. *Table 2* below outlines the statistical tests employed in this study.
Table 2: *Descriptive and Inferential Statistics Used for Data Analysis*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Statistical test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participant factors</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Proportion, Percentages (%), frequency tables, Pearson chi-square test</td>
</tr>
<tr>
<td>Gender</td>
<td>Proportion, Percentages (%), frequency tables, Pearson chi-square test</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Proportion, Percentages (%), frequency tables, Pearson chi-square</td>
</tr>
<tr>
<td><strong>Outer and middle ear pathologies</strong></td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td>Prevalence, Percentages (%), frequency tables</td>
</tr>
<tr>
<td><strong>Hearing loss</strong></td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>Percentages (%), frequency tables</td>
</tr>
<tr>
<td>Type</td>
<td>Percentages (%), frequency tables</td>
</tr>
<tr>
<td>Severity</td>
<td>Percentages (%), frequency tables</td>
</tr>
<tr>
<td>Laterality</td>
<td>Percentages (%), frequency tables</td>
</tr>
<tr>
<td><strong>DPOAE</strong></td>
<td></td>
</tr>
<tr>
<td>Pass or Fail</td>
<td>Percentages (%), frequency tables, Pearson’s correlation coefficient</td>
</tr>
<tr>
<td><strong>Tinnitus</strong></td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>Percentages (%), frequency tables</td>
</tr>
<tr>
<td>Type</td>
<td>Percentages (%), frequency tables</td>
</tr>
<tr>
<td>Severity</td>
<td>Percentages (%), frequency tables</td>
</tr>
<tr>
<td>Laterality</td>
<td>Percentages (%), frequency tables</td>
</tr>
<tr>
<td><strong>Cancer status</strong></td>
<td></td>
</tr>
<tr>
<td>Type of cancer</td>
<td>Percentages (%), frequency tables, Pearson chi square</td>
</tr>
<tr>
<td><strong>Treatment factors</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment duration</td>
<td>Percentages (%), Logistic regression models (odds ratio)</td>
</tr>
<tr>
<td>Cumulative dose</td>
<td>Percentages, Logistic regression models (odds ratio)</td>
</tr>
</tbody>
</table>
Reliability & Validity

Reliability

Reliability is the consistency of data collection measurements to obtain the same results when the same methodology is utilized or replicated (Leedy & Omrod, 2001). Owing to the methodological design of this study, threats to reliability that were identified were addressed through steps taken as outlined in Table 3 below.
Table 3: Measures to Ensure Reliability

<table>
<thead>
<tr>
<th>Reliability issues identified</th>
<th>Measures to ensure reliability taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replicability of the study: Since this study was retrospective, replicability of the data collection process using the study was a potential threat to reliability of the study.</td>
<td>The study used data obtained from ototoxicity monitoring using a set protocol that included: case history, otoscopic examination, immittance measurements, pure tone audiometry (conventional and EHF) and DPOAEs. The data abstraction sheet used for data collection was in line with the ototoxicity monitoring protocol used. Utilizing the ototoxicity monitoring protocol and the data abstraction sheet may enable replication of the study.</td>
</tr>
<tr>
<td>Accuracy of the data entries on the data abstraction sheet</td>
<td>The process of re-entering of data was carried out in a blinded randomized manner by using participant’s research numbers. A comparison of the two separate data entries was undertaken with an expectation of attaining more than 90% accuracy using the following formula: Agreement / (Agreement + Disagreement) x 100 (de Vet, Terwee, Knol, &amp; Bouter, 2006). A score of 94% accuracy was obtained.</td>
</tr>
<tr>
<td>Since the audiometric testing results obtained for this study were performed on children who were sick and prone to fatigue, the reliability of the clinical data could be compromised if these children were fatigued during testing and thus pressed the response button even when no stimulus was presented.</td>
<td>The clinicians at the data collection site utilized a set protocol for ototoxicity monitoring which was the same for all the patients they assessed for ototoxicity monitoring. Additionally, the reliability of the data entered was also indicated by making a note on the audiogram to indicate whether the results obtained were reliable or not (unreliable results included cases where the patient had false positive or false negative results). All the records with unreliable results were excluded from this study as they posed a threat to the reliability of the study.</td>
</tr>
</tbody>
</table>
**Validity**

Validity refers to the extent to which an empirical measure adequately reflects the meaning of the concept under investigation and measures what it is intended to measure. (Leedy & Omrod, 2001). The following steps to ensure validity were made:

*Construct validity* refers to the way in which a data collection tool measures what it is intended to measure. In this study, a data abstraction sheet was devised for the study, to record all the data required for the study, and a qualified audiologist was asked to judge the data abstraction tool to determine its applicability in the data collection for this study.

*Validity of the assessment used for monitoring:* All the tests used for ototoxicity monitoring have been validated for hearing function evaluation and ototoxicity monitoring. The DPOAE test has been validated as a measurement of cochlear hair cell function and its use in ototoxicity monitoring (McMillan, Konrad-Martin & Dille, 2012; Reavis et a., 2011). Pure tone audiometry, including EHF audiometry, is a measurement of hearing acuity and has been shown to be an effective behavioural method of evaluating auditory function in ototoxicity monitoring (Lavioe, 2013)

*Quality of data:* This study was retrospective and thus relied heavily on data entry into medical records for clinical care and not for research purposes. Only medical records with complete data necessary to participate in this study and that met the selection criteria were selected and therefore included in this study.
Ethical Considerations

Ethical clearance to conduct the study was sought and granted by the University of Cape Town’s Faculty of Health Sciences Human Research Ethics Committee prior to commencement of the study (see Appendix 1: Ethics Approval, University of Cape Town). Additionally, permission to conduct the study at RCWMCH was sought and obtained prior to data collection (see Appendix 3: Permission Letter to Conduct Study at RCWMCH). The following ethical considerations, adopted from the World Medical Association (WMA) Declaration of Helsinki (2014) were applied to ensure ethical adherence: confidentiality, informed consent, and risk and benefits for participating in the study. Additionally, these ethical considerations allowed the researcher to practice respect for persons and integrity. The ethical considerations are outlined in detail below:

- **Confidentiality**: According to the WMA Declaration of Helsinki (2014), every precaution should be taken to guard the privacy of research subjects and the confidentiality of their personal information. In this study, research numbers were assigned to medical records of patients who were included in this study to replace any patient identifying information. In addition, the data was stored in a lockable cabinet, and all electronic copies were password encrypted by a password known only to the researcher.

- **Informed consent**: Informed consent is defined as a voluntary agreement given by a prospective subject after careful understanding and consideration of all the information provided to take part in a study (NIH Office of Extramural Research, n.d.). According to NIH (n.d.), informed consent should be documented in written form and must include all the information presented orally to the prospective participant. The current study did not involve direct interaction with the participants, therefore consent to access patients’ medical records were obtained from the hospital management as the gatekeepers for the
data prior to study commencement (see Appendix 2: Letter to Request Permission to Access Records at RCWMCH).

- **Risks and benefits to participants:** Since this was a retrospective study, there was no direct benefits to the patients who were treated, however, there was the risk of loss of confidentiality for these patients. The risk of loss of confidentiality was improved by issuing and replacing all identifying information for patients with research numbers before copying the data onto the data abstraction sheet. Outcomes of the study will be shared with relevant departments at the hospital and this might potentially inform further improvements in the hospital’s efforts to improve patients’ care.

- **Justice:** Justice which is described as fairness, respect for people’s rights, and equality (Gillon, 1994; Naude & Bornman, 2016) was improved by ensuring all the medical records had a fair chance of being selected. Justice was further improved by selecting all the records that met the selection criteria. In line with the respect for human rights, the researcher removed all the identifying information of all the participants and replaced them with participant numbers to ensure their privacy was maintained.
CHAPTER 4: RESULTS

Introduction: This chapter presents the results of the current study in accordance to its aims and objectives. Prevalence of cisplatin-induced hearing loss, factors associated with likelihood of developing cisplatin-induced hearing loss as well as a comparison of three paediatric scales used to grade ototoxicity will be presented. The chapter concludes with a summary of the results.

Participants
A total of 122 medical folders of paediatric patients who underwent cisplatin-based chemotherapy at RCWMCH between January 2016 and December 2017 were accessed for review in this study. Records older than 2016 did not have DPOAE and EHF audiometry results and therefore could not be included in this study. Eighty-eight patients were referred to the audiology department for ototoxicity monitoring; however, only 58 of those referred for ototoxicity monitoring met the inclusion criteria for this study and were therefore selected for review (see Figure 3 below).

Figure 3: Participant Selection Process

- Total treated with cisplatin, n=122
  - Sent for ototoxicity monitoring, n=88
    - Included in the study, n=58
      - Incomplete data, n=20
    - Excluded from study, n=30
  - Not sent for ototoxicity monitoring, n=34
    - Lost to follow up, n=10
Table 4 below outlines the participant demographic characteristics, treatment information and types of cancer diagnosed.

**Table 4: Participant Demographic Characteristics**

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Number of participants (n,%)</th>
<th>Total with HL (n,%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10 years</td>
<td>44 (76%)</td>
<td>27 (69%)</td>
</tr>
<tr>
<td>11-15 years</td>
<td>14 (24%)</td>
<td>12 (31%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>22 (37,9%)</td>
<td>18 (46%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>9 (15,5%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Coloured*</td>
<td>14 (24,1%)</td>
<td>12 (31%)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (22,4%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33 (56,8%)</td>
<td>15 (38)</td>
</tr>
<tr>
<td>Female</td>
<td>25 (43,2%)</td>
<td>24 (62%)</td>
</tr>
<tr>
<td><strong>Type of cancer diagnosed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma, Hodgkin’s</td>
<td>3 (5%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Pulmonary Blastoma</td>
<td>1 (2%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>4 (7%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>6 (10%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>20 (34%)</td>
<td>16 (41%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>10 (17%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>CNS Tumours</td>
<td>14 (25%)</td>
<td>12 (31%)</td>
</tr>
<tr>
<td><strong>Treatment information</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative cisplatin dose (mg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 mg/m²</td>
<td>32 (55%)</td>
<td>14 (36%)</td>
</tr>
<tr>
<td>101-300 mg/m²</td>
<td>10 (17%)</td>
<td>9 (23%)</td>
</tr>
<tr>
<td>&gt;300 mg/m²</td>
<td>16 (28%)</td>
<td>16 (41%)</td>
</tr>
<tr>
<td><strong>Duration of treatment (months)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3 months</td>
<td>11 (19%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>4-6 months</td>
<td>47 (81%)</td>
<td>34 (87%)</td>
</tr>
</tbody>
</table>

[*] = Coloured = A multiracial ethnic group of people native to Southern Africa who have ancestry from various populations which includes Bantu speakers, Afrikaners and Khoisan (Dugard, 2015).
Prevalence of hearing loss

One the inclusion criteria for this study was that a patient must have normal hearing thresholds (hearing thresholds ≤ 15 dB HL in both ears). Therefore all (100%) the patients whose records were selected for review had normal hearing thresholds at the beginning of chemotherapy treatment. The prevalence of hearing loss was determined prior to (i.e. baseline), 1 month after initiating chemotherapy, and at the end of chemotherapy (exit audiogram).

A significant threshold shift can be described as (i) a change in hearing threshold relative to baseline of average of 10 dB or more at any 2 adjacent frequencies, (ii) change in hearing threshold of 20 dB or more at one frequency or (iii) loss of response at any three adjacent frequencies (ASHA, 1994). Based on conventional and EHF findings, a total of 39 participants (80%) were diagnosed with ototoxic hearing loss.

Nature of hearing loss

All participants diagnosed with the ototoxic hearing loss (n = 39) at the end of chemotherapy had a sensorineural hearing loss, and due to the nature of this loss, they were fitted binaurally with hearing aids (n = 22) or referred for fitting (n= 5) at their local hospitals.

Degree of the hearing loss

A decision was made to classify degree of hearing loss in this study using two sets of pure tone averages; cPTA (500, 1000 and 2000 Hz) which is typically used in a clinical setting and consistent with the Clark (1981) classification system and a high-frequency pure tone average (HF-PTA: 4000, 8000, and 12 000 Hz) to account for the high frequency nature of cisplatin-induced hearing loss. The degree of hearing loss observed was analyzed using frequency tables. At the exit evaluations, nine participants had lost their lives and four were lost to follow up. Table 8 below summarizes the degrees of hearing loss observed.
Table 5: *Hearing Loss Severity Utilizing cPTA and HF-PTA*

<table>
<thead>
<tr>
<th>Severity of hearing loss</th>
<th>Baseline</th>
<th>Screening at 1 month</th>
<th>Exit audiogram</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cPTA (n)</td>
<td>HF-PTA (n)</td>
<td>cPTA (n)</td>
</tr>
<tr>
<td>Slight (15-25 dB HL)</td>
<td>0</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Mild (26-40 dB HL)</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Moderate (41-55 dB HL)</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mod-Sev (56-70 dB HL)</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Severe (71-90 dB HL)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Profound (&gt;90 dB HL)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Hearing loss using the Clark (1981) Classification System*

cPTA: Conventional pure tone average

dB HL: decibel hearing level

HF-PTA: high frequency pure tone average
Otoacoustic emissions results

Patients also underwent otoacoustic emissions at baseline, at 1 month into cisplatin chemotherapy, and at the exit audiological evaluation as part of ototoxicity monitoring at this facility. At baseline and 1-month screening there were 58 participants, but at exit only 49 participants were reviewed; 9 records could not participate due to death or lost to follow up. The outcome of DPOAE assessments was consistent with that of pure tone audiometry with respect to proportion of patients who developed hearing loss during the course of chemotherapy treatment. Figure 4 below shows the outcome of DPOAE findings.

![Figure 4: Otoacoustic Emissions Findings](image)

Correlation between cPTA and DPOAE findings, and HF-PTA and DPOAEs

A Pearson’s correlation coefficient calculation was done to determine the correlation between cPTA and DPOAE findings as well as HF-PTA and DPOAE findings. A fair positive correlation ($r=0.659$) was found between cPTA and DPOAE findings whereas a strong positive correlation ($r=0.899$) was found between HF-PTA and DPOAE findings.
Other auditory pathologies

Because ototoxicity can also result in tinnitus, aural fullness and otalgia, this study also sought to document the prevalence of these pathologies in this patient cohort. A total of six patients reported a ringing, high pitched continuous tinnitus in both ears.

Patients also underwent otoscopic examination prior to, during and post treatment; to determine the presence of any outer or middle ear pathologies that would affect the audiometric testing and therefore the results. No structural abnormalities of the ear canal and tympanic membrane were reported in this patient cohort throughout treatment. Foreign bodies were reported in a total of two ears, which included a bean and a bead. Results regarding cerumen impaction were reported in the participants prior to, during, and post-treatment (see Figure 5 below). There were no other auditory pathologies reported.

Figure 5: Prevalence of Cerumen Impaction
**Factors associated with developing hearing loss during cisplatin chemotherapy**

Chi-squared test and odds ratio were used to determine whether there was an association between the following variables; age, gender, cancer type and developing hearing loss during cisplatin chemotherapy. The findings revealed that in comparison to patients older than 10 years old, those below the age of 10 years old were 59% more likely to develop hearing loss (OR:1.588, 95% CI:1.09-2.14; \( p=0.016 \)). That is, younger age (<10 years old) was associated with higher risk of developing hearing loss. With regards to gender, when compared to males, female participants were more likely to develop hearing loss (OR:0.34, 95% CI:0.25-1.87; \( p=0.039 \)). In terms of population groups, patients who were classified as black were more likely to develop hearing loss when compared to patients from other ethnicities (\( p=0.01 \)). For instance, when compared to patients who were classified as Caucasian, patients who were classified as black were 89% more likely to develop hearing loss (OR:1.89, 95% CI: 0.94-2.09). There were no associations between cancer type and hearing loss, thus development of hearing loss was independent of cancer type (OR:0.26, 95% CI; \( p=0.41 \)). *Table 6* below summarizes the associations between age, gender, ethnicity and cancer type with hearing loss.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ototoxicity (n=39)</th>
<th>Odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, &lt;10 years</td>
<td>24</td>
<td>1.588 (95% CI: 1.09-2.14)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>23</td>
<td>.34 (95% CI: 0.25-1.87)</td>
<td>0.039*</td>
</tr>
<tr>
<td>Cancer type</td>
<td>34</td>
<td>.26 (95% CI: 0.09-2.85)</td>
<td>0.41*</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>22</td>
<td>1.89 (95% CI: 0.94-2.09)</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

*Pearson chi-square*
Logistic regression was used to determine associations between cumulative dose, treatment duration and developing hearing loss during cisplatin chemotherapy treatment. Higher cumulative dose (>200 mg/m², \(p=0.047\)) and longer treatment duration (>4 months, \(p=0.017\)) were associated with higher prevalence of hearing loss.

**Grading of ototoxic hearing loss**

The second aim of this study was to compare three commonly used ototoxicity grading scales: the SIOP Boston, the Chang and the Brock. These scales are used in paediatrics in order to determine their ability to identify cisplatin-induced hearing loss early as well as their use in guiding audiological rehabilitation of patients in the current study who develop hearing loss during or following chemotherapy. At baseline, all the participants had normal hearing thresholds. At one-month follow up, 71% \((n=41)\) still presented with grade 0 hearing loss according to the Brock scale, 45% \((n=26)\) presented with grade 0 hearing loss according to SIOP, while 52% \((n=30)\) presented with grade 0 hearing loss according to the Chang scale. At exit, the number of the participants had been reduced to 49; nine records could not be included for analysis as 5 participants lost their lives due to cancer and 4 were lost to follow up. At exit, the number of the participants had been reduced to 49; a total of 9 were missing either due to losing their lives to cancer or being lost to follow up. A total of 55% \((n=27)\) of the patients were diagnosed with moderate to severe disabling hearing loss (grades 2-4) when utilizing the SIOP and 41% \((n=21)\) were diagnosed with moderate to severe disabling hearing loss according to the Chang Scales while 45% \((n=22)\) presented with moderate-severe disabling hearing loss when using the Brock scale. **Table 7** below provides a summary of the findings of a comparison of the three scales.
Table 7: Comparison of Audiometric Findings Using Ototoxicity Scales

<table>
<thead>
<tr>
<th>Grade</th>
<th>Baseline</th>
<th>Screening at 1 month after beginning treatment (n, %)</th>
<th>Exit audiogram (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Brock*</td>
<td>SIOP*</td>
</tr>
<tr>
<td>0</td>
<td>All the participants had normal hearing bilaterally</td>
<td>41 (70.6%)</td>
<td>26 (44.8%)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>2 (3.4%)</td>
<td>26 (44.8%)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>15 (25.9%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>0%</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>0%</td>
<td>1 (1.7%)</td>
</tr>
</tbody>
</table>

According to the AAA (2003), any patient with a hearing loss worse than 25 dB HL at any 2 frequencies above 2000 Hz should be fitted with hearing amplification for management AAA (2003). According to this criterion, 27/35 (77%) of patients whose medical records were reviewed for this study would have met the criteria for hearing aid fitting.

In terms of criteria for hearing aid fitting, the Brock scale recommends that only patients who develop grades 3-4 hearing loss be fitted with hearing amplification while the Chang and the SIOP scales recommend that patients who develop grades 2-4 should be fitted with hearing amplification. Therefore when comparing the three criteria used to grade hearing loss in terms of their ability to guide decision making regarding hearing aid fitting in line with the AAA protocol (2003), the following recommendations would have been made: according to the Brock scale, 3 participants in this study would have met the criteria to be fitted with hearing aids while 20 and 27 participants would have met the criteria for hearing aid fitting when utilizing the Chang and the SIOP scales respectively.

Chapter summary

The study findings revealed that a total of 39 (80%) participants presented with ototoxic hearing loss, with most presenting with moderate (59%, n=23) to severe (18%, n=7) hearing loss. In agreement with pure tone audiometric results, diminished or absent DOPAEs were observed in 67% (n=33) of the participants while tinnitus was reported in six (12%) participants. Younger age (<10 years of age), black ethnicity, female gender, higher cumulative dose (>200 mg/m²) and longer treatment duration (>4 months) were all associated with higher incidences of ototoxicity (p<0.05).

The SIOP Boston ototoxicity scale identified more patients with hearing loss early (i.e. at 1-month follow-up) and also made recommendations on hearing amplification that were more consistent with the AAA (2003) protocol.
CHAPTER 5: DISCUSSION

Introduction: This chapter discusses the findings of the current study and their impact in line with the study aims and is supported by literature. The chapter concludes with the limitations of the present study and the impact these limitations could have on the findings of this study.

Prevalence of hearing loss

Findings from this study indicated a high proportion of patients who underwent cisplatin chemotherapy at RCWMCH during January 2016 to December 2017 and developed hearing loss following chemotherapy treatment. Prevalence of hearing loss in this cohort of patients was 80%. This was the first study to document the prevalence of cisplatin-induced ototoxicity in paediatrics in South Africa and therefore the prevalence of hearing loss found in this cohort of patients could not be compared to the findings of similar local studies.

Prevalence of hearing loss following cisplatin chemotherapy in the paediatric population is variable. Variability in patient populations under study as well as the homogeneity or heterogeneity of the cancer types being treated can influence the prevalence of hearing loss. For instance, patients who undergo treatment for central nervous system cancers tend to have higher incidences of hearing loss following treatment when compared to those who undergo treatment for other types of cancer (Landier, 2016). Further, treatment factors such as cumulative dose received by the participants in different studies can also lead to variation in incidence of hearing loss reported in different studies (Brock et al., 2012; Helt-Cameroon & Allen, 2009; Li et al., 2004). For example, a study by Coradini et al (2007) documented cisplatin-induced ototoxicity in 94% of their sample, Yancey et al (2012) found an incidence of 42% (43/102), while Knight et al (2005) reported an incidence of 62% (42/67). Several factors have been attributed to this variability in incidence of hearing loss. The most common factors that can explain these differences include methodological issues across different
studies; (i) sample sizes, (ii) the use of different assessment tools to diagnose ototoxicity, and (iii) the use of variable criteria to define ototoxicity (Knight et al., 2017; Whitehorn et al., 2014; Yancey et al., 2012).

**Nature and degree of hearing loss**

The pathophysiology of cisplatin-induced ototoxicity is believed to be related to the formation of reactive-oxygen-species (ROS) and depletion of anti-oxidant scavenger molecules subsequently inducing calcium influx and cell apoptosis (Rybak et al., 2007; Yancey et al., 2010). Yancey et al (2010) further illustrated that one target of ROS-induced cochlear damage is the outer hair cells (OHCs). The latter is characterized by the nature of the hearing loss observed in this study sample which was sensory in nature, supported by the absence of the otoacoustic emissions, and typically affecting the higher frequencies before progressing to the lower frequencies.

In hearing loss degree (severity) classification, a total of 39 (80%) participants presented with mild to profound ototoxic hearing loss when utilizing a higher frequency pure tone average, and EHF audiometry, while only 49% (n=24) of the participants were diagnosed with hearing loss when utilizing conventional audiometry. This finding suggests that extended high-frequency audiometry, and the use of a higher-frequency pure tone average may be more effective in early identification of changes in hearing threshold rather than use of conventional audiometry and a cPTA. EHF audiometry can help with early identification of hearing loss as majority of patients may not report hearing loss until if affects the frequency range that is important for speech communication. Several studies have reported the effectiveness of EHF audiometry and its superiority to conventional audiometry when it comes to early detection of ototoxicity-induced hearing loss (Coradini et al., 2007; Knight et al., 2007; Knight et al., 2017). Owing to the demographic characteristics of this study’s sample, particularly age, early
identification of hearing loss would therefore be of paramount importance to overcome the negative impact of hearing loss.

**Grading of hearing loss using the SIOP scale**

In this study cohort, majority of the participants (55%, n=27) presented with SIOP grade 2 hearing loss or higher, with a total of 17 participants (35%) presenting with SIOP grade 3 hearing loss. As discussed in the literature review, SIOP grade 2 and higher hearing loss means disabling hearing loss (WHO, 2015) which may have debilitating effects on speech discrimination, a major disabling and debilitating effect of hearing loss, particularly in this study cohort which comprised of paediatric patients who are still acquiring speech-language, and reading and writing abilities (Gurney et al., 2007; WHO, 2015). A hearing loss of this nature and degree, particularly in this study’s age group, has been reported to leave a debilitating impact on communication and psychosocial development, reading and writing abilities, scholastic performance, and quality of life, for both the patient and their families and society at large (Butler, 2012; Humes & Bess, 2008; Phanguphangu, 2017; Theunissen et al., 2014).

**DPOAE findings**

In this study’s cohort, a total of 33 (67%) participants presented with absent otoacoustic emissions as evidenced by the PASS/REFER screening results at the exit assessment. A strong positive correlation was found between DPOAEs, with the EHF audiometry results citing ototoxic hearing loss in 80% of the sample. This finding suggests that in cases where obtaining behavioural audiometric findings including EHF audiometry proves difficult, DPOAEs can be used in early identification of ototoxic hearing loss. This can be useful, specifically in paediatrics where obtaining reliable EHF audiometry results can be challenging (Lewis et al., 2014).
2009). This is attributed to the fact that as a behavioural measure of hearing, EHF audiometry requires a patient to be fully awake and concentrating for the full duration of the test, and children who are undergoing cancer treatment can tire quickly and lose their concentration, resulting in unreliable results. However, findings from this study, along with other studies reported in literature (Brock et al., 2012; Knight et al., 2017; Yancey et al., 2012), indicate that DPOAEs can be used in early identification since DPOAE findings not only correlate with EHF audiometry but are also easier to conduct when patients are too ill to do pure tone testing.

**Other associated auditory findings**

This study also sought to determine other associated audiological findings such as cerumen impaction, tinnitus and aural fullness. Cerumen impaction is a major public health burden that affects almost 6% of the global population, and approximately 10% of the paediatric population worldwide (Stránský, Valterová, Kofroňová, Urbanová, & Zarevúka 2011). In the present study, all the participants had clear external auditory meatus with small amounts of cerumen pre-cisplatin chemotherapy whereas at the end of treatment, almost half of the participants (49%) had cerumen impaction. However, this high rate of cerumen impaction did not affect the results of this study as these patients were sent for cerumen removal prior audiological testing. This high prevalence of cerumen impaction is a novel finding in this study as previous studies do not report on cerumen impaction among their participants undergoing cisplatin chemotherapy.

While literature linking cisplatin chemotherapy to increased cerumen production is limited, this finding of a high prevalence of cerumen impaction in the study cohort is important as cerumen impaction may contribute to the burden of hearing loss (Butler, 2012; Phanguphangu, 2017). This finding may suggest that cisplatin may alter the functioning of the apocrine and sebaceous glands within the external auditory meatus. This could lead to overproduction of cerumen or a
slower clearing process thereof resulting in cerumen impaction. All the participants who had cerumen impaction were sent for cerumen removal prior audiometric testing for ototoxicity monitoring in this study. This finding, therefore, highlights the need, and importance of performing periodic otoscopic examinations in paediatric patients undergoing cisplatin chemotherapy in order to identify patients who might have cerumen impaction and provide timeous management.

Tinnitus is one of the clinical symptoms of ototoxicity (Gurney et al., 2007; Knight et al., 2017). In the present study, tinnitus was reported by 12% \( (n=6) \) of the participants during treatment. Although not widely understood, the pathophysiology of tinnitus is reported to be related to the brain’s response to deprivation of auditory stimuli resulting from damaged sensory structures of the cochlea such as the outer and inner hair cells (Benson, 2014). Benson (2014) reports that in a normal auditory system, there is an ordered tonotopic frequency representation from the cochlea to the auditory cortex in the brain. Should a region in the cochlea be damaged, there is an increase in the spontaneous firing rate in the brain resulting in abnormal neural activity that is perceived as tinnitus in the damaged cochlea (Atik, 2011).

Although 6/58 participants (10%) of the sample reported tinnitus in this study, this finding could be an under or overrepresentation as children rarely complain of tinnitus. A study by Martin and Snashall (1994) found that 85\% \( (57/67) \) of children presented with tinnitus although only 6\% spontaneously reported tinnitus to their audiologist. In a similar recent study by Humphriss, Hall and Baguley (2016), only 3.1\% \( (220/7092) \) spontaneously reported tinnitus to their clinicians although a total of 28.1\% \( (1992/7092) \) admitted, and even described their tinnitus characteristics when asked by their clinicians. This could be attributed to the fact that children may not have the vocabulary to explain the tinnitus or know that the presence of tinnitus is not meant to be there. Also, if they are already sick and bed ridden, this may hinder reports of what they may consider minor symptoms. Both the findings of these studies are
similar to those reported in the present study, which indicates that although the prevalence of tinnitus was low, it could be higher than the spontaneously reported prevalence.

**Risk-factors for hearing loss**

Patient factors such as age and gender have also been identified as risk factors for developing hearing loss (Gurney et al., 2007; Kushner et al., 2006; Peters et al., 2000). In the present study, children below the age of 10 years were more likely to develop hearing loss when compared to those above 10 years ($p=0.016$, OR:1.588). This finding is similar to that reported in literature stating that younger age is associated with higher prevalence of hearing loss (Brock et al., 2012; Knight et al., 2017; Yancey et al., 2012). Literature on gender as a risk factor for developing cisplatin-induced ototoxicity is variable. A study by Yancey et al (2012) indicated that males are four times more likely to develop ototoxicity while Li et al (2004) indicates that female gender is associated with higher incidences of ototoxicity. In the present study, female gender was found to be associated with higher incidences of hearing loss ($p<0.05$) and this finding is unique as there were more males in the sample when compared to females. This finding could be attributed to the fact that all the female participants who developed hearing loss received cumulative cisplatin doses of more than 200 mg/m$^2$ which was also found to be a risk factor for developing hearing loss. Therefore, the risk of developing hearing loss for these patients were increased due to the cumulative dose received.

The present study also investigated ethnicity as a risk factor for developing hearing loss when one is treated with cisplatin ototoxicity. In the present study, there was a higher proportion of patients who were classified as black when compared to other ethnicities. Additionally, the odds of developing hearing loss following cisplatin chemotherapy were found to be higher in patients classified as black than patients from other ethnicities. This finding suggests that patients who are classified as black could potentially be at a higher risk of developing hearing
loss when compared to other patients. This could potentially be due to genetic factors such as the genes TPMT and ACUP2 which are found in high proportions in black people compared to other ethnicities (Theissen et al., 2017; Whitehorn et al., 2014). Additionally, it should be noted that black people may be poorer than people in other groups and these children might be more likely to be malnourished, leading them to have lower serum albumin levels, meaning the proportion of drug that is not protein-bound is higher than that could be found in other well-nourished children (Zietarska, Krawczyk-Lipiec, Krai, & Zaucha, 2017). This phenomenon may account for increased ototoxicity from cisplatin and nephrotoxic antibiotics, among others.

Treatment factors such as treatment duration and cumulative dose, which have been reported to be risk factors for hearing loss following cisplatin-based chemotherapy, were also identified as factors that increase the likelihood of developing hearing loss following cisplatin-based chemotherapy in this study (Knight et al., 2005; Knight et al., 2017; Landier et al., 2016; Li et al., 2004; Whitehorn et al., 2014; Yancey et al., 2012). It was found that both longer treatment duration (>3 months) and higher cumulative dose (>200mg/m²) were statistically associated with hearing loss. The treatment duration findings were consistent with similar studies by Yancey et al (2012), Landier et al (2016) and Knight et al (2017). However, with regards to cumulative cisplatin dose, the present study found a relatively lower cumulative cisplatin dose (200mg/m²) to be statistically associated with hearing loss, when compared to 400mg/m² which is reported by Lafay-Cousin et al (2013), Yancey et al (2012), and Knight et al (2016). These findings therefore indicate that paediatric patients who receive higher cisplatin cumulative dose and undergo longer treatment duration are at higher risk to develop hearing loss as supported by Li et al (2004), Brock et al (2012) and Knight et al (2017).
Comparison of the ototoxicity grading scales

This study also sought to compare the commonly used ototoxicity grading criteria used in children with regards to responsiveness to auditory changes following cisplatin-based chemotherapy and their application in guiding decision-making with respect to audiological rehabilitation intervention following cisplatin induced ototoxicity. When utilizing the Brock Scale, almost half of the participants (46.9%) still had grade 0 hearing loss at exit when compared to only 20 and 24% when utilizing the SIOP and the Chang scales respectively. With regards to hearing aid fittings for management of hearing loss, only 3 participants would have been fitted with hearing aids when compared to the 20 and 27 which would have been fitted when utilizing the Chang and the SIOP scales respectively. These findings indicate that the Brock scale is not effective in early identification of disabling hearing loss and can therefore result in patients not received treatment for hearing loss, despite the fact that they should receive amplification for such a hearing loss (25-40 dB HL) given its negative impact on development (Butler, 2012; Gurney et al., 2006; Phanguphangu, 2017).

It is worth noting that although hearing aids are designed to improve hearing acuity in patients with hearing loss by providing amplification, patients with ototoxic hearing loss may still struggle with speech discrimination as the cochlear hair cells responsible for converting the amplified sound are dead, and the sound would still not be converted into sound impulses that the brain can encode (Tremblay & Miller, 2014). A study by James et al (2011) reported limited benefit from hearing aids but when those patients were implanted with cochlear implants, they reported significant improvement in speech discrimination. The reason for minimal benefit from hearing aids could potentially be due to the fact that hearing aids provide amplification of sounds that still have to be converted into sounds impulses sent to the brain from within the cochlear, whereas cochlear implants bypass the inner ear to stimulate the acoustic nerved directly (Illg, Giourgas, Kral, Büchner, & Lisinski-Schieday, 2013; Tremblay & Miller, 2014).
Therefore, although all the patients were fitted with hearing aids for management, negative impact of hearing loss such as scholastic performance, poor speech discrimination, and poor quality of life, in these patients could still be reported at a later stage in their lives. Therefore, the primary aim of monitoring the hearing status of these patients should be to prevent disabling hearing loss in them to avoid any negative consequences associated with hearing loss (Bat-Chava & Deignan, 2010; Daud et al., 2010; Preisler, Tvingstedt, & Ahlstrom, 2002; Wauters & Knoors, 2007).
CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

Limitations of the study

The findings of this study provide information that can potentially be useful for both audiologists and oncologists when it comes to clinical management of paediatric patients undergoing cisplatin-based chemotherapy. However, owing to the methodological limitations of this study, it is imperative that its findings be interpreted with caution. This is because the reliability of the data analyzed for this study depended on the clinicians who recorded these results. Secondly, because selection of medical folders that were reviewed was via convenience sampling, it was difficult to control for selection bias as no randomization was done.

Despite these limitations, to the best knowledge of this researcher, this was the first study to determine the prevalence of cisplatin-induced ototoxicity in a paediatric population in South African. Therefore, these findings shed light on the prevalence of cisplatin-induced ototoxicity in paediatric patients in South Africa. It is thus hoped that these findings will prompt action from clinicians who manage these patients to try to prevent disabling hearing loss in children who undergo cisplatin chemotherapy.

Conclusion

Based on the findings of this study, it was concluded that a high proportion (80%, n=39) of patients who underwent cisplatin-based chemotherapy developed significant change in their hearing thresholds. In addition, there was a higher proportion of participants with cerumen impaction at the end of cisplatin-based chemotherapy than at the beginning of chemotherapy.

Patient factors which included younger age, female gender and black ethnicity were identified as risk factors for the likelihood of developing significant hearing threshold change. In addition to patient factors, treatment factors which included a higher cumulative dose (>200 mg/m²) and longer treatment duration (> 3 months) were also identified as factors that increased the
likelihood of developing this significant change in hearing thresholds following cisplatin-based chemotherapy.

When comparing the three commonly used criteria for grading ototoxic hearing loss in paediatrics, the SIOP scale was able to identify more patients with hearing loss early (i.e. at 1-month follow-up screening) when compared to the two other scales. Additionally, the SIOP scale made recommendation about hearing amplification that were more consistent with the AAA Protocol (2003). Therefore, it was concluded that the SIOP scale identifies hearing loss early and makes recommendations regarding audiological treatment more consistent with the AAA Protocol (2003).

**Clinical implications and recommendations for future research**

Clinical implications from this study include (i) identification of at-risk patients and enrolling them on serial ototoxicity monitoring to enable early identification and intervention, (ii) utilization of DPOAEs in instances where it may be impossible to obtain behavioural results, (iii) recognizing the importance of periodic otoscopic examination to detect any pathologies such as cerumen impaction that can result in hearing loss, (iv) having management protocols in place for those who may present with such pathologies, (v) the use of an ototoxicity grading scale that responds to the needs of the patient population under monitoring, (vi) identification of risk factors for developing ototoxic hearing loss and placing patients on serial ototoxicity monitoring to enable early identification and (vii) the role of the audiologist in a cancer treatment team, and (viii) the use of the SIOP scale as it enables early identification of ototoxicity, makes treatment recommendations that are in line with the standard of practice and allows for consistent communication among professionals.
Findings from this study therefore recommend (i) a critical review of the current monitoring protocols regarding their effectiveness in early identification of ototoxic hearing loss in paediatric patients, (ii) the development of a validated paediatric specific ototoxicity monitoring protocol (iii) include a comprehensive baseline audiogram that incorporates full case history, otoscopic examination, immittance measurements, conventional pure tone audiometry, speech audiometry, extended high-frequency audiometry and DPOAEs, (iv) periodic monthly screening with DPOAEs and if any change in hearing status are observed, then a full diagnostic evaluation should be carried out, (v) a comprehensive exit audiogram plus yearly follow up screenings up to 2 years. Furthermore, owing to the methodological limitations of this study which include its retrospective nature and smaller sample size, this study recommends a prospective comprehensive large-scale study to determine a collective prevalence of cisplatin-induced ototoxicity in paediatric population.

Owing to the high prevalence of ototoxicity observed, this study recommends future studies in oto-protection, especially in paediatrics in order to prevent the development of this ototoxic hearing loss and therefore the negative debilitating effects of hearing loss on the individual and their society.
REFERENCES


Gillon, R. 91994). Medical ethics: four principles plus attention to scope. *British Medical Journal*, 309, 184-188


grading scales—a report from the children’s oncology group. *Journal of Clinical Oncology*, 32(6):527-539


88


http://www.socialresearchmethods.net/kb/sampnon.php


APPENDICES

Appendix 1: Ethics Approval, University of Cape Town

06 July 2017

HREC REF: 465/2017

A/Prof L Ramma
Communication Sciences & Disorders
Health & Rehab Sciences
Old Main Building

Dear A/Prof Ramma

PROJECT TITLE: THE AUDILOGICAL PROFILE OF PAEDIATRIC PATIENTS TREATED WITH CISPLATIN IN CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL, SOUTH AFRICA (MSc-candidate-M Phanguphangu)

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

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study. This is subject to all approvals from the local institutions i.e. Charlotte Maxeke and local HREC if required.

Approval is granted for one year until the 30th July 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student Chad Phanguphangu will be involved in this study.

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval before the research may occur.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

HREC 465/2017
Appendix 2: Letter to request permission to access records at RCWMCH

Division of Communication Sciences and Disorders
Faculty of Health Sciences
University of Cape Town
Telephone: 021 406 6347
Email: phnmuk001@myuct.ac.za
lebogang.ramma@uct.ac.za

Dear Sir or Madam

To whom it may concern

RE: A STUDY ON THE AUDIOLOGICAL PROFILE OF PAEDIATRIC PATIENTS TREATED WITH CISPLATIN IN JOHANNESBURG, SOUTH AFRICA

My name is Mukovhe Phanguphangu, a student currently conducting a research study as part of my MSc Audiology project, investigating the *audiological profile of paediatric patients treated with Cisplatin*. Cisplatin is an antineoplastic drug used for the treatment of the many types of cancer in both the paediatric and adult patients. However, cisplatin is also associated with ototoxicity which is characterised by a high prevalence of hearing loss in both paediatrics and adult patients. Childhood hearing loss can have an adverse impact on academic performance and communication ability. It is hoped that the results of this study will be significant and ultimately provide information that could guide the prevention, identification and management of cisplatin induced hearing loss in children. I therefore request permission to access medical records of paediatric patients who were treated with Cisplatin at your institution.

This study is aimed at determining the Prevalence and prevalence of cisplatin induced ototoxicity in paediatric patients. The information will be obtained by retrieving medical folders at Charlotte Maxeke Johannesburg Academic Hospital. The only risk identified for the study is loss of confidentiality which will be minimised by giving medical folders study numbers as opposed to using patient names. In addition, data collection will not hinder normal day-to-day functioning of the Audiology department. The data collected will be used for research purposes only and no patient names will be recorded to maintain their confidentiality. Please find the study proposal attached.
For your convenience, the consent form is attached. You are free to withdraw your consent at any time during the study. If you need any further information, or have any concerns, please do not hesitate to contact the investigator. If you have any queries or concerns regarding this study, please feel free to contact myself or my academic institution on the numbers provided below:

- Student Researcher- Mukovhe Phanguphangu: 0768785167
- Supervisor: Professor Lebogang Ramma: 021 406 6347 (Head of Department: Health and Rehabilitation Sciences, Faculty of Health Sciences, University of Cape Town)

Yours Faithfully

Mukovhe Phanguphangu
Consent Slip:

This certifies that I ______________________ hereby agree for Mukovhe Phanguphangu to conduct research as part of his Master’s degree in our facility.

All the documentation from the University of Cape Town’s Faculty of Health Sciences Human Research Ethics Committee regarding ethical clearance for the study has been provided. The study and the institution’s participation in it have been clearly explained in full to me by the researcher and I understand all the explanations given to me. I understand all the proceedings and requirements for the study from our institution and thereby give my support throughout the research period. The questions that I asked were answered to my satisfaction. I have contacts for the University and the researcher should I need to contact them at any time.

Name: __________________________  Date: ______________

Signature: ________________________
Appendix 3: Permission letter to conduct study at RCWMCH

Professor Lebogang Ramma; Mr Chad Phanguphangu
University of Cape Town

Dear Professor Ramma and Mr Phanguphangu,

APPROVAL OF RESEARCH

PROJECT TITLE: AUDIOLOGICAL PROFILE OF PAEDIATRIC PATIENTS TREATED WITH CISPLATIN IN SOUTH AFRICA

It is my pleasure to inform you that approval is hereby granted to conduct the above-mentioned study at the Audiology Department at Red Cross War Memorial Children’s Hospital.

Yours sincerely,

Silva Kuschke
HoD: Audiology
Dr M Phanguphangu
Red Cross War Memorial Children’s Hospital

Dear Dr M Phanguphangu

APPROVAL OF RESEARCH

PROJECT TITLE: THE AUDIOLOGICAL PROFILE OF PAEDIATRIC PATIENTS TREATED WITH CISPLATIN IN SOUTH AFRICA

It is a pleasure to inform you that approval is hereby granted to conduct the above-mentioned study at Red Cross War Memorial Children’s Hospital.

Yours sincerely,

[Signature]

Dr J Kawadza
Manager: Medical Services
Date: 22.11.17
**Appendix 4: Data Abstraction Sheet**

Division of Communication Sciences and Disorders  
Faculty of Health Sciences  
University of Cape Town  
Telephone: 021 406 6347  
Email: phnmuk001@myuct.ac.za  
lebogang.ramma@uct.ac.za

**RE: Data collection sheet for The Audiological profile of paediatric patients treated with cisplatin in South Africa**

| Patient | Age | Sex  | Race | Cancer type | Cumulative dose | Tx Duration | Otoscopy | Pt a | Pt Tb | Pt a 1k | Pt a 2k | Pt a 4k | Pt b | Pt b 1k | Pt b 2k | Pt b 4k | Pt 5k | Pt 1k | Pt 2k | Pt 4k | Pt 6k | Pt 8k | Pt 9k | Pt 10k | Pt 12k | Pt 16k | Tin | Audal fullness | Otolgia |
|---------|-----|------|------|-------------|-----------------|-------------|----------|------|-------|--------|--------|--------|------|--------|--------|--------|------|------|-------|-------|-------|-----|------|------|
| 1       |     |      |      |             |                 |             |          | R    | L     | R      | L      | R      | L    | L       | L       | L      | R    | L    | R     | L     | R     | L    | R     | L     | L     |     |               |       |
| 2       |     |      |      |             |                 |             |          | R    | L     | R      | L      | R      | L    | L       | L       | L      | R    | L    | R     | L     | R     | L    | R     | L     | L     |     |               |       |
| 3       |     |      |      |             |                 |             |          | R    | L     | R      | L      | R      | L    | L       | L       | L      | R    | L    | R     | L     | R     | L    | R     | L     | L     |     |               |       |

---

102
### Appendix 5: The Clark (1981) Hearing Loss Classification System

**Table 8: The Clark (1981) Hearing Loss Classification System**

<table>
<thead>
<tr>
<th>Thresholds in decibels (dB)</th>
<th>Degree of hearing loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>-10 to 15 dB</td>
<td>Normal hearing</td>
</tr>
<tr>
<td>16-25 dB</td>
<td>Slight hearing loss</td>
</tr>
<tr>
<td>26-40 dB</td>
<td>Mild hearing loss</td>
</tr>
<tr>
<td>41-55 dB</td>
<td>Moderate hearing loss</td>
</tr>
<tr>
<td>56-70 dB</td>
<td>Moderately-severe hearing loss</td>
</tr>
<tr>
<td>71-90 dB</td>
<td>Severe hearing loss</td>
</tr>
<tr>
<td>&gt;90 dB</td>
<td>Profound hearing loss</td>
</tr>
</tbody>
</table>
### Appendix 6: SIOP Ototoxicity Grading Scale

**Table 9: International Society of Paediatric Oncology ototoxicity grading scale**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>( \leq 20 \text{ dB HL} ) at all frequencies</td>
</tr>
<tr>
<td>1</td>
<td>( &gt;20 \text{ dB HL} ) SNHL above 4000 Hz</td>
</tr>
<tr>
<td>2</td>
<td>( &gt;20 \text{ dB HL} ) SNHL at 4000 Hz and above</td>
</tr>
<tr>
<td>3</td>
<td>( &gt;20 \text{ dB HL} ) SNHL at 2000 Hz and above</td>
</tr>
<tr>
<td>4</td>
<td>( &gt;40 \text{ dB HL} ) SNHL at 2000 Hz and above</td>
</tr>
</tbody>
</table>

---

*dB* = decibel, *HL* = hearing level, *SNHL* = sensorineural hearing loss, *Hz* = hertz