The use of precision medicine on children with refractory epilepsy in South Africa: Caregivers' experiences, perspectives and expectations.

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Declaration

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

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Abstract

Background: Precision Medicine (PM) is a model whose goal is to tailor healthcare to meet the individual patient's treatment and management needs. Precision Management of Epilepsy in South African Children (PME) is an on-going study at the University of Cape Town (UCT) gathering preliminary insight into the potential of PM initiatives which include remote monitoring with a wearable device, a phone app and a genetic and pharmacogenomics study in a South African setting. Feasibility and acceptability of new innovations is dependent on caregivers. This sub-study aims to better understand the caregivers' experiences, perceptions and expectations of the PME initiatives.

Methods: Ethical approval was obtained from UCT for this qualitative sub-study (HREC 775/2018). Twelve participants were purposively recruited from a cohort of 40 caregivers of children with refractory epilepsy recruited for the PME study attending Red Cross War Memorial Children's Hospital in Cape Town, South Africa (SA). Face to face semi-structured interviews were conducted and themes were extracted using a thematic framework approach.

Results: The knowledge of the aetiology of epilepsy was limited for most participants whose beliefs included medical, spiritual and traditional causes. Poor seizure control despite medication has resulted in an ongoing search for sources of cure and the right medication(s) and dose which impacts on adherence. The majority of participants showed limited understanding of what precision medicine is and did not fully understand the PME study. However, most felt that if properly implemented, these measures would be beneficial in caring for Children with Epilepsy (CWE). The mHealth devices introduced new feelings and challenges. The four themes which emerged were: 1) Cause of epilepsy: uncertainty and conflicting views; 2) Need for healing; 3) PME mHealth devices; 4) Feasibility of Feasibility of implementation of PME initiatives.

Conclusions: The cause of epilepsy was generally misunderstood but caregivers felt that PM could help unlock the unknown cause of the refractory epileptic seizures. Most caregivers harbour insecurities about treatment efficacy and are in a constant search for optimal therapy. Adherence to medication is central to controlling seizures but was inconsistent for most participants for a number of reasons including health care access and uncertainty about the benefit gained. The mHealth devices, particularly the phone app, was perceived to be helpful especially in improving adherence but created an additional burden for many participants. This sub-study generated beneficial information for understanding caregivers' current level of understanding of epilepsy and the PME initiatives and the potential benefits and challenges in future implementation of PM in SA.

Dedication

This minor dissertation is dedicated to my father, Peter Nathan Muchada.

Your wisdom inspired and encouraged me to follow my dreams.

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List of abbreviations

AEDs	Anti-epileptic drugs
ATR	African Traditional Religion
CT	Cape Town
CWE	Children with Epilepsy
UCT	University of Cape Town
EEG	Electroencephalography
ETG	Epilepsy treatment gap
IBE	International Bureau for Epilepsy
ICT	Information Communication Technology
ILAE	International League Against Epilepsy
LCS	Living Conditions Survey
LMICs	Low- and Middle-Income Countries
NGS	Next Generation Sequencing
PM	Precision Medicine
PME	Precision Management of Epilepsy
PMI	Precision Medicine Initiative
PROs	Patient related outcomes
QOL	Quality of life
RCWMCH	Red Cross War Memorial Children's Hospital
RE	Refractory epilepsy
SA	South Africa
SSA	Sub Saharan Africa
Stats SA	Statistics South Africa
SUDEP	Sudden unexpected death in epilepsy
UK	United Kingdom
VNS	Vagal nerve stimulation
WHO	World Health Organization

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CHAPTER 1: STUDY BACKGROUND AND RATIONALE

This chapter provides background information on the topic under study as well as the rationale, aim and objectives of the study.

Introduction

Epilepsy, a major public health challenge, affecting about 70 million people globally, is a well-known, chronic, non-communicable neurological disorder which can have significant physical and psychological consequences most commonly affecting children (Ba-Diop, 2014). It represents up to 1% of the global morbidity and mortality burden with Africa accounting for up to 20% of the global burden of epilepsy (World Health Organization, 2004). The uncontrolled and unpredictable seizures (convulsions) characterising the condition place a significant burden on the affected individuals, carers and society (Golyala and Kwan, 2017). The burden is more pronounced in Low- and Middle-Income Countries (LMICs), particularly in sub-Saharan Africa (SSA) where severe cases are reported, often associated with poor seizure control (Ba-Diop, 2014; Jost *et al.*, 2018). Innovative precision medicine (PM) strategies for optimising care of the individual patient and reducing the burden of epilepsy could benefit LMICs. However, there is little data on the role of PM in LMICs.

To gather preliminary data on the potential benefits of integrating certain PM initiatives in the South African setting, a study titled Precision Management of Epilepsy (PME) in South African children is on-going at the University of Cape Town (UCT) in collaboration with the United Kingdom (UK) company, Aparito. This includes developing and evaluating the following three PM initiatives in the local South African public health sector in the management of children with medically refractory epilepsy attending Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town (CT), South Africa (SA). These three initiatives include molecular genetic diagnosis; pharmacogenomics analysis of potentially relevant variants and home monitoring technologies including a wearable device and smart phone app. (HREC REF 797/2017). Participants recruited in the PME study had saliva swabs collected for genetic and pharmacogenomic testing and a smartphone app was loaded onto the caregiver's phone to provide medication reminders, record seizures and other patient reported outcomes (PROs). Where a caregiver did not have a suitable phone, one was provided for the duration of the study. In addition, when tolerated and acceptable to the affected child and caregiver, a "sports watch" to wear was given to capture data on heart rate, ambulation, sleep pattern and temperature. No studies on feasibility and acceptability of these PM initiatives to caregivers in the South African context have been done. This sub-study aims to explore the perspectives and experiences of caregivers to children recruited into this study and their expectations of these PM initiatives using a qualitative approach to

collect in-depth data. Most of these caregivers reside in informal settlements around CT and the majority are Xhosa speaking. The background will address the epidemiology, management and burden of epilepsy relevant to this context as well as aspects of the PM initiatives currently being explored.

Epidemiology

Studies suggest that the incidence, prevalence and mortality of epilepsy are affected by place and age. Young children, the elderly and those living in LMICs, especially on the African continent, have a higher incidence of epilepsy (Treiman, 2010; Ba-Diop, 2014; Jost *et al*., 2018). About 80% of the epilepsy population is found in LMICs where incidence and prevalence are reported to be approximately double that of developed countries (Yeni *et al*., 2016). Ba-Diop, (2014) reports an annual incidence of 81·7 per 100 000 (95% CI 28·0–239·5) in LMICs compared to 45 per 100 000 (30·3–66·7) in higher income countries. Another comparative study by Ngugi *et al.*, (2013) recorded a prevalence of 15.4 per 1000 and 10.3 per 1000 for rural and urban residents respectively in LMICs compared to 5.8 per 1000 in developed countries. Estimates of prevalence of epilepsy vary widely between and within LMICs and are described to be as high as 105 per 1000 persons in certain parts of Africa. This wide variation has been attributed to several factors including the type of analysis methods used, the nature of epilepsy studied, the specific population/s studied and the distribution of risk factors (Mugumbate and Zimba, 2018; Akinyemi *et al*., 2016; Ngugi *et al*., 2013). In SA, where the condition still carries a lot of stigma and misconception, a lifetime prevalence of 7.3 per 1000 children in a rural district was reported in a study conducted by Wagner and colleagues in 2014. Epilepsy South Africa currently reports the incidence of epilepsy in SA to be about 1 in 100 (Epilepsy SA information, 2017). Globally, people with epilepsy are reported to have about three times higher premature mortality rate compared to the general population which is supported by a review of six studies on the mortality in patients with epilepsy in SSA (Ba-Diop, 2014). This review included a Gambian study which reported a mortality ratio of 77 per 1000 for those with epilepsy over a two-year period, compared to 8 per 1000 for the general population in that country.

Cause of Epilepsy

"To suffer from epilepsy in Africa often means to also suffer from a very specific psychological and social trauma". This statement by Jilek – Aall *et al*., (1997: 784) puts into perspective how epilepsy is often viewed in African societies. Epilepsy is a feared, misunderstood and stigmatised disorder affecting patients and caregivers. The common perception that epilepsy is a spiritual or a contagious condition instead of a neurological illness results in social stigma that some patients see as a greater challenge than the clinical symptoms (Wilmshurst *et al*., 2014; Hunter, 1987). Mugumbate and Zimba

(2018) expand on this by highlighting the influence of religion on how epilepsy is perceived in Africa. They report that epilepsy is seen to be a result of spirit possession, witchcraft or a demonic attack in African Traditional Religion (ATR) and as the consequence of evil spirits in certain Christian and Islamic beliefs. To further illustrate the influence of religion and cultural beliefs, the term used by Xhosa people to refer to epilepsy is "ukuxhuzula" which describes the spasmodic actions during a seizure. They believe that "ukuxhuzula" is a result of "Amafufunyana" (evil spirits), visions of bad things like a snake or a mermaid, "imoya emdaka" (bad wind) which is created to induce fits in someone or failure to appease one's ancestors (Loveday, 1990).

Despite the various views shared above, the cause often remains elusive for people in African communities just as it does in the traditional medical model where the cause of epilepsy is considered "idiopathic" or unexplained in about 50% of cases. In the other half, the cause can be traced to different factors which have a pathological impact on the brain (Fisher *et al*., (2014). Studies have attributed childhood epilepsy to lack of oxygen, toxins, traumatic brain injury (before, during, or after birth), strokes, central nervous system (CNS) infections or diseases, alcohol and drug abuse, brain tumours, neuroregressive illness and fever in addition to genetic factors (Burden and Schurr, 1980; Sands and Minters, 1979; Ba-Diop, 2014). Six aetiological categories that are in common use have been identified by Scheffer *et al*., (2017): structural, genetic, infectious, metabolic, immune and unknown (idiopathic). These authors go on to suggest that the classification of epilepsy may also be considered in terms of symptoms as this can have direct implications on management and prognostic counselling.

Genetic causes of epilepsy

Previously, up to 70% of epilepsy was considered idiopathic but with recent advances in the development of molecular genetic techniques, it has been found that more than 50% have a genetic basis and at least 0.4% of the general population are now believed to have genetic epilepsies (Dhiman, 2017; Orsini *et al*., 2018). Of the genetic variants thought to have a predisposition to epilepsy, most are de novo and not inherited from either parent, implying that a patient can have a genetic cause for seizures even in the absence of a family history of epilepsy (Dhiman, 2017). Genetic testing offers the foundation for more informed early diagnosis which in turn may reduce overall cost, enhance predictive accuracy, facilitate personalised therapy, help erase the misconceptions and stigmatisation surrounding the condition as well as alleviate the anxiety which befalls the family in the search for a diagnosis (Ream and Patel, 2015; Wang *et al.,* 2017). Next generation sequencing (NGS) has proved useful in revealing gene mutations causing unexplained epilepsy in about a third of the patients and can predict disease occurrence with up to 100% precision for certain variants (Koeleman, 2018).

Identification of disease-causing gene mutations offer insight into the pathophysiology in monogenic epilepsies as well as in polygenic forms which can help to inform treatment options (Avanzini, 2018). Examples of this are the use of sodium channel blockers in patients with *SCN1A* associated Dravet syndrome and the ketogenic diet therapy in patients with *SLC2A1* generalized epilepsy (Dhiman, 2017). As there is phenotypic and genetic overlap between epilepsy syndromes, the development of NGS gene panels with known epilepsy genes has been recommended for the identification of pathogenic gene variants (Firth and Hurst, 2017). Studies have reported a variable diagnostic rate ranging from 10 to 50% using a gene panel approach in early onset seizures (Rim *et al*., 2018; Zhang *et al*., 2015). Currently, there is little knowledge on neurogenetics in African populations and what is described is focused on North Africa with little data from SSA (Akinyemi *et al*., 2016). Therefore, to incorporate innovations such as genomic medicine in SSA and other LMICs, consideration must be given to how receiving a genetic diagnosis will impact on the individual and the family. Poduri *et al*., (2014) have addressed some ethical and practical aspects of genetic testing that should be implemented in order to ensure the benefits of genetic information outweigh the potential harms. In particular, the authors emphasise the need for pre- and post-test genetic counselling to help patients and their families make informed testing decisions and adapt to the results.

Refractory epilepsy

Despite the availability of many treatments and therapies, about a third of the epilepsy population has uncontrolled seizures known as intractable or refractory or drug resistant epilepsy, most of whom live in LMICs (Meng *et al.*, 2017). Various descriptions of what Refractory epilepsy (RE) refers to have been suggested by different authors. Meng *et al.*, (2017) refer to RE as failure to achieve control on medication and include poor response to other therapies like dietary modifications such as the ketogenic diet, vagal nerve stimulation (VNS) or epilepsy surgery. Yeun *et al*., (2018) postulate that RE results in part from non-adherence to medication, intolerance to medication (side effects) or failure of response to treatment. These authors define RE as being “drug resistant” epilepsy when two or more anti-epileptic drugs (AEDs) in adequate doses have failed to control the events. This is the definition used for recruitment to the PME study at UCT.

RE places a significant burden on the patient, medical fraternity, caregivers and society at large. Accordingly, Laxer *et al.*, (2014) highlight that the burden is increased by experiences of comorbid illnesses, social stigmatisation, psychological dysfunction, lower quality of life (QOL) and a decreased life expectancy. Furthermore, epilepsy increases premature mortality due to factors such as vascular diseases, pneumonia, accidents, sudden unexpected death in epilepsy (SUDEP) and suicide amongst others. The authors indicate that children with RE account for the greatest burden in the epilepsy

population as these children not only require the most home care but also need more attention to their treatment and management due to limitations in physical and cognitive function.

Caring for a child with RE is multidimensional, requiring a knowledge of the child's health status, seizure type and frequency as well as their developmental and educational potential (Raina, *et al*., 2004). Caregivers are burdened by the lack of predictability and severity of seizures, the possible side effects of medication and insecurity concerning the efficacy of treatment. These factors can generate fear and anxiety in patients and the people who interact with them and can result in parental mental health issues that affect family functioning and can affect adherence to treatment (O'Dell *et al.*, 2007; Bilgiç *et al.*, 2018; Reilly *et al*., 2018). There is evidence that many factors contribute to drug-resistance in epilepsy including genetic aetiology, individual response to drugs and adherence to prescribed medication (Meng *et al*., 2017).

Individual response to drugs (Pharmacogenomics)

Pharmacogenomics is defined by Balestrini and Sisodiya (2017), as the study of the contribution of genetic variation to how individuals respond to medications and includes aspects such as how drugs are absorbed, transported, metabolised and cleared as well as behave at the site of action. The authors acknowledge that there are genetic factors contributing to ways in which individuals respond to medication with regards to seizure control and adverse drug reactions in epilepsy. Dhiman (2017), highlights that the progress made in the field of genomics and pharmacology has in some cases made predicting the variations in treatment outcomes for patients with the same disease and on the same treatment possible. *ABCB1, UGT2B7, UGT1A3, CYP2C9, CYP2D6* and *CYP2C19* are examples of genes in which variants may have a potential effect. *CYP2C9* variants are an important determinant of response to phenytoin, accounting for about 90% of phenytoin metabolism (Dandara *et al*., 2014). In the same vein, Dhiman, (2017) suggests that unnecessary phenytoin toxicity can be prevented by identifying the poor metaboliser *CYP2C9* or *CYP2C19* gene alleles in patients and administering lower doses of phenytoin to them. How pharmacokinetics and pharmacodynamics of antiepileptic drugs can influence therapeutic regimens is described by Balestrini and Sisodiya (2017). Dandara *et al*., (2014) and Akinyemi *et al*., (2016) note the scarcity of pharmacogenomic variants contributing to the neurobiology of brain disorders in African populations and stress the need for local data which may enhance diagnosis and therapy options in people of African ancestry.

Non-adherence

Adherence to AEDs has been identified as crucial to the attainment of optimal therapeutic levels in the management of children diagnosed with epilepsy in several studies as reflected below. Modi and

colleagues (2014) discovered that adherent patients were more likely to be seizure free than those with early treatment non-adherence. Non-adherence, which may be defined as being when a patient takes less than 80% of the prescribed medication, results in inadequate control of epilepsy with a poor quality of life characterised by frequent seizures, increased cost of health care, frequent hospitalisation and regular visits to emergency departments (Jacob *et al.*, 2017). Nearly a third of epilepsy patients on AEDs are non-adherent (May *et al*., 2018). Jacob *et al.*, (2017) indicate that place of residence, age and co-morbidities all have an impact on adherence. Their study confirmed earlier findings on the impact of socioeconomic status on adherence when they found better adherence in western Germany than in eastern Germany which is economically less affluent. Lower socioeconomic status is typically associated with higher non-adherence (Modi *et al*., 2014).

Non-adherence among children is related to certain patient, medication, caregiver, and environmental factors. These include the length of time the patient has been taking drugs, the high cost and quantity of tablets that must be taken, the use of other therapies, psychosocial support and financial restrictions (Yang *et al*., 2018). Lack of counselling and awareness about epilepsy as well as forgetting to take or to administer medication and seizure severity and frequency are reported as additional factors influencing adherence (Nazziwa *et al*., 2014). A study in Kenya found traditional beliefs, living long distances from health facilities and the high cost of drugs to be contributors to non-adherence (Carter *et al*., 2012). The availability of and access to drugs, especially for poor people and how this influences adherence was highlighted in a Malian study which found that most of the local pharmacies didn't have the drug phenobarbital in stock although up to 60% of patients were found to be seizure free when taking appropriate doses regularly (Bruno *et al*., 2012).

Challenges in Managing Epilepsy in Africa

Identification of the underlying cause, seizure control using AEDs as well as avoiding and treating co-morbidities are the focus in epilepsy management (Ba-Diop, 2014). However, management is inadequate in Africa, where up to 90% of people living with epilepsy are not getting proper treatment (Carter *et al*., 2012). Several studies have identified factors such as geographic difficulties, limited health-care systems, high treatment cost, poor transportation, misunderstanding epilepsy cause, treatment and prognosis, cultural and religious beliefs as well as seeking traditional rather than medical treatment that all affect accessing treatment and can result in non-adherence and contribute to the large epilepsy treatment gap (ETG) in Africa (Carter *et al*., 2012; Mugumbate and Zimba, 2018, Hunter *et al.,* 2016). A Kenyan study likewise found that having focal seizures, long duration of epilepsy, distance from health facilities, cost, traditional beliefs and negative attitudes towards medical care were factors which negatively impacted access to medical treatment (Mbuba *et al*.,

2012). For some the influence of stigma on management is more important while, for others, inadequate health facilities with limited access to AEDs play a bigger role (WHO, 2004).

The ETG has been widely studied by several researchers and groups, among them the International League Against Epilepsy (ILAE) who have defined ETG as "the difference between the number of people with active epilepsy and the number of people whose seizures are being appropriately treated" (Carter *et al*., 2012). This is most significant in SSA where a WHO systematic review conducted in 2010 reported an ETG of more than 95% (Ba-Diop, 2014). The WHO define the ETG differently as the percentage of persons seeking treatment for epilepsy compared to those who are adherent to it. Corrective measures that eliminate stigma are needed in order to help reduce the treatment gap (Ba-Diop, 2014). Key to this is the intervention of governments and partnerships between stakeholders, while at the same time, epilepsy associations should continue to fight against discrimination of those with epilepsy (Mugumbate and Zimba, 2018). The ILAE has also gone on to redefine epilepsy as a disease not a disorder to emphasize the impact of epilepsy to all stakeholders. Much as others might feel that "disease" increases the stigma, conditions such as cancer and diabetes receive better medical care with less stigma because they are described as diseases not disorders (Falco-Walter *et al*.,2018).

Sadly, in Africa, regional organisations have not always been forthcoming with support programmes to effectively implement initiatives recommended by the international associations. In short, Mugumbate and Zimba (2018) concluded that everyone, from laypeople to epilepsy associations and governments, should collaborate more to bridge the ETG. They further state that the ETG remains very wide in Africa because of non-prioritisation of epilepsy awareness and governments failure to avail affordable treatment and medicines. They go on to suggest other necessary interventions to reduce the ETG such as making sure that health-care resources are equally available in both rural and urban areas, rolling out awareness and support programmes for all stakeholders and improving the delivery and accessibility of drugs.

Mugumbate and Zimba (2018) writing for the International Bureau for Epilepsy about the past, present, and future of epilepsy in Africa, indicate that the general population often hold the view that epilepsy is a non-medical condition but a cultural or religious one, whose symptoms cannot be treated with AEDs. They suggest that these beliefs influence treatment choices resulting in limited or delayed medical intervention. Delays of as long as 13 years in some cases occur before intervention. This is while patients and families seek therapy from non-medical individuals believed to have knowledge in managing the condition such as elders, faith and traditional healers, herbalists and prophets. These 'therapists' are believed to have the powers to exorcise the evil spirit or demon which is often believed

to cause the condition. In the authors' view, these beliefs contribute to the stigmatisation of epilepsy and non-prioritisation of its management programmes by governments.

Accurate reporting of seizure occurrence is key to the success of treatment programmes for epilepsy with specific attention to frequency, type and length of a seizure as this has a direct influence on evaluating therapy options for an individual as well as determining novel drug efficiency. As confirmation of this, all the neurologists interviewed by Bidwell (2015) expressed the need to view a patient's seizure on video before prescribing medication. Other studies have shown that subjective reporting of seizures is very unreliable. In a study by Nijsen, (2005) seizure detection using EEG was 29 times more likely than self-reporting and seven times the number observed at clinics. This study concluded that only about half of the seizures that occur are reported by patients. Inaccurate reporting was replicated in Fisher's study where participants recorded zero seizures in their self-reporting diary compared to 12 detected by an accelerometer watch (2017). The failure to report seizures accurately has been a great challenge to management programmes in Africa where this inaccurate recounting together with unpredictable seizure occurrence significantly reduce the QOL of families affected by epilepsy (Bidwell, 2015; Ulate-Campos *et al*., 2016).

The challenges described above indicate the need for finding innovative, high-quality seizure control and epilepsy services, which will need to be suitable to LMICs, to mitigate the challenges faced in the management of epilepsy in SA and other parts of Africa.

Precision Medicine (PM)

PM is a medical model that proposes the customisation of healthcare to the individual patient. Jameson and Longo (2015) define PM as "treatments targeted to the needs of individual patients based on genetic, biomarker, phenotypic or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations" (pg. 2). The authors place emphasis on adaptation of healthcare to suit individual patients thereby reducing likely side effects emanating from treatment. Wang *et al*, (2016) acknowledge that this precise treatment for individuals and diseases is the new focus of global health care. They emphasise the importance of PM in reducing the fatality of major complex diseases, such as epilepsy, and the role of technical innovation in medical services at reduced cost to drive this forward.

The goals and aims of PM have been extensively described by various authors with Van Eyk and Sobhali, (2018) describing its central goal as the provision of the correct treatment to a particular patient at the right time in accordance with their specific genetic makeup. This view is in keeping with what former United States of America President Obama said about PM's goals and promise when

launching the Precision Medicine Initiative (PMI) in 2015. He said "… delivering the right treatments, at the right time, every time to the right person...". In concurrence, Aronson and Rehm (2015) set the goal of PM as the enhancement of clinicians' ability to quickly, efficiently and accurately determine the most suitable therapy for individual patients. In a nutshell, PM is about identifying, classifying, and stratifying patients for targeted treatment using information such as from the patient's genotype for better diagnosis and management.

Epilepsy is one of the earliest disease areas to implement the principles of PM into management to improve the safety and effectiveness of AEDs. With the recent knowledge acquired on the genetic aetiology, focus in epilepsy has shifted towards understanding the underlying cause more than treating the symptoms. This includes specific emphasis on the individual, not the "average", patient's responses to therapy (Schork, 2015). This approach has led to the incorporation of PM in epilepsy therapy development and decision making in many stages of care (Zuberi and Bleunkos 2018). The use of genetic testing can improve diagnosis and offer knowledge on the disease pathophysiology thereby improving treatment by reducing adverse effects and enhancing efficacy when compared to clinical diagnosis alone (Striano *et al.,* 2018). As mentioned earlier, increased predisposition to drug resistance can sometimes be identified through pharmacogenomics before treatment and allow for the selection of patients with less susceptibility to resistance.

Much as PM initiatives have been shown to be more cost-effective than clinical strategies alone in more resource equipped countries, they need to be distinctly streamlined if these promising goals are to be achieved locally. Duffy *et al*., (2016) supported this by pointing out that implementation of new initiatives requires health care providers to understand the target population in order to overcome the teething obstacles. There is little data on the role of PM in LMICs.

Technological mHealth devices in Management of Epilepsy

As mentioned, medication non-adherence and inaccurate reporting of seizures are two of the major challenges in the management of epilepsy. Their impact is important enough to indicate that there is a need for remedial action. Central to the quest to get accurate seizure records and enhance adherence is the use of technology mobile Health (mHealth) devices that can either record or detect seizure occurrence more accurately as this could mean better treatment plans for individual patients. This may include the possibility of predicting the occurrence of the next seizure, a development which will boost patient and family confidence. Digital technology and wearable devices, whose availability has recently increased, are used to detect seizures though they have not been adopted in routine epilepsy care (Bruno, 2018). When connected to a smartphone via Bluetooth, wearable mHealth

devices can improve seizure reporting through home-based monitoring thereby enhancing management of children with epilepsy (CWE) in LMICs (Paesschen, 2018).

The wearable devices and disease-specific mobile apps used by Aparito in the feasibility trial of remote monitoring in the main PME study, are designed to provide low-cost remote patient monitoring outside the hospital environment. This technology should allow for more effective individualised therapy through the provision of real-time data, which can be easily shared between patient, carers and clinicians and will in turn enhance diagnosis, treatment and development of drugs (Godfrey *et al*., 2018). The collection of data remotely using wearables and videos is more convenient for patients in that it reduces the need for extensive travel to health care sites and could reduce the subjectivity associated with self-reporting of patient health while in clinic. Bidwell *et al*., (2015) suggested that the use of devices able to detect inert seizures and video record seizures at night can provide more accurate seizure counts.

The Hesvit wearable mHealth devices used in the study are small and attractive for children, with a relatively long battery life requiring no input from the patient. These are set to capture data on heart rate, ambulation, sleep pattern, temperature, calories and barometric pressure allowing for real-time assessment of children who can be difficult to monitor. They are not, however, seizure detection devices. Despite that, information relating to a child's average temperature, recorded through a watch, can sometimes be used to predict seizures which are often precipitated by fever (Ulate-Campos *et al*., 2016). The other attributes of the mHealth devices used for this study are in keeping with those described by Nijsen *et al*., (2005) and Schulze-Bonhage *et al.*, (2010) who state that mHealth devices must be user friendly and most importantly they must offer comfort to the patient especially when they are sleeping. The foregoing is in keeping with findings of a study by Hoppe *et al*., (2015) focusing on user preferences in wearable mHealth devices who concluded that non-obtrusive instruments that resulted in minimal interference with daily routines were preferable. In a study by Tovar Quiroga *et al*., (2016), people with epilepsy and their caregivers showed interest in using seizure detection devices since undetected seizures carry the risk of SUDEP and they emphasized the need for affordable mHealth devices which can generate an alarm immediately after the seizure.

The Aparito smartphone mobile app used by participants in this study has four domains. It includes a real time medication reminder with the ability to record adherence or reasons for non-adherence; an events recording section which allows for recording of seizures detailing duration, type and allowing for video upload, or any other reportable events; a health care visit documentation section and finally a series of patient reported outcomes focused on sleep quality and quality of life experiences (Aparito n.d. Atom5 Platform). This is hoped to improve adherence to treatment by reminding patients or

caregivers of treatment prescriptions and tracking doses taken. The ability of smartphone apps to mitigate the challenge of non-adherence by providing prompts to caregivers about medication times and types has been reported by Ahmed *et al*., (2018) and Ulate-Campos *et al*., (2016). The potential of wearable mHealth devices in detecting and capturing nocturnal seizures in an objective and continuous way to provide a more accurate seizure occurrence record compared to patient self-reporting and, in that way, provide a guide to effective treatment and management decisions has been reported (Bidwell *et al*., 2015; Bruno *et al*., 2018).

Despite the possible benefits of mHealth initiatives there are challenges associated with their implementation globally which not only depend on access to technology but also on technical support in the medical fraternity and poor technical expertise in information communication technology (ICT) among health practitioners among other factors (Furusa and Coleman, 2018). Adoption is much lower in LMICs given the challenges of limited e-health infrastructure, poor policies and limited health sector budgets (Lam *et al*., 2016; UNICEF, 2016; Busagala and Kawono, 2013). Other factors which Kiberu *et al*., (2017) found to influence adoption in sub-Saharan Africa include high disease prevalence, high population growth resulting in a discrepancy between the small number of health workers and the large population they serve, costly telecommunication facilities, poverty, lack of government commitment and war.

As alluded to above, mHealth initiatives including wearable technology do have the potential to improve the management of epilepsy in SA given the increasing affordability and availability of smart phones, cellular access, bandwidth and more affordable wearable devices. According to Bruno and colleagues (2018), the successful implementation of such technology is dependent on the user's engagement with it as well as its accessibility and acceptability. Therefore, establishing the acceptability and feasibility of using such technology in Africa is essential.

Rationale for the Study

As described by Mugumbate and Zimba, (2018), most people on the African continent still view epilepsy as a non-medical condition but rather a cultural, religious, or spiritual one which potentially is unresponsive to low-cost AEDs which may influence any care provided for patients with epilepsy. This perception is also expected to be prevalent in SA where epilepsy management is worsened by standards of care that are limited with regards to screening for underlying aetiologies as there is no diagnostic testing available for epilepsy genes in the public sector. The potential for including PM initiatives which focus on individualising care by introducing home monitoring technologies (mHealth) and genetic and pharmacogenomics testing in CWE is being piloted through the PME study. The feasibility and acceptability of these initiatives has not been investigated in SA or other LMICs to date. The outcome is largely dependent on the caregivers of affected children, making it imperative that their perceptions and expectations of PM and its place in epilepsy diagnosis, treatment and management in the local setting are understood. In addition, a comprehensive understanding of the caregivers' lived experience with epilepsy will be of value. There are no studies published on technology-based monitoring of epilepsy in Africa and very little on the genetic aetiology and pharmacogenomics of epilepsy or what this may mean to those affected by the disorder in SSA. Due to the lack of data in this area, this sub-study of the PME study aims to address some of these questions utilising a qualitative approach.

Aims and objectives

Aim

To examine the experiences, perceptions and expectations of caregivers to children with refractory epilepsy attending epilepsy clinic services at RCWMCH recruited in the ongoing Precision Management of Epilepsy in South African children study.

Objectives of this study

The study's objectives were to explore:

1. The caregivers' perceptions of the cause of epilepsy and its treatment.
2. The caregivers' understanding of PM in managing epilepsy and how they perceive the benefit.
3. The caregivers' experiences with the technology used in the PME study.
4. The caregivers' expectations of PM.

CHAPTER 2: METHODOLOGY

Introduction

This chapter will describe the methods used in the study. The study design and framework as well as the study population, research setting, participant recruitment, data collection and data analysis will be included. Ethical considerations and research trustworthiness will be explored.

Study Design

This study is designed to gather the views, experiences and expectations of caregivers to children with refractory epilepsy on PM in the management of refractory epilepsy. A pragmatic qualitative approach which focuses on individuals to get an informative description of their real-life experiences as described by Savin-Baden & Major, (2013) was used in this study. This methodological approach is often used to obtain a holistic picture for describing variations in situations, issues or phenomena where little is known, and theories are largely unavailable (Vivar *et al*., 2011). The approach aims to explore a variety of meaningful properties of real-world settings, such as people's perceptions, lived experiences, feelings, views and the significance of the meanings that they give to their own personal situation (Yin, 2016). Rapport *et al.,* (2015) indicated the importance of qualitative data collection methods in understanding patients' health-care experiences which can also help researchers to understand their views on service provision.

The current study seeks to unlock the participants' world of experience in caring for CWE and taking part in the PME study. This information is helpful to the researcher in getting a sense of how the caregivers perceive PM and help identify potential challenges with integrating these initiatives in the South African setting. The participants' experiences were elicited through semi-structured, face to face interviews. This exploratory, flexible method of inquiry that is sensitive to the social and cultural settings is useful in producing comprehensive information which may not be discovered or unlocked when questionnaires are used. It allows the researcher to enter the participants' world, capture their voice and experiences and attempt to understand the world from their perspective. As more information and a better understanding of significant data are acquired, the qualitative researcher can change the investigation path and move in new directions (Kumar, 2014).

Study Population

A purposive sampling method was used to select the participants. This sampling chooses samples deliberately with the goal of having participants that are most relevant to the research and have the most likelihood of providing beneficial data (Patton and Cochram, 2002). In this study, a caregiver is a

primary provider of care to a child with epilepsy. The criteria used to include participants in this study were as follows:

1) Caregivers to children aged between 4 and 18 years with RE whose DNA samples had been extracted for the NGS epilepsy gene panel analysis in the PME study.
2) Caregivers who had received the Aparito smartphone app while the children in their care have received the wearable device and have been using them for at least 3 months.
3) Caregivers above the age of 18 years at the time of recruitment.

Caregivers who had not been using the smartphone app and the wearable device for at least three months were excluded from this study since they had had too little exposure to the mHealth devices to give a thorough opinion. A total of 11 participants were recruited sequentially as they arrived within the timeline of recruitment for their normal follow-up appointments while the 12th and final participant was purposely chosen to test saturation as described in the next section. These individuals were recruited from a cohort of 40 caregivers who provided informed consent for the ongoing parent PME study. The children in this study all attend epilepsy clinic services at RCWMCH in CT, SA.

Participant Recruitment

The researcher, who played a role in recruiting participants in the PME study, together with other recruiters, approached the participants during the child ‘s clinic visit informing them about this sub-study, it’s aims and objectives as well as voluntary participation. For those individuals who agreed to be in the sub-study, an interview date and time was set up at the participant’s earliest convenience. Effort was made for the interview date to coincide with the child’s follow up date at RCWMCH for convenience sake. It was emphasised that involvement in this study would in no way influence the ongoing participation in the PME study or the present or future medical care of the child.

Each participant received an information pamphlet (Appendix A) describing the scope of this study. This information letter was available in English, Afrikaans, and isiXhosa. Consent was obtained from those who agreed to participate by the researcher, and each individual participating in the study was requested to sign a consent form (Appendix B) informing them they could withdraw from the study whenever they so felt.

After signing the consent form, participants were given a copy of the signed form. Participants were made aware that all interviews would be conducted in a private setting and that the duration of each interview was approximately an hour. They were also informed that the interviews would be conducted in English, isiXhosa or any other language the researcher who is fluent in five African languages was proficient in and would be audio-recorded. Each participant was notified that if they

required an interpreter, an appropriate interpreter would be available to them during the interview. It was important to provide this option of having an interpreter to reduce the chance of introducing potential bias that comes with choosing to only interview participants fluent in the researcher's language(s).

Data saturation was obtained after the 11th Interview. In order to test this, a 12th participant was purposively chosen due to their different background to test that saturation had indeed been obtained. Saturation was the point when sampling more data was no longer leading to new information related to the research question (Bricki and Green, 2007). Demographics of participants were collected as shown in chapter 3, Table 1.

Research Setting

Not only is the accessibility of the venue important to participants, when choosing it, but also its safety and privacy (MacFarlane *et al*., 2014). Therefore, a private room at RCWMCH was used for the interviews when the participants came for the child's routine check-up. This place was selected because of its familiarity to the participants which could have encouraged free expression of feelings and experiences. Furthermore, this venue, in preference to their homes, suited both the researcher and participant considering the data that emerged about personal safety in the areas they reside in. The interviews were audio-recorded by the researcher and took, on average, 40 minutes to complete.

Data Collection

For consistency and reliability of data, the researcher conducted all 12 interviews (MacFarlane *et al*., 2014). Data was collected from all the participants through open ended semi-structured questions (Appendix D). These interviews were carried out in an informal and conversational style and were audio-recorded. A socio-demographic questionnaire (Appendix C) comprising closed-ended questions was utilised to obtain preliminary information about the participant and to build rapport between the researcher and participant. Prior to the interviews starting, test interviews were conducted by the researcher with her supervisor and a genetic counsellor and the questions were altered accordingly. This was done to ensure that the questions were eliciting responses that addressed the research aim and objectives. The use of a question guide comprising a set of predominantly open-ended interview questions allows the interviewees to make meaning of their own lives, experiences, and cognitive processes and encourages them to have the time and opportunity to reconstruct these in their own words (Yin, 2016). This method of data collection allows one to gain consistent data across individuals and an in-depth understanding of unknown phenomena as it explores the participant's own views and

meanings comprehensively (Bricki and Green, 2007). The main objective of this method of data collection is to describe a complex social world from a participant's perspective.

An interpreter was required for one interview in Afrikaans since the participant had shown preference for her mother tongue. An interpreter with a background in genetics who is fluent in Afrikaans was chosen to ensure uncompromised data collection when compared to the remaining interviews conducted by the researcher.

Data Analysis

Data collected during interviews was analysed using an emergent thematic framework approach in close discussion with the project supervisors. This approach uses a systematic process that thoroughly looks at data collected by the researcher to identify common recurring issues and organising them into themes and associated sub-themes which summarise the collective views (Spencer *et al*., 2003; Vivar *et al*., 2011). The researcher was guided by steps on conducting thematic analysis described by Braun and Clarke, (2006).

The researcher and translator transcribed the audio recorded data verbatim to provide a record of what was said during the interviews. For confidentiality participants were assigned pseudonyms and where participants referred to an individual using their name, that individual was given a letter of the alphabet. 11 of the 12 interviews were transcribed by the researcher herself and this enabled her to be well familiarised with the data. Reading through the transcript of the only interview transcribed by the translator offered the researcher familiarity with the data.

After familiarisation of the interview data through transcribing and reading the transcripts, initial codes were assigned by highlighting and attaching labels to lines of text in the transcripts. Each transcript was given equal attention to ensure a thorough, inclusive and comprehensive analysis. A spreadsheet programme "Microsoft excel 2016" was used to construct patterns of participants' descriptions of salient expressions and opinions as well as codes. This process enabled the researcher to group and compare similar pieces of information thereby sorting them into categories that were developed into emerging themes. As many codes as possible, both emerging and predetermined, were analysed for potential themes. The codes were placed together with the supporting extracts from the interviews. An inclusive set of themes was determined through an inductive process of continuous revisiting of themes and transcripts with project supervisors which brought overlooked text to the foreground. A deductive process of thoroughly examining the transcripts was done to verify the inclusion of all data collected in the identified themes. The researcher then interpreted the meaningful

content of the grouped collected data themes by searching for patterns, associations, concepts and explanations. For consistency, verification of the analysed data was shared between researcher and supervisors. In this way, the results give a deeper understanding of the participants' perceptions and reveals the variability in their understanding of epilepsy and the potential for PM acceptance.

Research Trustworthiness

To analytically tell the participants' stories within the context of the research question, the researcher immersed herself in the data by simultaneously collecting and analysing it (Hennink *et al*., 2011). This rigorous ongoing analysis throughout the study was essential for determining successive sampling decisions based on what arose from the analysis. Through asking a suitable preliminary question and adapting the other interview questions where necessary, the researcher achieved rigour. To check suitability and connection of coded data, the techniques used for coding and recording were analysed and reviewed. Having additional readers, trained in qualitative research, mutually agreeing upon themes, and interpretations ensured reliability and enhanced trustworthiness.

The researcher remained open to unexpected data, ideas and issues and set aside any personal expectations and experiences of the phenomena under study to avoid bias and understand the phenomena (Yin, 2016). Recognition of the researcher's social and psychological standpoint and awareness of the impact her other roles might have on the researcher role were important. Analysis in close discussion with the project supervisors reduced the biases that come with just one person analysing the data and reflexiveness ensured data analysis was not impinged on by the researcher's own values and biases.

Ethical Considerations

Ethical Approval

The UCT Health Sciences Research Ethics committee approved this sub-study before the start of the study (Appendix E).

Informed Consent

Crucial elements to obtaining a consent that is informed and ethically valid from a research participant are voluntarism, disclosing relevant information, and ability to make decisions (Del Carmen and Joffe, 2005). For this study, prospective competent participants were given a clear and precise scope of the research in a non-persuasive manner to allow them to autonomously choose to participate. They were

provided with information sheets and consent forms regarding the study and the information was precisely explained in their preferred language. They were free to ask questions and could decline or terminate participation anytime without this impacting on medical care in any way. Voluntary participation was emphasised.

Privacy and Confidentiality

Privacy and confidentiality of participants was prioritised and ensured by storing all confidential and identifying documents in a place only accessible to the researcher. The recorded interviews were deleted from the audio recorder soon after uploading them onto a password-protected computer and were transcribed verbatim. Only pseudonyms were used to save the data and all identifying labels or names of individuals were removed. All the collected data was backed-up on a memory stick and locked away in a cupboard and will be destroyed upon publication of the study.

Risks/harm and benefits

All participants were adults and the study itself involved no risk to the individual except talking about difficult experiences which are sometimes emotional. If a participant, at any point during the interview, no longer felt comfortable or if there were any questions that induced emotional distress that they did not feel comfortable exploring, they were made aware of the option not to answer the questions. The researcher had a background in genetic counselling which equipped her with empathetic skills to recognise and manage emotional distress.

There were no direct benefits to participants except contributing to a greater good of helping to gather preliminary data on the potential benefits of integrating different PM initiatives in the South African setting. The indirect benefit to the participants was that they had the opportunity to share their stories and be given a platform to make sense of their situation and their lives more effectively. The benefit of storytelling as a powerful instrument of communication that allows individuals with similar conditions or in similar situations to be heard as well as having a therapeutic effect has been reported in several studies (Dickson-Swift *et al*., 2007; Koch, 1998; Lupton, 1998). The information that was gained from the interview process will lead to greater understanding of managing epilepsy and implementing PM initiatives in this setting in South African children. This information will be beneficial for health care practitioners and may improve the understanding of the role of genetic counselling in epilepsy by genetic counsellors in SA.

CHAPTER 3: RESULTS

Introduction

The findings of the study including the participant demographics as well as the themes that the collected data generated will be presented in this chapter. Pseudonyms will be used for all whose names were mentioned. To support the themes, interview extracts will be used.

Participant Demographics

Of the 12 participants in the study group, 10 are the mothers of the child, one is the father and one is the grandmother of the affected child. All the affected children had some cognitive impairment as a result of severe epilepsy and were on minimum of three AEDs. The age of caregivers ranged between 29 and 54 years as shown in Table 1 below. The distribution of participants is in keeping with Kovacs *et al.,* (1985) notion that primary caregivers who protect and provide care to ensure the child's well-being and health are usually the mothers. Most study participants lived in an urban setting, nine in informal housing which, in Cape Town, is usually a shack constructed from zinc and plastic; two lived in formal brick housing and only one participant lived in a rural area. In keeping with South Africa's complex socio-political history, in Cape Town formal housing is more commonly found in more affluent, low population density areas on the periphery of the city where most residents are white South Africans while informal housing is much further away from the city in areas largely characterised by high population density and economic hardship and inhabited mostly by people of Black African ancestry. According to a Stats SA report (2018), up to 11% of the urban population of South Africa live in informal settlements. The majority of participants were unemployed and were in stable relationships. Most had a high school education but only two obtained tertiary education. Two participants had previous experience with epilepsy in the family which could have impacted on their current perception of epilepsy. Daher *et al*., (2017) are of the view that a participant's previous experience is an important concept for attaining an in-depth understanding of their perspective which ensures a more informed qualitative comprehension of the phenomena under study. Pseudonyms chosen by the participants were used to protect their identity. Seven of the 12 interviews were in isiXhosa, three in English, one in Shona and one in Afrikaans.

Table 1- Demographic Information

Participant	Relationship to child	Age of participant	Age of child	Previous experience with epilepsy	Living with partner	Education level	Residence	Employment status	Language
Unathi	Mother	45	10	No	Yes	Primary School	Informal	Unemployed	IsiXhosa
Baby	Mother	50	8	No	Yes	High School	Rural	Unemployed	Afrikaans
Bongi	Grandmother	50	9	No	No	Primary School	Informal	Unemployed	IsiXhosa
Rochel	Mother	35	6	No	Yes	High School	Formal	Unemployed	English
Noe	Mother	36	14	No	No	College	Informal	Employed	IsiXhosa
Ivy	Mother	54	10	No	No	High School	Informal	Unemployed	IsiXhosa
Fortunate	Mother	29	6	No	No	High School	Informal	Employed	Shona
Joe	Father	43	7	Brother in law	Yes	High School	Informal	Self-employed	IsiXhosa
Thandi	Mother	40	14	No	Yes	High School	Informal	Unemployed	IsiXhosa
Sue	Mother	39	16	No	Yes	College	Formal	Employed	English
Zoe	Mother	52	12	No	Yes	Primary School	Informal	Unemployed	IsiXhosa
June	Mother	32	11	Nephew	Yes	High School	Informal	Employed	English

Themes and Sub-themes

While analysing the data in search of themes, the burden of care that epilepsy imposes on the caregivers emerged frequently. As this was not a primary objective of the study, the researcher did not analyse this information in detail but will however broadly discuss it later as it has interlinked relevance. After analysing the transcripts as outlined in chapter 2, four main themes emerged from the collected data. These were 1) cause of epilepsy: Uncertainty and Conflicting views; 2) the need for healing; 3) PME and the mHealth devices; 4) Feasibility of implementation of PME initiatives. Table 2 below summarises the identified themes and sub-themes.

Table 2- Summary of the themes and sub-themes

Theme	**Sub-themes**
1. Cause of epilepsy: Uncertainty and Conflicting views	
2. Need for healing	1. Therapy and the perceived efficacy of medication 2. Managing health care needs 3. Adherence
3. PME mHealth devices	1. Understanding PME 2. Perception of PME 3. Experience with the devices
4. Feasibility of implementation of PME initiatives	1. Owning a smartphone 2. Engagement with the devices 3. Obstacles and barriers

Theme 1: Cause of epilepsy: Uncertainty and Conflicting views

Most participants in this study showed an understanding of the cause of epilepsy that was limited and not deep rooted ss their perceptions regarding the cause included mixing medical, spiritual and traditional ideas. Participants like Unathi expressed uncertainty in their opinions and had potentially contradicting views on the aetiology by saying:

> *"When we went to clinic, they said maybe it was due to worms...They told me it was 'imbeleko' (An African ritual to introduce a child to the ancestors) and that I needed to slaughter a goat…I think its evil spirits" (Unathi)*

Other perspectives on possible causes of epilepsy shared by caregivers included teratogens. To quote:

> *"I used to drink alcohol and I think that is where it came from" (Rochel)*

> *"Like, I will say the medication (ARVs) I used also contributed a lot because it was my 1st child to get this epilepsy maybe that medication has gone into his blood system and causing the seizures" (Ivy)*

Other factors identified as possible causes were environmental and medical in nature. Participants said:

> *"I have always suspected that he might have ingested something wrong while playing and we didn't notice it and now that thing is sitting inside his body and causing the seizures" (Bongi)*

> *"Ey! I really don't know. Let us just say maybe it's a medical problem somewhere you see" (Joe)*

A few were able to suggest a link to genetic factors. This is illustrated by the quote below:

> *"I don't know but this sometimes goes with genes. But I don't know, (sighs and lifts up shoulders). Like I still don't have a proper idea up to now, as in what could have caused this" (Noe)*

Like the comments from Unathi, others also considered evil spirits and witchcraft to be implicated in seizures. They articulated:

> *"I really don't think it's something that was meant to be like God's will, I actually feel she was bewitched…We have been to traditional healers who have confirmed that she was indeed*

bewitched, it's like they wanted to kill her while still in my womb and they failed and ended up fixing her to be like this" (Fortunate)

"I think it's imimoya emdaka! (bad winds)" (Zoe)

These quotes were often only one part of the explanation provided by the same person as many participants would later refer to other or additional causes or beliefs in the aetiology of epilepsy. The examples illustrate a limited understanding and common health concerns as potential causes of epilepsy were mixed with more complex traditional beliefs such as evil spirits and witchcraft. Some of the participants however made statements that suggested they understood there may be a medical and even a genetic contribution.

Theme 2: Need for healing

The inability to achieve seizure control with two or more AEDs classifies epilepsy as refractory as described in chapter one and has resulted in an unending search for cure by the caregivers in this study. Due in part to the conflicting views on the cause as highlighted in theme 1, many participants shared how they were on a never-ending quest for answers on cause as well as cure and had made several attempts to control the seizures from different causal viewpoints. A continuous struggle to find the right medication(s) and dose requiring the navigation of the health care system and managing numerous medications whose efficacy they sometimes doubt was evident in the interviews. Participants expressed inconsistency in their adherence to medication due to various reasons such as concerns about side effects of current medication, insecurity concerning the efficacy of the treatment as well as the hope for finding new or different therapeutic treatments.

Sub-theme 1: Therapy and the perceived efficacy of medication

This study revealed that all participants use medical treatments to control seizures, however, due to poor seizure control even when the child is on medication and varying causal beliefs, many of them expressed belief in other approaches to treating epilepsy such as consulting spiritual and traditional healers, prophets, ancestors and performing cultural rituals. This is illustrated by the following statements:

"We used to go to church at first or they would come to our house and pray for her and stuff like that. But other than that, I didn't take her anywhere else to see where it came from" (Rochel)

"The spirit healers are trying. They give us holy water for him to drink and burn. But it is not getting better" (Zoe)

Some caregivers combine these therapies as expressed by Unathi, who has tried different methods to improve her child's seizures. She said:

"I went to consult prophets who gave me some holy water that I used to give him. They were trying to heal him, but they failed…So last of last year, we slaughtered a goat, but nothing changed still …His grandfather used to speak to him and the ancestors...we didn't even go to the doctors and he eventually stopped getting seizures……but they started again"

Altering the child's diet has also been a way of seeking to reduce seizures. For some this is medically directed such as with the ketogenic diet, but for others this just meant a more generally "healthy diet". Even if it proved helpful in reducing the frequency of seizures, dietary changes were difficult to maintain as alluded to below:

"*I was on the, on the, on the nigenic diet, maybe digketic (struggling to pronounce Ketogenic diet) and for a month he didn't get seizures, but I didn't know, the other children give him chips and sweets and he then didn't eat the diet well" (Baby)*

"*I am not giving him a lot like of the chocolates, they said I must give him a lot of fruits but it's helping me, I will say… I have been paying R23, R25 until it's gone up. It was R19 before, R22, R24 for 1litre of soya milk. Look at that? You are paying for that. So, it's been expensive for years because I have been using that" (Ivy)*

In this search for a cure most of the participants agreed that medical treatment had been the best option. Respondents said:

"Aiiiii! (Exclamation) These pills my sister I think they work. They really work. Although sometimes he just gets sick and then I don't understand what it means since he would have taken his medication you see, then I wouldn't know. But now it's not the same as before, it's better" (Thandi)

"Sometimes, the medication does help a lot. Because like without the medication 'A' (child's name removed) can't sleep" (June)

"I have faith and belief in them (pills) as I can see their effect unlike the traditional meds which when I give him, they don't make him right but the pills make him calm down and he goes for a long time without getting seizures, even a month" (Unathi)

However, due to the refractory nature of the illness and the difficulty of controlling seizures some caregivers doubted the efficacy of the medication as shown by this sentiment which a participant shared:

"Ey! (Sigh) This treatment she is taking, we don't really see the difference. We can't see its effect because sometimes soon after taking the treatment, she gets sick at the same time, you see? It makes us wonder what the medication is for and how it works; we don't even know" (Joe)

Another uncertainty stemmed from the side effects of the treatments which some caregivers felt were more detrimental than the seizures themselves. This, together with uncertainty about efficacy, resulted in some discontinuing the medication or altering the dosage themselves to avoid the side effects. Comments expressed include:

"With the medication, I only notice that if you are giving him a lot of Epilim that is when he gets the seizures almost every month. But as I go slower with Epilim, then it's not every month" (Ivy)

"…It's just the teacher says he sleeps too much at school with that medicine so that's why I don't give him that medicine when he goes to school, I only give him the epilepsy one" (June)

"She seems to be responding well to the medication. That's how I am seeing it because she can now even go for days without the seizures…Yaa (Yes) sometimes it helps but sometimes I feel like it's not working…I noticed when she drinks these pills she gets so weak so much that she cannot even go to school. So, I decided to stop the meds to avoid the weakness" (Fortunate)

The comments shared above show that most participants continued to use at least some medical treatments which they considered best in controlling seizures in conjunction with other therapies. Due to the refractory nature of the illness, some participants expressed doubt about the efficacy of the medication resulting in inconsistent adherence and the continuous search for optimal therapy. Participants hoped PM would provide the solutions as illustrated in Theme 3.

Sub-theme 2: Managing health care needs

Because epilepsy is difficult to treat and requires a holistic approach from different healthcare providers, caregivers are burdened by the need to navigate the complex health care system characterised by many visits to the healthcare facilities. Transport costs, time spent travelling to hospital, difficulty accessing services and time off work all take their toll on caregivers. They voiced these challenges by saying:

> "*I stay very far. I take three taxis to get here… and sometimes I am needed here three times a month, I can't manage that and work" (Fortunate)*
>
> *"I take a taxi now because the bus actually takes longer. I used to take the Rocklands bus but then one day she wasn't feeling well and there was too much noise in the bus as well so, I decided that day to actually take a taxi because it is actually easier and cheaper as well". (Sue)*
>
> *"Then sometimes they will refuse to give me more or they will give me for five days and expect me to come back for more after five days. You getting hard time to collect meds!...So they lost my folder and they put a wrong folder number and all the time when I go to the pharmacy I find them with an old script until I have to travel back here to Red Cross. It's a hard time to have an epileptic child!" (Ivy)*

In addition, the challenge of managing the complexities of changing medication and accessing these medicines came up in all the interviews as a difficult reality for the caregivers through statements such as:

> *"They started us in the first place on many, many pills. But every time then I came here, and I explain the doctor how his seizure is. Then the doctor sometimes says, "I'm increase one of them and sometimes he takes one of them from me" (Baby)*
>
> *"They only added the clobazam I think last year because the seizures did continue with the Epilim and the lamotrigine, so they added the clobazam, and now that she is on these three, it's really better" (Rochel)*
>
> *"The pills are less now before I think he was taking 16 tablets, 16 or 18 per day. So now he takes four in the morning, four in the afternoon, and five at night you see" (Noe)*
>
> *"They just kept changing the medication, but it didn't help" (Fortunate)*

"She changed the medications from this one to that one up to the one she is on currently, but we don't see the change" (Joe)

The above quotations speak to some of the challenges which caregivers face in accessing and negotiating health care for a complex disorder like refractory epilepsy in a child.

Sub-theme 3: Adherence

Throughout the interviews, adherence to medication was recognised as important in controlling seizures. However, the motivation to adhere differed among participants. Some adhered because they felt the medication was effective in controlling the seizures to some extent. On the other hand, others grudgingly adhered simply because they felt obliged to do so even if they did not see a benefit. This can be seen by these two contrasting quotes:

"If I don't give him his pills at the right prescribed time, he gets sick, so I have to stick to the times prescribed by the doctors I need to …" (Unathi)

"Yaaaa (exaggerated agreement), we feel like it's even worse because, but we can't stop the medication since we have already started it" (Joe)

Some showed inconsistency in their adherence to medication in response to how they perceived the efficacy of medication in controlling the seizures at particular times. For example:

"Yaaaa sometimes it helps but sometimes I feel like it's not working...like I once stopped giving her the meds" (Fortunate)

"Sometimes I ask myself do I have to give him these tablets or what. Is it for 'A' these tablets to drink or is it something else? Sometimes I do ask myself and then I don't give him" (June)

Many participants also highlighted other challenges which influenced medication adherence. They said:

"Yes, sometimes I do forget to give him…" (June)

"He tries to cheat and spit the pills or lie about having taken them, so I guard him to make sure he is swallowing" (Bongi)

"He opens his mouth and drinks it we crush it and mix with water he will drink it; we just need to guard him and check that he doesn't spit because nowadays he has some naughtiness" (Noe)

Given that remembering times and dosage is a major challenge for most participants, they felt that being part of the PME study and receiving the phone app has improved their adherence through the reminders. To quote:

"But because of my age, I sometimes forget to give medication, I found the phone very helpful in that aspect. It was reminding me when it was time for meds... So, I realised it was helpful to receive reminders as it made me give the meds promptly it does encourage or motivate us to give the pills" (Bongi)

"The phone gives me more learning about giving medicine in time" (Baby)

Some participants and other secondary caregivers were motivated by the thought that they were being monitored by doctors through the PME mHealth devices. Noe said:

"So, now if I don't give, the devices will report that I am not giving the medication. So, these monitoring devices will motivate you knowing that you are being guarded". Even at school they always say "Yuuu this watch is going to sell us out to that doctor that this child didn't get his medication. So, if they hadn't given him his pills or what, they quickly give him"

Adherence was acknowledged to be important in controlling seizures but was influenced by various factors. Some participants were adherent because they felt the medication was effective while others only gave the tablets from a sense of obligation. For others inconsistent adherence was the result of practical challenges such as forgetting the medication times or not knowing the correct medication to give. Reminders through the mHealth app on times and types of medication were believed by most participants to be beneficial in improving adherence.

In a nutshell, this theme and its subthemes show that participants found it challenging to navigate the treatment for RE and faced multiple difficulties in dealing with the healthcare systems in a bid to ensure correct medication and doses. There was hope that the PME study would be helpful in terms of optimising treatment and promoting adherence.

Theme 3: PME mHealth devices

This theme speaks about how getting new phones and watches was the highlight of the study for most participants who have no means of affording these mHealth devices under normal circumstances. Most of the caregivers recruited did not own cell phones with the necessary capabilities to run the Aparito app or connect to the wearable device, so they needed to be provided with a smartphone for the study period. Although most participants appreciated this, it also introduced new challenges which added to the burden of caring for a child with epilepsy. In addition, the returning of study phones proved difficult for those participants who had completed the study as they had become attached to them. This likely reflects some of the socioeconomic realities of the study population as well as the potential security the engagement may have provided. Even those who lost the mHealth devices during the study period expressed sadness over the loss.

Sub-theme 1: Understanding of PME

Despite having consented to take part, most of the participants showed a lack of understanding of exactly what the PME study was about. To most, PME was more about the mHealth devices than anything else. This could be explained by the fact that the mHealth devices were the tangible aspects of the study which they could relate to and most of the recruitment initiation time is spent instructing participants in their use. When asked what their understanding was of the PME study, most caregivers focused on the mHealth devices as described above and showed little understanding of the genetic and pharmacogenomics testing aspects. Sue said:

> *"I don't know actually. Because it's them that approached me when I came here for my appointment. They just called me and told me there is a new system that is there now, and they gave us phones and watches"*

Other responses that came up suggested that participants did not recall much of the genetic testing aspect of the study. These are:

> *"Yes, I remember, I was there when you took his saliva but eish (sigh) I can't remember what you said it was for… (Smiles and looks embarrassed) but you did tell me" (Bongi)*

> *"Yaa! Dr X said she was taking it for… Oh God! What did she say by the way? How can I put it? She said she wanted to check mmm Oh! I have forgotten but she explained. Isn't its genes?" (Noe)*

However, a few participants like Unathi, as previously described in (theme 1, subtheme 1), showed some understanding of the genetic aspects of the PME trial. She said:

> *"We tested saliva for the cause of the epilepsy, whether it is something he inherited or it's just something that started with him"*

Most of the statements quoted above illustrate a limited understanding of what the PME study entails.

Sub-theme 2: Perception of PME

The exposure to the PME initiatives gave most participants the perception that, if properly implemented, these measures would be beneficial in caring for CWE in SA. Most felt that medication prompts improved their adherence pattern while some felt that recording seizures improved the accuracy with which seizures could be reported. They had this to say:

> *"There is a lot of good things about this, like I explained to you I think it was in 2014 when he used to get seizures for three hours and we would watch for three hours full so that we can explain to the doctors what he was doing. That was not nice. Now I can just record" (Ivy)*

> *"That is helpful because you can just capture events every day and you don't have to remember everything when you go for follow ups" (Fortunate)*

For some, it gave them a sense of recognition and was a platform for sharing information about their child while at the same time, relieving some of their stresses and feeling of isolation associated with being caregivers. Bongi said:

> *"It gives us the sense that we are being recognised and being noticed. So, what makes most people lose hope is the feeling that they are being neglected or ignored"*

> *"It helps, because you have someone to talk to about your child. So, it all comes out and like now, when you get home, you feel relieved that you spoke about how you feel about your child, you spoke about them. Because we are constantly in fear and we worry because of this sickness"*

One parent voiced how she thought PME gave her hope that her child would be cured one day. She said:

"I just want to hear something that will suit my heart and that is going to relieve my heart and to believe that my child one day will become healthy and he is going to become something different in life, that he will be successful" (Ivy)

While for some, the hope was that PM would provide answers on cause as shown by their following responses:

"It might be helpful since I don't know what caused him to be like this, whether it was due to someone's deeds or what caused it I don't know, so maybe if they can say it's his creation or it was inherited from my side or his father's side" (Unathi)

"I was just so grateful for someone to call me to say that they want to do research and stuff just to see what's going on with the epilepsy and where it comes from…I think it's helpful to know where its coming from because I can remember at birth like she wasn't like that, I don't know what went wrong" (Rochel)

"you guys collecting saliva what-what to see genetically if there is a certain mismatch. I don't know" (Joe)

"They are checking if it's coming from his father or from me" (Zoe)

When asked what they expect to get from the PME initiatives, participants strongly believed it would help them find the optimal treatment. To quote:

"I want this condition to be somehow controllable you see. Right now, I don't see any (pauses) because she is still sick like before, so I don't see the change. Maybe they could suggest another one (medication) which she can respond to, depending on her genetic make-up" (Joe)

"It can help, because, these pills that you give them are not the same, also the children are different. The way they react to the pills varies, the one that my child takes, I don't think it will be suitable for another child. Because maybe that one's genes are stronger" (Noe)

Other participants were in addition hoping to be exonerated from being blamed for causing the illness. This seemed to be relevant in their belief that if inherited, it would be possible to identify which side of the family was responsible. They stated:

"I don't want them to say this child got this from my family, at-least if it could be found that he got this from his father's side" (Unathi)

"I just want to hear if it's my genes or the father's genes. And also, how to treat him" (Zoe)

One participant hoped the genetic testing would give reassurance that the child is "normal". Bongi said:

"I just expect to hear that my grandchild is fine, (laughs) Yhuuuu! Just that he is alright"

Some participants felt that they had not seen any benefit yet and were concerned that they had not had any feedback

"*Well I haven't really eh, nobody has discussed with me ummm what they have picked up" (Sue)*

It appeared that most participants felt PM was likely to be beneficial despite their lack of fully understanding of the genetic aspects of the research.

Sub-theme 3: Experience with the devices

Since most of the participants had no prior experience with mHealth devices like electronic watches and smart phones, receiving them introduced new feelings and challenges. For some participants the phone introduced new worries as they were initially unsure of how to use the phone. This concern was expressed by some in this manner:

"I was scared at first wondering what the phone was about… I was scared of that phone because I would ask myself yooooo, you see this phone, what does it say?? Also, I worried about not being able to respond properly or press the wrong buttons" (Bongi)

"So, I am on the phone all the time and I will WhatsApp Sr Y, "Sr Y, did you get the stuff I did this morning please just check meds so that I can…stuff like that. So, I am really worried all the time" (June)

"I must say I got scared because it doesn't look like mine and it looked too advanced for me" (Zoe)

After adjusting and getting used to the phone, some participants became comfortable and embraced the mHealth devices. They said:

"With time I got used to it and I actually started enjoying having it so much that I was really hurt when it got stolen" (Bongi)

"I understand how it's working now. I have just never done the video story and that I must just understand and try to do it" (Sue)

"They knew I had this fancy phone, and how to switch on the data and then I just learnt" (Zoe)

Despite being reassured that safety was the priority and should take precedence over any engagement with the technology, participants were fearful of their safety as they lived in high crime rate areas which put them at risk of being mugged.

"And sometimes when I am in a dodgy place and I must enter some information on the phone, I don't do it because of fear of being seen with such a phone so I wait till I get home. So, this phone was making me live like that" (Unathi)

"This is my first time to take it somewhere. I always leave it at home. I am scared that it might be grabbed by those thieves" (Zoe)

This fear of safety was not unjustified as one participant went further to explain that her house was targeted as the thieves knew she had a smart phone.

"…but the night it was stolen, someone entered in the house, they knew I had this fancy phone, they came specifically for that phone" (Bongi)

However, the participant from a rural area had less safety concerns as confirmed by her statement:

"I feel safe, there is no thieves" (Baby)

Their personal safety is a major source of anxiety for the participants and this insight is vital to be aware of when considering the obstacles to this kind of approach, which will be further discussed in theme 4 below.

The phone also caused tension in certain homes due to the constant battle among family members who wanted to use the study phone. These household conflicts can be illustrated by the following quotations from the data:

"I don't know, I really don't know (laughs) I am so on my nerves all the time. I say oh my God why are you doing this, you can't do this, the doctor is gonna see you because the phone belongs to the doctors and it's on the doctors computer and everything you can't take photos don't do that, don't do this, just leave it! I am on my nerves the whole time" (Baby)

"They steal this one to the room for the games. Maybe that is why it's now blocked; they are deleting the doctor's things. Shuuuu (sigh), they are giving me a hard time. They are giving me a hard time! Because they are stealing it every now and again" (Ivy)

"It's a challenge yes because the smaller one is also now, "Let me see! Let me see! I wanna take a photo! blablabla!" and then I must now hide it when he is sleeping now, I take it out and do my stuff" (Rochel)

Using app and smartphone sometimes created added burden for the caregivers.

"Isn't it sometimes a lot of times there is a lot of SMS's that come through. They keep on giving SMS's that keep on reminding you about double data and stuff like that so when an SMS come through, I don't even bother reading it" (Sue)

"I quickly do my chores and I go on the phone" (Nandi)

"Well I told the school that the watch was given by the doctor and told them its function and they should try to guard it" (Fortunate)

Some participants felt that having the phone has improved their ability to communicate, with regards to healthcare emergencies. They said:

"Because sometimes there is no one at home, I don't have a phone, she will get sick, what do I do now, but, now I have a phone I can just call my boyfriend 'can you please come pick us up we must go to the doctor and stuff like that' so, it's really helpful" (Rochel)

"At-least we phoned Dr X (PME study coordinator), and she advised me not to take him anywhere because I wanted to hear if I can just take him to a GP… So, you see now, how was I even going to know about all these things if they were not there? That one is one of the things that I say you see what you guys came with…" (Noe)

The sentiments expressed in this theme reveal that most participants had limited understanding of PM as a concept especially the genetic aspects which were understood by only a few. However, all participants felt the PME initiatives would be beneficial in improving adherence and seizure reporting if properly implemented and instilled hope that therapy optimisation and cause could be found. The mHealth devices introduced new feelings and challenges for most participants since they had little prior experience with technology making navigation of the mHealth devices an additional burden. In addition, most participants expressed the sentiment that owning the mHealth devices posed a risk to

their safety which has an impact on the feasibility of introducing similar devices into routine care in similar settings.

Theme 4: Feasibility of implementation of PME initiatives

The feasibility of implementing PM initiatives is mostly dependent on the caregivers whose acceptance and engagement with the initiatives is essential for a successful outcome. The participants strongly felt that the caregiver's understanding and ability to engage was crucial. The factors that influence the caregiver's engagement with the initiatives, some of which are regarded as obstacles that can be overcome, and some as barriers that can hinder the effective implementation, are highlighted in this theme. In the low resource setting studied, many factors associated with caregivers' socio-economic status were highlighted by participant's experiences with the mHealth devices. This information is needed to determine the feasibility of implementing these initiatives.

Sub-theme 1: Owning a smartphone

The constant care required in looking after a child with epilepsy resulted in most caregivers sacrificing their jobs which adversely affected their financial position. This in turn made it difficult to afford 'luxury' items like smartphones. To emphasise this, a participant said:

> "*Before this I didn't even have a simple phone. I am now five and half years at home, I quit my job. You can see how long I didn't have a phone …Because there are many people that don't have the luxury to, you see the money you have must be used for the children to eat, clothes, school. Not to buy such phones and watches" (Rochel)*

While some participants had cell phones, the phones were either not compatible with the study App or there was no space to download and save the App.

> *"I had a simpler version of a smartphone that could do WhatsApp, but it wasn't compatible with the study app" (Unathi)*

> *"Yes, I do. But it's just that there was no space in the phone, that's why they gave me that one" (Sue)*

As a result, all the participants interviewed needed to be issued with a study phone on enrolling into the study.

Sub-theme 2: Engagement with the devices

For these home monitoring mHealth devices to be of maximum clinical utility, data must be captured continuously and passively by the wearable device and be supplemented with parental data input reported via smart phone apps. The continuous gathering of data is influenced by the caregiver's understanding of the functioning of the mHealth devices, which can seem quite complicated as well as willingness or enthusiasm to engage. Some participants showed a very low level of engagement. Understanding how the mHealth devices work is paramount for full engagement. Most participants expressed how they struggled with using the smartphone. Zoe said:

> *"I don't want to lie because I didn't understand how this phone works and all along it was just not working well. So maybe now, when I come back for next appointment, I will be able to say more. It was just sitting there not doing anything"*

Some participants admitted that they had initial challenges but with time learnt how to use the mHealth devices. They said:

> *"My role on that phone was not easy to understand at first, but now that 'X' and 'Y' have explained, I have understood that I need to go to wearables so that it can send information from the watch. I used to just let him wear it but not aware that I play a role of sending info using the phone" (Noe)*

> *"You see in the beginning, I didn't understand anything about these things, but I was doing all that I was told to do. But now I can see and understand what they want from me" (Unathi)*

In most cases where there was a secondary or substitute caregiver, it was apparent that the efficacy of the mHealth devices was affected since the secondary caregivers didn't understand how the mHealth devices work. This was highlighted in cases where the substitute caregiver was not present at the time of issuing of mHealth devices and did not understand the mHealth devices. One participant whose substitute caregivers are her mother and grandmother said:

> *"Granny was like 'I am not going to touch that phone' I am still struggling to understand my simple non-smart phone, how will I ever know where and how to press that phone? You guys should press it. The person I try to incorporate into this to actually know it is my mother, but she also isn't so enthusiastic about it, her problem is that she is not into phones" (Noe)*

The two mothers who were not present at the time of issuing of mHealth devices expressed how they also struggled to understand the phone functions initially by saying:

"The only thing is in the beginning, my husband didn't tell me clearly what to do and where to press after they showed him at the hospital but with time, I learnt a couple of things" (Unathi)

"Granny brought the phone home, so that's why I am confused about this watch and phone" (June)

Some participants' level of engagement was affected by how they felt about the mHealth devices and their enthusiasm varied. One participant said:

"I haven't been using it much. I just basically… it's just in the cupboard. I don't like using it. So hopefully as of today or as of tomorrow or whatever, I will start using it more and understand it more" (Sue)

Baby, the only participant from a rural area, expressed how the device had generally uplifted her social status. Due to this when she had to hand over the phone on completion of the study, she described this as a loss for her. These sentiments came out when she said:

"People think we are fancy. He's got the watch, and I have the fancy phone, they envy us"

"But I am sad about my phone"

Participants exhibited a variable level of engagement with the devices which, in part, may have been the result of uncertainty in using the new phone especially in the initial stages.

Sub-theme 3: Obstacles and barriers to using mHealth devices

The potential value of the mHealth devices was shown to be affected by many factors that participants described. Although some participants were enthusiastic and willing to engage, there were some aspects associated with their socio-economic status that significantly limited or hindered this. For some who live in the informal settlements known as 'shacks', electricity for charging the mHealth devices was one of their main obstacles and poor network connectivity was another. This is highlighted as follows:

"Also, you see, here in these shacks we also face challenges of network and electricity because when it rains, the electricity trips, even when it's windy. So, the battery is always flat, and the phone is off most of the time. Also, there are network issues, you are always offline so sometimes I fail to update or send certain things because of network/data problems" (Unathi)

Despite being provided with enough data to run the app by the PME study, other uses of data brought a financial burden. For example:

> *"Just that child of mine is now downloading the stuff so the data is finishing, and I go and buy data, so I told him "No! Just leave this stuff because this is not yours*" (Rochel)

The continuous passive gathering of data through the wearable was affected as most children did not wear their watches consistently. Many of the affected children have significant intellectual disability which confounds the problem. Various reasons for this came up in the interviews such as ability to tolerate the wearable, lack of responsibility, rules at schools (not allowing wearables), and safety concerns. Some of the participants said:

> *"It was because it irritated his skin so much that he would pull it off, maybe it was too tight and that flashlight at the back was perhaps burning him" (Unathi)*

> *"But his watch is broken. Yaaa its broken now. I think it make him wet and he makes so (pulls it), and then the other side of it got lost" (Baby)*

> *"So, the teacher asked the 1st day "what is this?" coz they are not allowed to wear something" (Rochel)*

> *"Yhooo A! When I put the watch on, and then he takes it off again" (June)*

> *"At first with the watch. Yes, doctor said she must keep it on hey. So, at night when we go to sleep, she will fiddle the whole time with the watch. But then again when she gets to sleep, I just tighten it and then she sleeps" (Rochel)*

> *"They probably asked him to give it to them and because his mind is not so sharp, he just removed it and gave them not knowing that it's being stolen" (Bongi)*

> *"And the one that got lost, I think he got sick at school and someone took it" (Zoe)*

Another obstacle to continuous data gathering was the mHealth devices' limited battery life, Sue highlighted this through this statement:

> *"And the thing with the watch also is the battery gets flat very quickly and so doesn't even last a full day, so I'll maybe charge it and she will go to school with it, and it will basically die in the day already"*

As highlighted earlier in theme 3, the high crime rate in the communities where most participants live is a major obstacle to implementation. Personal safety may be compromised as owning these mHealth devices put participants at risk of robbery. As a result, the efficient use of the mHealth devices was compromised as most resorted to leaving the mHealth devices at home. This barrier to effective use of the devices in our participants was very significant and weighed heavily on the participants who had safety concerns in mind when considering the feasibility of implementing such initiatives in this population. Some experiences shared read:

> *"Haaaaaa, sometimes I didn't like having that phone because (takes a deep breath) they steal phones in my neighbourhood, they steal phones I am telling you" (Unathi)*
>
> *"It's always indoors. Because they can steal it" (Zoe)*
>
> "*Sometimes you can't get hold of me because I leave it at home to avoid being robbed. Also, sometimes when you attend gatherings or even funerals, you don't even get a chance to charge it because it can be stolen. So, you leave it off until you return home" (Unathi)*
>
> "*So, when he is going to play far from the house, I make sure he leaves it at home because if they see him wearing it, they will attack and beat him up just for that watch. You see?" (Unathi)*

Theme 4 highlights that the feasibility of implementing these PME devices was shown to be influenced by the participants' understanding of and willingness to engage with the mHealth devices. Most participants perceived the devices to be complicated which resulted in lower engagement. Continuous capturing of data was compromised by such factors as unavailability of electricity and network connectivity as well as inconsistent wearing of watches and use of phones due to the fear of becoming a target or victim of crime.

CHAPTER 4: DISCUSSION AND CONCLUSIONS

The current study, conducted in a resource limited South African public-sector setting, sought to explore caregivers' experiences, perceptions and expectations towards the PME study initiatives for optimising care for CWE. This included their knowledge of epilepsy cause as well as their experience with the technology used. Gathering data on the potential benefits of integrating technology-based monitoring, genetic aetiology and pharmacogenomics in the management of children with apparently drug resistant epilepsy can contribute to South African epilepsy services by determining potential acceptability and understanding the challenges in implementing such initiatives. Understanding health-care needs and experiences of a population enables the formulation of effective service delivery strategies (WHO, 2001; Rapport *et al.,* 2015). The information gathered would inform the feasibility of implementing these initiatives in SA given the limited use of technology and the complexity in understanding epilepsy and its treatment. The findings of the study suggest that the initiatives are believed to have potential in improving care for CWE. The interviews do however reveal several obstacles which need to be overcome if effective implementation is to be realised.

Although this wasn't an objective of the study, the findings highlighted the burden which living with a child with epilepsy places on the caregivers that compound their socioeconomic hardships that dominate their lives. It is important to acknowledge and appreciate these challenges as they help to put the themes discussed into perspective. In describing their experiences with living with a child with epilepsy, the participants expressed that it was "very difficult", "very hard", "not nice", "not easy", "frustrating", "stressful" and "painful". These perspectives are reflections of their everyday experiences and interactions with their world - information which is helpful in getting a sense of their QOL and useful in identifying potential issues with integrating PM in such populations. This aspect was also measured through the PRO data collection and will be reported on in the main PME study and may verify this further. While reported in previous studies by Reed (2013), this study identified the complexities associated with providing care to CWE that range from role adaptation to changes in parenting style which alter family functioning. Much as the caregivers in this study perceived adaptation to diagnosis and the requirements of treatment plans as a manageable challenge, they were still burdened by the grief of having a sick child and the constant attention needed by the child. In some cases, this resulted in caregivers sacrificing their freedom, independence, career and future childbearing. Findings from this study point to caregivers being overloaded by caring for the child such as the constant guarding of the child to protect them from outside danger and from self-harm, the need to keep a proper record of seizures and administer medication(s), and dealing with stigma and discrimination that the child and family are subjected to from society such that participating in the

research was taxing. The participants experienced feelings such as fear and anxiety emanating from lack of predictability of seizures, their severity, the possible side effects of medication and uncertainty regarding efficacy of the treatment. The foregoing sentiments were previously reported in Harden *et al*., (2016) study where parents reported feelings of uncertainty and confusion coupled with endless worrying about the physical and emotional well-being of their child. The time and effort put into managing the child's best interests were causes of frustration. It is in the context of these burdens that the major themes which emerged from this study can be understood further.

The themes identified in this study are discussed in relation to existing evidence. They will be discussed in the context of participants' perception of cause and treatment of epilepsy; participants' understanding, perception and expectation of PME and participants' experiences with the mHealth devices. This chapter will also highlight the limitations of the study, provide a conclusion and give insight into the findings' implications for practice and future research.

Perception on cause and treatment of epilepsy

Caregivers' perspectives on epilepsy cause and treatment are important factors in determining their potential to accept and engage in medical PM initiatives. A deeper understanding of the social and cultural scope of an illness as well as its underlying cause is important in identifying challenges that could affect acceptance or engagement with management plans and can determine their effectiveness and sustainability (Manderson, 1998). Within theme 1, the current study found that the ability to identify the causative agent and the reason for seizure occurrence was limited. This is in keeping with the findings of a study carried out in Khayelitsha, Cape Town, a similar setting to the current study, by Keikelame in 1998, which concluded that there was no understanding of the cause of epilepsy in most respondents. The limited understanding of cause was illustrated by the conflicting ideas expressed by several participants in this current study. While most participants acknowledged that epilepsy was a condition with medical connotations, they simply could not identify the cause as being limited to a biomedical explanation but pointed to spiritual, traditional and cultural factors as other causes and contributors. These perceptions mirror the findings of studies by Mugumbate and Zimba (2018) and El Sharkawy *et al*., (2006) that found that misconceptions about epilepsy originating from superstitions about its 'external' causes like witchcraft result in it being considered more of a spiritual than a medical condition in Africa. A few participants believed that epilepsy had some genetic aetiology. Orsini et al., (2018) state that more than 30% of all epilepsies have a genetic origin, as such, these findings reflect accurate understanding. These perceptions of cause were independent of gender or level of education of the participant but there were notable differences of opinion based on ethnic and cultural background. Most of the participants of African culture shared that epilepsy

was a result of bewitchment by others while those of mixed ancestry largely perceived it as a medical condition but they also exhibited a lack of deeper understanding of the underlying cause. This leads to the hypothesis that understanding of cause was limited regardless of age, gender, education level and ethnicity. A never-ending quest for answers for these participants stemmed from limited understanding of epilepsy cause.

Similar to findings of a study by Jacobs *et al*., 2016 who found inadequate adherence to AEDs in SA, this study found that epilepsy is poorly managed with participants reporting inconsistent adherence. This seemed to be related to the misunderstanding of the cause and the stigma around epilepsy in the studied population. Keikelame (1998), also found that epilepsy was both misunderstood and poorly managed in a similar community. Factors which most participants identified as causing inconsistent adherence were failure to remember the correct times and dose of medications, running out of medication with barriers to access as well as the child's ability and willingness to take the drugs as illustrated in theme 2. These factors influencing adherence mirror May *et al*., (2018) findings on how patients perceive the management of AEDs and barriers to their regular intake which found taking several types of tablets, unpleasant taste, side-effects and forgetfulness to be the main barriers to adherence. Although all participants in this study were administering medication to the child in their care, the varying levels of belief in the efficacy of the medication also had an influence on adherence patterns and the self -directed changes caregivers made with the medication. This finding concurs with Jacobs *et al*., (2016) study which concluded that adherence to medication regimens was dependant on the perceived efficacy of these regimens and willingness to bear the side effects of AEDs. Some participants in this study were troubled by side effects which left them in a dilemma between having an alert child with seizure activity or a sedated, but seizure free, child. As shown in theme 2, some participants combined medical treatments with alternate therapies with those of African lineage showing a propensity for cultural and spiritual treatments in addition to medication which many had limited confidence in given that seizures persisted. This tendency to resort to other therapies was previously reported in a study by El Sharkawy and colleagues (2006), who found that those who believed that epilepsy had 'external' causes preferred such treatments as pouring liquid on the child's body or wearing of external charms. The foregoing reflects the ongoing struggle parents often face with refractory epilepsy. Even though they feel medication may be helpful, there are times that breakthrough seizures leave them doubting the efficacy of the treatment and seeking other solutions. Respondents were also burdened and frustrated by numerous hospital visits for check-ups, several types of tablets prescribed, frequent changing of prescriptions in search of therapeutic response and the limited healthcare services. Those that were employed found it challenging to balance the regular hospital visits and work. Considering the views raised on treatment and other

therapies, it can be surmised that medical management plans were not always strictly followed with inconsistent adherence to medication and most participants vacillating between believing in medication and other therapies.

Understanding and perception of PME

Several caregivers did not fully understand what PM meant in the context of the PME study which focused on genetic and pharmacogenomics studies as well as mHealth monitoring with only a few understanding the genetics and pharmacogenomic aspects. This misunderstanding raises questions about participants consenting to partake in a study whose aims and objectives they didn't fully grasp. As indicated by Marshall *et al*., (2006) participants may feel pressured to consent due to their vulnerability associated with socio-economic and political status. In addition, there is the difficulty of attaining a fully informed consent from participants into a study as the researcher may not adequately inform all participants of all the aspects of a study as highlighted by Mason, (2002). This data suggests that it would be appropriate to go back to the participants in the PME study and provide more information to ensure they understand and consent to all aspects of the research. It also suggests the need to provide information sheets in simpler formats with more graphics and illustrations or videos. Ideally consent should be obtained by a person other than the patient's main physician. In keeping with the idea that participants sometimes do not fully understand all aspects of a study, Tin dana *et al*., (2012) concluded that research participants have less understanding of complex genomic research aspects which might not necessarily interest them and that even the best practice in design may not fill such gaps during consenting. The study revealed that the participants' points of reference were the mHealth devices as shown in theme 3. This could be explained by the fact that beyond the consenting session, the mHealth devices were the only reminder or contact that the participants had with the study after consent and the baseline visit. When asked what they understood about the genetic aspects of PME, most participants could only refer to the saliva samples which were collected but they struggled to explain the reason why the samples were collected. This could be attributed to the fact that so much time and focus was needed in learning to use the devices that other aspects were forgotten. A few participants however did make mention of the genetic aspects relating to the saliva sample collected. The PME initiatives were perceived to be beneficial by most participants as this gave them new hope in understanding the cause of epilepsy, the reasons for refractory seizures and drug resistance in their children with RE as well as in finding suitable treatments for the children. The feeling that research studies are beneficial was reported by Decker *et al*., (2011) who report that participants experience benefit from research participation and gain something positive. The participants' perceptions were not unfounded as they have been reported before with Striano *et al*., (2018) highlighting that finding the genetic causes of epilepsy may offer more accurate information on

disease progression and seizure occurrence as well as allowing individualised treatments through prediction of drug response which improves efficacy and safety of epilepsy therapies.

Participants who felt guilty and blamed themselves for the child's epilepsy hoped that the PM initiatives would provide answers on the cause which could exonerate them from such feelings. Feelings of fear, anger and guilt are common in parents especially when the cause of illness the afflicting the child is unknown (Norberg *et al*., 2005). The lack of feedback on the collected saliva samples and the information collected on the App left some participants wondering about the benefit of the PME initiatives. This is not a novel feeling as the importance of feedback to research participants has been previously reported on. Green *et al*., (2013) outline that feedback is necessary when the result has medical implications with possible corrective measures while Kerasidou, (2015) believes that feedback would help build trust with participants. Although little is known about technology-based monitoring in epilepsy in Africa, there is increasing evidence that these PM approaches are of value in epilepsy globally. This suggests that any future efforts must make sure that the outcome and results are conveyed back to the parents via the app.

Experience with mHealth devices

Wearable mHealth devices whose successful implementation depends on their acceptability to users and their willingness to engage with them, have become available. but not put into epilepsy care currently. (Bruno *et al*., 2018). The caregivers in this study likewise felt that the success of these PM initiatives was dependent on understanding, accepting and engaging with the mHealth devices and the attitude and enthusiasm or resistance to adopt the technology. These sentiments expressed in theme 4 are consistent with Fishbein and Ajzen (1975), whose study found that a person's attitude towards new interventions influenced their intention to adopt and embrace them. In the studied population there were many practical factors associated with caregivers' socio-economic status which influenced acceptability and accessibility which could affect the implementation of these initiatives in such settings.

To begin with, all these participants had to be issued with smartphones with better capabilities upon enrolling into the PME study for them to have access to the Aparito app. Participants either didn't have smartphones or had phones that were not compatible. To give credence to this an October 2018 Pew Research Centre report found that a large proportion of the SA population still uses basic cell phones, with 40% having basic phones while 9% don't have phones at all. This study found that the major reason for not owning a smartphone was affordability (Silver and Johnson, 2018). This could be because the participants in this study included those who are more vulnerable to poverty and are

faced with economic hardships and unemployment among other financial challenges. A Stats SA Living Conditions Survey which provides detailed information on households' living circumstances estimates that over half of SA's population (55.5%) live in poverty with higher levels in informal settlements where most of these study participants reside. Most participants admitted to needing time to adjust to the new life brought about by the mHealth devices.

Upon receiving the mHealth devices, the participants were faced with new feelings and challenges, such as the worry and fear associated with not being sure how to operate the mHealth devices. This resulted in them doubting their ability to cope, particularly the older caregivers. This tendency to self-doubt was first highlighted by Bandura, (1977) when he identified it as a determinant in adopting new behaviour. Determinants in acceptance of a technology that have been identified by Davis *et al*., (1992) and Hsiao (2013), are user friendliness and perceived efficacy. Another worry for most participants was the risk that owning the mHealth devices posed to their safety. Anxiety about the high crime rates in the studied populations was manifested in most interviews. These sentiments by the participants were not unfounded as Stats SA, (2019) reports that crime levels have been on the increase since 2016, especially incidents of crime perpetrated on individuals. The survey found that Western Cape residents also thought that crime in SA has increased and this could explain why the participants were uneasy with using the mHealth devices outside their homes. Two participants shared their encounters with housebreak-ins which reflects the reported static that housebreaking is one of the most common crimes in SA. Much as the accumulation of data through efficient use of the mHealth devices is important, priority must be given to the immediate safety of the individuals over the need for data when implementing such healthcare services.

It was found that consistent use of the wearable mHealth devices was not easy to attain, probably due to the difficult living circumstances under which the studied population live. Ability to tolerate the wearable was also a factor which likely contributed to the high level of inconsistency and was often associated with the intellectual and, in some cases physical disability of the affected children. For maximum tolerability the mHealth devices must offer safety and comfort for both the patients and caregivers (Nijsen *et al*., 2005; Schulze-Bonhage *et al*., 2010). Our findings are consistent with Hoppe *et al*., (2015) whose study focusing on user preferences on wearable mHealth devices concluded that non-obtrusive mHealth devices that resulted in minimal interference with daily routines were preferable. Limited access to networks as well as inconsistent supply of mobile data were among the other major challenges that most participants highlighted. This is not surprising as Gilbert's (2019), report indicated that only 54% of the South African population has access to the internet compared to the global average of 57%. Data is expensive since there are only three mobile network operators

accounting for about 90% of the overall South African market. They however expect to see an increase in the purchase of smartphones and improved access to network since there is a marked rise in the number of people with broadband connections and 4G services with discounted bundles have broadened nationwide. In summary, it can be said that the obstacles and barriers highlighted interfered with the continuous passive monitoring of the patients and data accumulation. In addition, a few participants exhibited a lack of enthusiasm for the research which affected engagement. The foregoing leaves the successful implementation of these innovative approaches to health care in this population hanging in the balance and highlights the possible difficulty of implementing initiatives more widely.

Despite these challenges, the mHealth devices did have positive aspects. Participants shared that the medication prompts received on the phone had improved their adherence to medication, this is in agreement with findings by Dayer *et al*., (2013) who discuss the potential that smartphone apps for medication adherence have for improving adherence by providing reminders. Some participants also expressed how the smartphone had enabled them to record seizures in real time thereby alleviating the burden of recording seizure occurrence manually while at the same time ensuring the accuracy which is normally absent in delayed self-reported seizure occurrence. Several studies have highlighted the inaccuracy resulting from seizure counts based on diary and patient- or caregiver reports and have pointed out the need for novel, feasible, automatic seizure documentation techniques that can improve the quality of reported seizure data such as wearables and smartphones (Elger and Hoppe, 2018; Blachut *et al*., 2017; Patel, 2016). Another positive aspect was that the phone improved communication for the caregivers as they could now communicate with health personnel and others more directly in times of emergency without necessarily having to visit the hospital. Concurrently, caregivers in the Bruno *et al*., (2018) study viewed the mHealth devices as tools to lessen the anxiety associated with monitoring CWE constantly and to enhance communication with healthcare providers via objective reporting. In agreement, Roman *et al*., (2015) highlight the possibility of reducing medical costs through decreased hospital visits by collecting data through wearables.

Conclusions

The methodology employed in this study obtained a holistic picture of the participants' world of experience in caring for CWE and participating in the PME study. This information is of value for understanding how the caregivers perceive epilepsy, its treatment and PM and could help identify potential benefits and challenges with integrating PM initiatives in the South African setting, especially given that no such studies have been performed previously.

The themes which emerged were 1) Cause of epilepsy: uncertainty and conflicting views 2) Search for healing 3) PME mHealth devices 4) Feasibility of implementation of PME initiatives . These four themes encompass and focus on the main areas of discussion which are the participants' perception of cause and treatment of epilepsy, their understanding, perception and expectation of PM and their experiences with the PME mHealth devices.

A major finding was that the understanding of the cause of epilepsy was not clear as shown by the diverse ideas that participants expressed when considering the likelihood that PM would provide answers on the cause of refractory seizures. Although all children were on AEDs, adherence was inconsistent due to caregivers' insecurities about the treatment's efficacy. This resulted in combining AEDs with home remedies and traditional practice and at times self-adjusting medication in the hope of improving the health of the CWE. This information is important for health care providers to children with RE. Participants hoped that the PME study would lead to better therapy which was what they were seeking.

Even though they had given "informed" consent to taking part in the PME study, most participants had limited knowledge and did not fully understand what PM meant in the context of the study. Despite this, they perceived that there was potential to improve care for CWE. In particular the smartphone app was considered to be helpful in improving adherence as it provided reminders on time and dose for each medication.

Another key finding was that the mHealth devices introduced new challenges for participants as many had no prior experience with such technology. These mHealth devices were perceived to be adding burden to the existing and overwhelming burden of care experienced by some caregivers, and this limited their engagement. The security risk posed by owning the mHealth devices in high crime areas limited their usefulness in collecting clinical information consistently. Other challenges associated with caregivers' socio-economic status and quality of life were identified and these need to be overcome if the PM initiatives are to be successfully implemented in low resource settings such as this.

Study Strengths and Limitations

The methodology used gave strength to this sub-study, specifically the qualitative approach, consisting of interviews that are semi-structured and guided by open-ended questions which aimed to ensure that respondents shared their experiences freely. Another strength of the study was that the researcher conducted the interviews herself which made it possible for the interview to be guided by prompts. The fact that the interviewer was fluent in three of the four languages which were preferred by the interviewees reduced the likelihood that meaning was lost in translation. Since the researcher

and the participants were familiar with one another from exposure through the parent PME study, there was good rapport. This could also have been a hindrance as participants might not have been honest in certain aspects due to this previous association. Participants expressed benefit from sharing their experiences during the interviews.

The study used non-random sampling techniques and was limited to a small sample size of 12 subjects at a single public sector children's hospital in the Western Cape province of SA, making it imperative that caution is taken when drawing generalisations from this study findings aimed to generate hypotheses that can be answered in future studies and are too few to represent the views of all SA caregivers caring for children with epilepsy. The research setting was limited to the hospital environment and might have impacted participants' responses. Another limitation could be that the researcher was conducting this kind of research for the first time which might have had an impact on the quality of the first interviews compared to the later ones as she got used to the role.

Study implications and recommendations

Despite the limitations, the study findings offer a deeper understanding of the experiences of caregivers of children with RE in SA and will provide valuable findings and insight in informing the potential of PM initiatives to add benefit to care of the local population of CWE. Given that the participants had limited understanding of the cause of epilepsy it is important that an integrated approach which can enhance knowledge of epilepsy cause, treatment, the burden it places on individuals, caregivers and communities, its genetic associations and the place of PM in the management of epilepsy as a "whole" is adopted in SA. This could potentially be in the form of educational videos provided via the app. In addition, advocacy for the implementation of innovative strategies like PM in LMICs would be valuable. Knowing that smartphones were a luxury for most participants implies that phones, data and electricity all need to be made affordable along with improved network and Wi-Fi accessibility, if widespread remote monitoring is to be feasible. With regards to the security issues around owning the mHealth devices, it follows that the safety of individuals be prioritised over the need to gather data and must be considered. To aid understanding of epilepsy genetics and its management, trained genetic counsellors have an important role to play in the provision of accurate and effective counselling.

Participants in the PME study should receive another opportunity to engage with the genetic aspects of the study to ensure they are truly "informed" of what they consented to and, where feasible, results or feedback should be returned to participants. Future app design should also include being available in the home language of the user and being as simple and easy to use as possible. Apps developed for

simpler cell phones and not only for sophisticated smartphones should be considered. Tech development should target compatibility with the cell phones that have the highest availability in the target population to move the PM research forward. Subject to the main PME study analysis, the value of the wearable data might also indicate that just the app for supporting medication adherence and real-time reporting of seizures may be sufficient to support care. Reducing the need for Bluetooth enabled cell phones would certainly improve feasibility as managing a phone alone – without the wearable – may be more acceptable to caregivers that are already burdened with care needs.

Since this was a feasibility study in a small sample at one hospital, further studies are needed among larger populations and diverse communities in Africa to ascertain the potential benefits and challenges regarding the implementation of PM initiatives more widely.

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Appendix A: Information sheet for participant recruitment

Dear Parent/Caregiver,

My name is Irene Farisai Muchada and I am a student at the University of Cape Town, doing a Master's degree in Genetic Counselling. I am doing a research project and would like to invite you to participate in my study.

The study aims to assess caregivers' experience with Precision medicine (PM) and expectations on the ability of PM to improve health care in refractory epilepsy.

This study has been initiated through the Division of Human Genetics at the University of Cape Town and is for a minor dissertation for the completion of a Master's degree in Genetic Counselling.

You have been invited for involvement in this research because:

- A child in your care has refractory epilepsy.

-You are a participant in the Precision Medicine Management of Epilepsy in South African children (PME) study.

If you are willing to participate, I would like to discuss with you about your experiences with caring for a child with epilepsy. We will also talk about your understanding of the PM initiatives, your experiences with it and your expectations of it in the management of epilepsy. The discussion will take about an hour, at Red Cross War Memorial Children's Hospital. This can be done when you come with your child for clinical follow up. The interview will be audio recorded. Any identifying information, such as your name, will be kept confidential and will only be known by the researcher. Some parts of the audio-recorded interview may be used in reporting of this study.

Your participation will be entirely voluntary, and you can withdraw from the study at any point, with no consequences for either you or your child. This being a research study, there will be no personal medical benefits. Some of the questions that will be asked may be of a sensitive nature, but you can choose not to answer any questions you feel uncomfortable with.

If needed, referral to appropriate health care professionals can be arranged.

The Human Research Ethics Committee at the Faculty of Health Sciences, University of Cape Town, has approved this sub-study. If you have any questions about your rights as a participant, please contact:

Prof Marc Blockman, Chair of the Human Research Ethics Committee on 021 406 6496.

If you have any questions about the research project, please contact me at:

Mchire001@myuct.ac.za or by phone at 021 404 6235

or the project supervisor Dr Karen Fieggen at karen.fieggen@uct.ac.za or by phone at 021 4066298.

If you are interested in participating in this study, please read the Consent Form attached.

Appendix B: Participant Consent Form

Study Title: The use of precision medicine on children with refractory epilepsy in South Africa: caregivers' experiences, perspectives and expectations.

1. I have been invited to participate in the above research project because I care for a child who has refractory epilepsy.
2. I understand that both the questionnaire and the interview will be handled confidentially. The data will be used for this research project as well as publications/dissemination of information, but I, as a participant, will not be identified.
3. I understand that some of the questions may cause an emotional reaction, but the risk of harm is small, and should I require further counselling, the researcher will make arrangements.
4. I understand that the interview will be audiotape-recorded. These recordings will only be available to the researcher, supervisors and examiners and will be destroyed after the research is completed. My information will not be identifiable in any dissemination of the study.
5. I understand that I am free to decide not to participate or to withdraw at any time without consequences.
6. I understand that there will be no medical benefits from this study.
7. I understand that the registered Human Research Ethics Committee at the Faculty of Health Sciences, University of Cape Town, has approved this study. I have been given contact details should I need to contact the committee about my treatment as a research participant.
8. _____ has explained the information of this study to me and my questions have been answered satisfactorily.

I hereby declare that I have voluntarily agreed to participate in the above research study and that I agree to have my interview audiotape recorded.

Signature _____

Signed at _____on_____2019

Appendix C – Socio-Demographic Questionnaire

To be completed by the participant:

1. **Participant number**: ____ **Pseudonym:** _____
2. **Age**: _____
3. Gender (please circle): **Male/Female/Non-Binary /Prefer not to say**
4. Self-identified Ethnicity (please circle): **Black/White/Mixed ancestry/Other** _____
5. How are you related to the child with epilepsy? (please circle): **Parent/Caregiver**

   If **Caregiver**, what is your relationship to the child _____
6. Do you live with other people? (please circle): **Yes/No**

   If **yes**, who are they? _____
7. Have you ever lived with other people with epilepsy? **Yes/No**

   If **yes**, who are they? _____
8. Are you in a stable relationship (please circle): **Yes/No?**
9. Education level (please circle): **Primary school/High school/Tertiary education/None**
10. Employment status (please circle): **Employed/Unemployed**
11. If employed, what work do you do? _____

Appendix D– Preliminary Open-Ended Interview Guide

- So, you have completed a questionnaire about your household, perhaps you can now tell me about **how it has been like living with a child with epilepsy**?

- Probes:
  - Caregiving (fears, anxiety, uncertainty,
  - Other children
  - Partner
  - Work
  - Relationships–with friends and in community (How community views the child/stigma)
  - Has it affected the way you associate/go out?

-Since you found out about your child's epilepsy, what **treatments** have you tried?

- Probes:
  - Traditional healers/spiritual leaders etc
  - Views on **AEDs**
  - Adherence

-What do you think could have **caused** the epilepsy?

- Probes:
  - Genetics, spiritual, events

- So, you are participating in a study called PME. Could you **tell me a little bit about that study**?

- Probes:
  - What it **involves**
    - Genetics, Pharmacogenomics & Monitoring

-What are you expecting to get from the **blood tests**?

- So, they say PME trial is about **'personalising' the care** for epilepsy patients. Could you share with me what **you understand** about that?

-They gave your child a small **device** to wear and installed an app on your phone. Could you describe to me **what you think it is for**?

-How has been your **experience** with the device?

- Probes:
  - Familiarity with the devices
  - Easy/user friendly?
  - How people react to it (safety)
  - Helpful or not?
  - Challenges? (data, charging, time)

- What are your **thoughts on the PME** project in caring for children with epilepsy?

- Probes:
  - Short- and long-term benefits
  - Challenges

Appendix E – Ethics Approval

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone (021) 406 6492
Email: sumayah.arieffdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

14 December 2018

HREC REF: 775/2018

Dr K Fieggen
Division of Human Genetics
Level 3, WBN
IDM-FHS

Dear Dr Fieggen

PROJECT TITLE: THE USE OF PRECISION MEDICINE ON CHILDREN WITH REFRACTORY EPILEPSY IN SOUTH AFRICA: CAREGIVERS' EXPERIENCES, PERPECTIVES AND EXPECTATIONS (MSc-candidate-IF Muchada) sub-study linked to 767/2017

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

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 December 2019.

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: Irene Muchada will also be involved in this study.

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.

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

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938