MMED Dissertation

Demographic and aetiological factors of paediatric status epilepticus at Red Cross War Memorial Children's Hospital: 2016-2018

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DECLARATION

I, Sarahlouise Chingwali- Nsanta, hereby declare that this dissertation is based on my original work 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. This work has not been reported or published prior to registration of the above-mentioned degree.

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Acknowledgements, formats and contributions

I would like to thank my supervisors Professor Jo Wilmshurst, Associate Professor Heloise Buys. I would also like to thank Dr Richard Burman.

SCN was responsible for protocol, data collection and write up. JW was the principal investigator and supervised the protocol, study design, data collection and the writing of the manuscript. HB was involved in supervising the study design, data collection, data analysis and writing of the manuscript. RB was responsible for the design of the online data capturing tool.

The format of the thesis is a publication ready.

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ABBREVIATIONS

CNS	Central nervous system
CSE	Convulsive status epilepticus
EEG	Electroencephalogram
ILAE	International League Against Epilepsy
JICNA	Journal of the International Child Neurology Association
LICE	Italian League Against Epilepsy
RCWMCH	Red Cross War Memorial Children's Hospital
SE	Status epilepticus
WMA	World Medical Association
UWFA	Underweight -for-age
TBI	Traumatic brain injury
HIV	Human Immuno Deficiency Virus
TBM	Tuberculous meningitis
ICU	Intensive care unit
TB	Tuberculosis
ED	Emergency Department

SELECTED JOURNAL FOR PUBLICATION

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ABSTRACT

Background: Status epilepticus is a common medical neurological emergency in childhood which is often serious and life threatening. There is paucity of data with regard to aetiology and demographics of affected children in resource-limited countries.

Objective: To describe the demographics and the common causes of convulsive status epilepticus in our local paediatric population.

Methods: A retrospective review of the clinical records of children who presented in convulsive status epilepticus to the medical emergency department (ED) of Red Cross War Memorial Children's Hospital (RCWMCH), in Cape Town, South Africa, between May 2016 and May 2018 was completed. Demographics, clinical characteristics, and characterisation of convulsive status epilepticus were assessed.

Results:

Of 119 children, 63 (53%) were male; their median age was 29.6 (IQR 14.8-76.1) months: 22 (18%) were under one year of age, 63 (53%) were 1-5 years, and 34 (29%) >5 years. There were 31 (26%) children who were moderately-severely underweight-for-age; 5 (4%) children were HIV-infected. Fifty (42%) children were known to have epilepsy of whom ten reported poor compliance with their antiseizure medication, 20 (17%) children had cerebral palsy, 40 (34%) had developmental delay, and nine (8%) had a history of previously treated tuberculosis (TB)- of whom six had pulmonary TB, one TBM, one with extrapulmonary TB and one with disseminated TB. During the captured episode of CSE, 55 (51%) children were brought by ambulance, the rest self-presented using private or hired transport; 33 children received a benzodiazepine agent pre-hospital, 19 had aborted by the time of arrival at hospital, but 72 (62%) required antiseizure medication in the ED. In their seizure semiology, 82 (71%) children had generalised convulsive seizures and 34 (29%) had focal seizures; with 85 (73%) being prolonged events and 32 (27%) being multiple events. Aetiology according to ILAE classified 74 (62%) as secondary to acute infective cause, 12 (10%) had an electroclinical syndrome, 9 (8%) were remote and 25 (22%) were unknown. A recorded tympanic membrane temperature of ≥38°C was found in 41 (37%) of 112 children, supporting a diagnosis of febrile status epilepticus in these children. Imaging was undertaken in 45/119 (38%), with 28 (62%) being abnormal. Cerebral spinal fluid findings were abnormal in 7 (12%) of 57 children who had

lumbar puncture done and there were no deaths in the cohort. Most children, 87 (73%), were stabilised adequately for admission in the short stay ward, however eight required admission to ICU.

Conclusion: Acute infections are the most common cause of CSE in our setting with the highest proportion of children presenting in the infantile age range, this is concordant with other studies, but our results show a higher percentage of infective causes.

Chapter 1: Publication-Ready Format

Title page

Demographic and aetiological factors of paediatric status epilepticus at Red Cross War Memorial Children's Hospital

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Abstract

Background: Status epilepticus is a common medical neurological emergency in childhood, often serious and life threatening. A paucity of data exists on the aetiology and demographics of affected children in resource-limited countries.

Objective: To describe the demographics and the common causes of convulsive status epilepticus in our local paediatric population.

Methods: A retrospective review of the demographics, clinical features, and characterisation of CSE of children who presented to the emergency department of Red Cross War Memorial Children's Hospital, in Cape Town, South Africa, between 2016 and 2018 was completed.

Results: Of 119 children, 63 (53%) were male; their median age was 29.6 (IQR 14.8-76.1) months: 22 (18%) were <12-months, 63 (53%) were 1-5 years, and 34 (29%) >5years. Thirty-one (26%) were moderately-severely-underweight-for-age and 5 (4%) were HIV-infected. In seizure semiology, 82 (71%) had generalised convulsive seizures and 34 (29%) had focal seizures; with ILAE-classified aetiology 74 (62%) were secondary to acute infective cause, 12 (10%) electroclinical syndrome, 9 (8%) remote and 25 (22%) were unknown. A recorded tympanic membrane temperature of ≥38°C was found in 41 (37%) of 112 children, supporting the diagnosis of febrile status epilepticus in these children. Fifty (42%) were known with epilepsy related breakthrough seizures. Imaging was abnormal in 28 (62%) of 45 children. Cerebrospinal fluid findings were abnormal in 7 (12%) of 57 children. Most children, 87 (75%), were stabilised adequately for admission in the short stay ward, however eight required admission to the ICU. No deaths were recorded in the cohort.

Conclusion: Acute infections are the common cause of SE in our setting, concordant with other studies.

Keywords: convulsive status epilepticus, children, semiology, aetiology, epidemiology

INTRODUCTION

Convulsive Status Epilepticus (CSE) is defined as continuous seizure activity without an arresting phase or recurrent seizures without regaining consciousness in between for more than 5 minutes.[1] There is a variance with the estimated prevalence and mortality of paediatric CSE. It has been noted that the rates tend to be higher in the first few years of life. [2-7] Further, a similarity in these rates has been observed in studies conducted across high-income countries [8]. Paediatric CSE is considered to be a serious medical emergency worldwide associated with morbidity and death. [9,12]

According to global literature that was reviewed in 2018, about 3 to 42 per 100,000 children are affected by CSE per year, with an approximated 3% mortality [9]. In sub-Saharan Africa however, the incidence of SE appears to be higher. This may be attributed to the high burden of infectious and non-infectious (chronic) diseases in addition to late presentation to hospital. According to a Kilifi hospital based-cohort study that was conducted on a rural Kenyan population, the lower limit of the incidence of CSE was 35/100,000/year in children aged 0-13 years.[12] This was considered an underestimation as many children demised before reaching hospital. The incidence was eight times higher than a London based cohort once probable cases were also included. [10-12]

Age is a fundamental element when considering the epidemiology of CSE. Furthermore, substantial differences also exist within the paediatric population specifically between younger versus older children in terms of incidence, aetiology, prior history of seizures or neurological deficits.[13] Children who present to hospitals in sub –Saharan Africa commonly have fever-related seizures, mostly due to malaria.[10] This may have a regional bias, but other infective causes documented in similar resource poor settings include respiratory tract infections, gastroenteritis, and neonatal seizures.[1,10-12,14,15]

The aim of interventions for CSE are to stop the seizure, provide adequate symptomatic support and to treat the underlying cause. These interventions reduce adverse outcomes of CSE. In order to achieve effective treatment, an early robust (aggressive) medical intervention and identification of the predisposing factors for prolonged seizures that can be modified is required. In addition, resource-limited settings cannot follow the same treatment protocols prescribed by centres from the resource-equipped countries due to lack of access to medications and ICU services. This has required a more bespoke approach to the management of these

patients. This includes the use of phenobarbital the use of which, despite not being promoted in resource-equipped countries, has been found to be safe and effective as a second-line treatment for the management of paediatric CSE.[16] Unfavourable outcomes post an episode of paediatric CSE include subsequent epilepsy, permanent neurological deficits, cognitive impairment, and death.[17] Aetiology is an important determinant of the outcome as evidenced from some epidemiological studies and clinical series. Therefore, rapid identification of aetiology prevents subsequent neurological morbidity and mortality. [7,18-20]

There is paucity of data on the aetiological and demographic factors that play a role in paediatric CSE in sub-Saharan Africa, specifically, South Africa. Most research undertaken is from high income countries and it is not known if the same trends apply in resource limited sub -Saharan African countries as well. Therefore, the aim of this study was to explore the aetiological and demographic factors that play a role in paediatric CSE in South Africa and to compare the findings to other regions.

METHODOLOGY

Study Design and participants

This retrospective descriptive study was conducted over a 24-month period (May 2016- May 2018) at Redcross War Memorial Children's' Hospital (RWMCH), in Cape Town. All children presenting in CSE were included in the study.

Study Setting

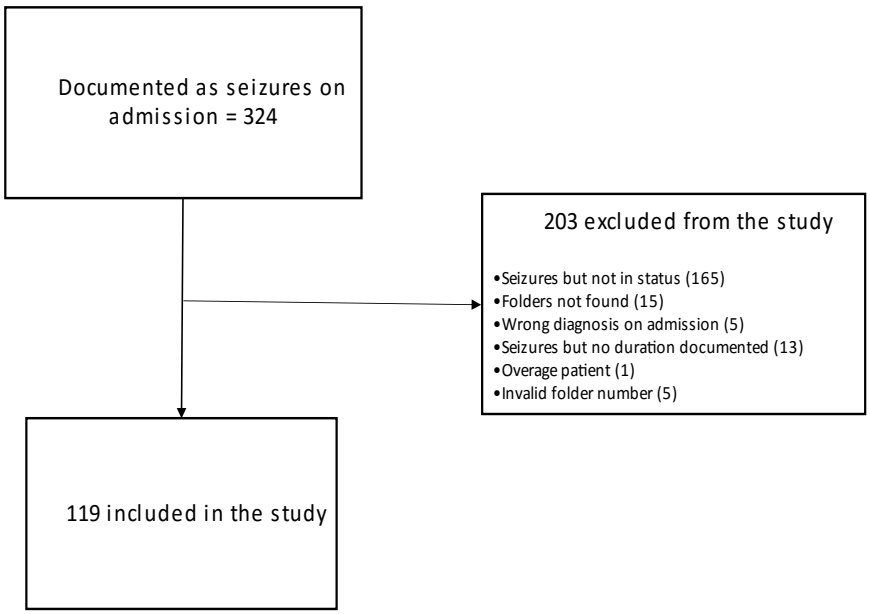
RCWMCH is a tertiary facility providing comprehensive and dedicated paediatric services with a full range of subspecialities at quaternary, tertiary, and secondary levels of care to children. RCWMCH is the largest children's hospital in sub-Saharan Africa and provides healthcare to a wide sector of the population from rural, peri-urban and urban areas. All children received standard-of-care according to the status epilepticus protocol at RCWMCH. This includes monitoring of heart rate, respiratory rate, blood glucose level, blood pressure and peripheral temperature, with varying interventions such as lumbar puncture and empirical antimicrobial cover for children with suspected infective cause, antiseizure medication levels where indicated and neuroimaging for children who have focal seizures.

Data collection

The main outcomes of interest included the demography of African children with CSE, the aetiology and semiology of CSE in accordance with the ILAE classification.[1] All children meeting the inclusion criteria were included. Children were included if they presented to the medical emergency unit in convulsive status epilepticus.

We collected demographic data, clinical data and special investigation findings on all children who presented in CSE to the medical emergency room. The initial recruitment process involved identifying all children from the emergency room admission register who were documented as having seizures upon admission in the medical emergency room. Children excluded from the study comprised those who were not in CSE, those whose folders could not be found, diagnosis other than seizures on admission, seizures with no documented duration, children over the age of 13 years and children with invalid folder numbers. One hundred and nineteen children met the inclusion criteria (**Figure 1**).

Figure 1: Flow diagram of the study recruitment process



To assess if other co-morbidities, such as growth and nutrition, previous illness, and compliance with medication, are major aspects to patient outcome, patient data was extracted from medical records. Data variables included demographics, date of admission, mode of transportation, weight-for-age z-scores, past medical history, drug history, seizure information, adherence to anti-epileptic drugs, admission ward, special investigation findings and final diagnosis at discharge.

Definitions

CSE was defined according to the ILAE criteria [1], that is - a prolonged or recurrent seizures without regaining consciousness in between for more than 5 minutes. Classification of CSE was done according to the ILAE Task Force on classification of SE using the following four axes framework: semiology, aetiology, age, and EEG correlates.[1] Our study did not include

EEG correlates, neither did it include the detailed treatment regimens and management of the children as this was covered in the Burman et al., [16] study. Thereafter, the diagnostic axes provided a framework for describing our study population.

Statistical Analysis

Background demographic characteristics describing the study children were summarised as frequencies and percentages and tabulated. Continuous data were tested for normality and the appropriate conventional descriptive methods, mean ± SD or median (interquartile range), were used to describe the dataset. The data were entered anonymously into a secure RedCap® database and analysed using STATA, release 16, College Station, Texas, USA.

Ethics and Consent

Confidentiality and anonymity were maintained at all times, and the data were only accessed by the investigators via a password protected computer. Ethical approval for the study was formally endorsed by the Faculty of Health Sciences Human Research and Ethics Committee, UCT (HREC 622/2017) and ran in accordance with the 2013 Declaration of Helsinki.

RESULTS

The demographics and past medical history are shown in **Table 1**. At the time of admission, the median age was 29.6 (IQR 14.8 - 76.1) months. All the patients who were HIV-infected (n=5, 4.2%) were on antiretroviral treatment. In terms of nutrition, thirty-one (26%) children were moderately- to-severely underweight for age, no other nutritional indicators were documented.

Table 1: Demographics of children presenting with convulsive status epilepticus

Variable	n (%)
Sex, male	56 (47)
Median age, (IQR) months	29.6 (IQR 14.8-76.1)
Age categories	
< 1 year	22 (18)
1-5 years	63 (53)
5-12 years	33 (28)
>12 years	1 (1)
Nutritional status (weight-for-age z score)	
Normal	88 (74)
Moderate UWFA	15(13)
Severe UWFA	16 (13)
HIV status	
**Infected	5 (4)
Uninfected	113 (95)
Unknown	1 (1)
Premorbid conditions*	
Cerebral palsy	20 (17)
Epilepsy	50 (42)
Developmental delay	40 (34)
**HIV encephalopathy	4 (3)
Congenital heart Disease	1 (1)
Underlying syndrome	8 (7)
Previous TBM	1 (1)
Previous TBI	3 (3)
Preterm <37w	20 (17)
HIE at birth	2 (2)

*NB: Some children presented with more than one premorbid condition.

** Of the 5 who were HIV-infected, 4 had HIV encephalopathy

Legend: IQR-interquartile range; UWFA-underweight-for-age; TBM- tuberculous meningitis; TBI-traumatic brain injury; HIE- hypoxic ischaemic encephalopathy

In terms of referral source, 54 (48.7%) children were self-referred and came directly from home, 31 (26%) were referred by community health centres, with 55 (51%) children being transported to the hospital by ambulance. Of our cohort, 50 (42%) of the children were known with epilepsy and 44 (88%) of these were on antiseizure medications, 10 (23%) of whom reported a history of non-compliance. Twenty -one (42%) of the children known to have epilepsy had drug levels done, 5 (20%) of whom recorded sub-therapeutic levels. The remaining children (n=16, 80%) had levels within therapeutic range. The total number of children receiving a benzodiazepine prehospital was 33 (28%) and 72 (62%) required antiseizure medication in the emergency department. Time to seizure cessation was not well documented.

With regard to investigations, 57 children had a lumbar puncture - 7 (12%) of these were abnormal – one with moderate pleocytosis (32 polymorphs and 55 lymphocytes) and raised protein content (11.68g/L) cultured *Mycobacterium tuberculosis* in the cerebrospinal fluid and the rest had non-specific mild pleocytosis and cultures were negative, polymerase chain reaction assay for viruses was not routinely done at that time. Computerised tomography head imaging was conducted in 45 of 119 (38%) children with 28 (62%) of the 45 being abnormal. Some abnormal findings included cerebral oedema (3), tuberculous meningitis (TBM) (1), empyema (1), hydrocephalus (1), pansinusitis (2), cerebral infarction (1), neurocysticercosis (1), venous anomaly (2), brain atrophy (2). Two patients were noted to have functional ventriculoperitoneal shunts in situ.

The seizures were further classified according to semiology and aetiology, see **Table 2**. The most common seizure semiology was generalised CSE (n= 82, 71%) due to an acute aetiology (n=74, 62%).

Table 2: Semiology and aetiology according to the ILAE

VARIABLE	N (100%)
Semiology	
Generalised	82 (71)
Focal evolving into bilateral CSE	34 (29)
Axis aetiology	
Acute (infectious/stroke)	74 (62)
Electroclinical syndrome	12 (10)
Remote	9 (8)
Progressive	0
Unknown	24 (20)

Legend: ILAE-International League Against Epilepsy; CSE- convulsive status epilepticus

A recorded tympanic membrane temperature of ≥38°C was found in 41 (37%) of 112 children. The final diagnosis at discharge in 74 children in CSE with an acute infectious aetiology is as illustrated in **Table 3**. Forty-seven of those with an infectious aetiology had an upper respiratory tract infection. Thirteen had a lower respiratory tract infection, 7 had a CNS infection, 5 had acute gastroenteritis and other infections included otitis media (4), urinary tract infection (1), neurocysticercosis (1) and congenital cytomegalovirus (CMV) infection (1).

Table 3: Final diagnosis at discharge in 74 children in CSE with an acute infectious aetiology

Diagnosis associated with CSE	Number (%)
Upper respiratory tract infection (pharyngitis, tonsilitis, sinusitis)	47
Lower respiratory tract infection (pneumonia)	13
CNS infections (meningitis, encephalitis)	7
Acute gastroenteritis	5
Otitis media	4
Sepsis	2

Cytomegalovirus	1
Urinary Tract Infection	1
Neurocysticercosis	1
Total*	81

Legend: CSE- convulsive status epilepticus; CNS – central nervous system.

*There is an overlap in patients who presented with more than one diagnosis at discharge.

Eight children were admitted to ICU, whilst most children 87 (75%) stable enough for admission to the short stay ward. Reasons for admission to ICU included required airway protection related to - recurrent seizures (1), episodes of apnoeas post antiseizure drugs (2), depressed level of consciousness (3) and two were post operation - incision and drainage of an abscess and insertion of an extra ventricular drain respectively. No mortalities were reported in our study.

DISCUSSION

In this study we have been able to describe the demographics and aetiologies of CSE in 119 children who accessed care at a public children's tertiary hospital in an African setting. Our study found that 22 (19%) of our child cohort were infants. This is similar to a cross-sectional study from Iran by Barzegar et al., [21] where 20.9% of their 43 children (under the age of 15 years) were less than 12 months of age. These results support that children less than 1 year are more affected by CSE. This can be attributed to the enhanced excitation of the immature brain, which further renders the developing brain more susceptible to seizures. According to Epstein et al., [24] younger children have a lower threshold to seizures, especially febrile seizures at lower febrile temperatures. Gurcharran et al., in a multi-centre population-based study also noted that the peak age incidence of CSE in children in Virginia, Minnesota and London was less than one year.[9] Other studies from Iran [21], Taiwan [22] and London [23] showed that 21 (46.5%), 73 (51.8%) and 76 (55%) respectively of children were in the age category of 1-5

years, concordant with our finding of 63 (53%). This is also supported by the Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT) studies, although they specifically focused on the infantile age group.[24]

Nearly a third (26%) of our children were moderately to severely malnourished which is comparable to a retrospective Kenyan study (children aged 1 month to 13 years), which reported malnutrition in 32% of their 155 confirmed CSE cases.[12]This was the only comparative study for nutritional data, and this could possibly be explained by the fact that the other studies were from high income countries where malnutrition may not be a major health concern. According to the South African Child Gauge 2020, one in four South African children under the age of five (27%) are stunted. Although we did not dwell on classification of the cerebral palsy, we speculate that these children may often have some form of feeding difficulty as possibly did the other children (n=56, 47%) with a chronic underlying medical condition; and hence this could also be a confounding factor for us having a high number of children being underweight-for-age (UWFA).[25] In addition, a significant number of the patients seen at RCWMCH come from very poor and marginalized communities.[26]

A recorded tympanic membrane temperature of ≥38°C was noted in 37% of our patients. Similarly, a multicentred study of 3 785 Chinese children (aged 29 days to 18 years) reported 36.8% (1 385) [27] were pyrexial, and a Kenyan study reported 48% of their confirmed CSE cases presented with a fever.[12] Though we do not routinely test for human herpes virus 6/7, it has been identified as one of the common causes of fever in young children presenting with febrile status epilepticus.[24]

In terms of transportation and referrals, 43% of our children utilised private transport whereas 48% of the patients were self-referred. This gives us an indication that children who self-present or use private transport are less likely to receive antiseizure medication prior to arriving at a health facility and this increases the likelihood of having a prolonged seizure. This was supported by the fact that only 33 out of the 119 actually received a benzodiazepine pre-hospital. Though we could not calculate the exact time to intervene, we can conclude that it was prolonged based on the mode of transportation, self-referrals from home and the small number receiving benzodiazepines prior to hospital arrival. This is further supported by a study done in South Africa [16] in which the time to intervene was calculated at 50 minutes. In some

resource-limited countries seizures last longer compared to high-income countries because the local population has limited access to hospitals, clinics, and emergency medical transport. [12]

Despite the high prevalence of HIV disease, traumatic brain injuries, tuberculous meningitis (TBM), and hypoxic ischaemic encephalopathy in South Africa [28,29], the documented past medical history in this present study identified relatively small numbers of these conditions. In an acute setting, the priority is to stabilize the patient hence the past medical history may not be adequately documented, and this may lead to an underestimation of these conditions. Children with traumatic brain injury are more prone to developing seizures which can later evolve into post-traumatic epilepsy. [30,31] In our study, a previous history of traumatic brain injury was noted in 2.5% of children. Our study revealed that one patient had a history of TBM, and another had TBM related to the acute presentation. Seizures are a common presentation in TBM and are more likely to be experienced in childhood due to the immaturity of the immune system, the CNS and the blood brain barrier. If seizures are recurrent and uncontrolled, they can evolve into SE with resultant brain damage.[32]

The seizure semiology (**Table 2**) was varied with generalised tonic-clonic being the most common accounting for 71% of our patients. This finding was in accordance with previous reports by Wang et al., from China who described 66% (2317) of their cohort aged 1 month to 18 years as having generalised tonic clonic seizures.[27] In the same Chinese study, acute symptomatic aetiology of SE accounted for 42.8% (1 819), with an unknown aetiology accounting for more than half of their cases 58.8% (2 503), electroclinical syndrome 1.6%, and progressive aetiology 0.6%. By contrast, our study had a higher number of acute symptomatic aetiology at 62% and our unknown aetiology only accounted for 21%. Our electroclinical syndromes and progressive aetiology cases were much higher at 10% and 8% respectively. An 8-year retrospective analysis of 76 South African children (aged 1 month to 13 years) admitted to a tertiary paediatric intensive care unit (PICU) with CSE reported a much higher acute symptomatic aetiology at 80%.[14]

Most seizures in our study were due to an acute aetiology with the commonest causes identified as respiratory tract infections, otitis media, acute gastroenteritis and CNS infections, concordant with findings from earlier studies.[12] By contrast, a prospective study of 70 Indian children (aged 6 months to 12 years) by Kumar et al., described the commonest acute aetiology

attributed to CNS infections such as viral encephalitis, pyogenic meningitis, tuberculous meningitis, and cerebral malaria.[33]

Patients with pre-existing epilepsy are more vulnerable to breakthrough seizures with intercurrent infections.[34] Our study reported 42% of the children as having pre-existing epilepsy. This coupled with the high number of infections, the history of non-compliance to ASMs (23%), and the low levels of ASMs detected in 20% of those on medication could have been contributing factors to the occurrence of the seizures. We recorded 21 (42%) of the children on ASM with a drug level, signifying that more than 50% of the children did not have a documented drug level. In an acute setting, the priority may have been to stabilise the patient.

Most of our cohort with an acute infection (60 out of 74) had a diagnosis at discharge documented as respiratory tract infection. This included pharyngitis, tonsilitis, sinusitis and pneumonia. According to a review article by Bomwalhd et al., respiratory viral infections can be associated with neurological manifestations such as seizures and status epilepticus.[35] Viral respiratory diseases are a critical health problem and account for the high rates of morbidity and mortality predominantly in the immunocompromised, young children, and the elderly. [36] Acute gastroenteritis accounted for five of our patients. Similarly, a review article by Kim from Korea described children with mild acute gastroenteritis who presented with both febrile and afebrile seizures. [37] Though we did not dwell on the specific aetiology of the acute gastroenteritis, Higuchi et al., from Japan described the clinical features of convulsions with rotavirus and norovirus gastroenteritis as similar, except for fever. [38] A case-control study of 165 children aged 6 months to 5 years, conducted by Mayhar et al., in Iran showed that there was a significant link between urinary tract infections and febrile seizures. [39] Our cohort reported one patient who presented in status epilepticus with a proven diagnosis of a urinary tract infection.

Higher rates of epilepsy are associated with the presence of intracranial calcifications in congenital infections such as Toxoplasmosis, Other infections, Rubella, Cytomegalovirus, and Herpes Simplex (TORCH) aetiologies.[40] The study identified one case of congenital CMV. The risk of postnatal seizures is higher in patients with congenital CMV and in children with congenital infections associated with intracranial calcifications. Suzuki et al., reported that 37% of their 19-patient cohort with congenital CMV developed epilepsy. [41] The proportion of children in our study presenting with CSE secondary to a CNS infection was 12%. This was

lower than reported in the Chinese retrospective multicentred study (4 255 children aged 1 month to 18 years) at 22% (932) [27] and 81% from a prospective Indian study of 70 children (aged 6 months to 12 years).[33] At our institution this may be attributed to the fact that we do not routinely test for all viruses on cerebrospinal fluid, due to resource constraints. Additionally, requesting an extensive viral panel on cerebrospinal fluid may not have altered the management of status epilepticus significantly except in the cases where herpes or CMV are identified. Further there may be regional biases because the area in which the Indian study was conducted has an increased incidence of Japanese encephalitis.

Whereas the study identified an acute aetiology as the commonest cause of CSE, we also noted the evidence of local influence in reported studies. In a cross-sectional study from India, Shriyan et al., reported that 52.8% of their 104 CSE cases (1 to 12 years of age) were attributed to an acute infection, 41% of those acute infections were due to neurocysticercosis and 14% tuberculous meningitis. [42] Similarly, our study had acute aetiology detected in 62% of children, but with only one case each of tuberculous meningitis and neurocysticercosis. In contrast, a Kenyan retrospective study of 388 children aged between 1month and 13 years and a prospective Nigerian cross sectional-study of 39 children (aged 4 months to 8 years), both noted many of their patients presented with malaria (65% and 70% respectively). [12, 43] As the Western Cape province is not a geographical malaria zone it is not surprising that none of our patients presented with malaria.

The zero mortality rate in this study was comparable to that reported by high income settings, as illustrated by an epidemiological study of 120 children (1 month to 15 years) from Japan[44] and a 5-year retrospective review of 137 children (aged 1 month to 15 years) admitted to the paediatric ICU (PICU) in London.[23] This could be attributed to the fact that our patients are able to access treatment within 5 minutes of admission to the emergency ward[16] and the hospital staff are able to manage CSE appropriately. In contrast, studies from Nigeria,[43] Kenya [12], Pakistan [45] and India [33] have reported high mortality at 23%, 22%, 11% and 31% respectively. Deaths can be attributed to the underlying cause of CSE or as a result of the complications of the CSE itself [33] and infective causes are associated with an increased risk of mortality.[3,6,7] Increase in mortality in resource poor countries can be attributed to unorthodox cultural practices where patients with CSE are taken to traditional healers prior to seeking medical attention.[28] Kumar et al., also highlighted poor literacy and the lack of transport which delays accessing treatment. [33] This results in a prolonged time interval from

onset of CSE to the commencement of treatment, as evidenced by the South African study.[16] Further, poor management of CSE in hospitals, lack of staff to manage CSE appropriately and the lack of equipment such as infusion pumps and ventilators contribute to high mortality rates in Sub-Sahara Africa. [10-12,43]

In this retrospective study, the long-term effect of CSE in our cohort remains unknown. This information was also not routinely documented in the patients' folders. In this regard, a neurodevelopmental follow up plan should be clearly documented for every child presenting in CSE.

Based on our study findings and the above comparisons, we conclude that the aetiological spectrum of CSE in resource limited countries is divergent when compared to resource equipped countries. The aetiologies differ further within the sub-Saharan African setting due to local endemic influences as in the case of malaria, tuberculosis and neurocysticercosis. [3,12,40,43,45] Notably, whereas these comparisons were made within a similar population group, the definitions of CSE differed and therefore we may have deviations from the methodologies and the directness of the study question.

According to the UNAIDS Global HIV AIDS statistics (2020), most people living with HIV are in lower middle-income countries.[46] Inclusion of HIV data was relevant for our study as South Africa has high prevalence of HIV in its paediatric and adult populations. Surprisingly, despite the high HIV prevalence our study identified a low percentage (4.2%) of children who were HIV positive and all of whom were on antiretroviral treatment, however despite this, four of the five children had evidence of advanced neurological damage related to HIV encephalopathy. Few studies reported on HIV data in the paediatric population with seizures. In one retrospective case control study of children aged 10 months to 176 months Burman et al., reported that 28 (54%) out of their 57 HIV positive patients with seizures had HIV encephalopathy and 11 had CSE at presentation. [47] We believe that our study has added new data in terms of the low impact of HIV status in the aetiology of paediatric CSE, or at least highlighted that poorly controlled HIV disease is to be avoided as it can lead to HIV encephalopathy which may be associated with CSE.

The introduction of nutritional data in this category of children is important. The study findings have highlighted that these children are not only predisposed to poor nutrition in our setting

but other compounding factors such as feeding difficulties and chronic underlying medical conditions further contribute to their poor nutritional status.

Study limitations

As this was a retrospective study, we relied on handwritten medical notes made by attending clinicians during admission for accurate record keeping; medical record documentation was therefore variable. The duration of the seizures and time to seizure arrest affects the pathways to care and planning and were important but challenging to measure due to variable documentation. CSF PCR assays for viruses were performed at a later stage in the ward hence this data may have been unavailable at the time of initial admission. Furthermore, we had no follow up data routinely documented in most of our patients which we would promote in future rigorous prospective studies, to formally elucidate the impact of CSE, particularly at a vulnerable age, on neurodevelopmental outcomes.

RECOMMENDATIONS AND CONCLUSION

Recommendations

Suggestions for future research includes exploring the aetiological variances in those admitted to the paediatric intensive care unit. Additionally, it would be beneficial to obtain more data on the effectiveness of pre-admission intervention programs including the pathways to care for this category of children. We also need to improve pathways to care from home in addition to raising awareness for children with epileptic syndromes who would benefit from early interventions. As the study was conducted pre- COVID pandemic, it would be worthwhile assessing if there have been any significant changes post the pandemic.

We need to establish the circumstances surrounding non-compliance and the sub-therapeutic ASM levels. This can be improved by ensuring drug supply is always adequate and placing emphasis on compliance education. Additionally, since few children had drug levels done, we need to feedback to the clinicians the importance of knowing the drug levels in this category of children.

Conclusion:

Acute infections are the common cause of CSE in our setting with the highest proportion of children presenting in the infantile age range. This age distribution is concordant with other studies, but the present study results revealed a higher percentage of acute infective causes. Improved access to healthcare and timely intervention can reduce insult on the developing brain.

Declarations:

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I would like to thank my supervisors Professor Jo Wilmshurst, Associate Professor Heloise Buys and Dr Richard Burman. I would like to acknowledge the nurses and doctors who provide care to children at our hospital, the medical records department, and most of all- our patients- the children from whom we learn so much.

Author contributions

SCN was responsible for protocol, data collection and write up. JW was the principal investigator and supervised the protocol, study design, data collection and the writing of the manuscript. HB was involved in supervising the study design, data collection, data analysis and writing of the manuscript. RJB was responsible for the design of the online data capturing tool.

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Conflicts of interest:

The authors declare there are no conflicts of interest.

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Chapter Two: Appendices

Appendix 1: Research protocol

DEMOGRAPHIC AND AETIOLOGICAL FACTORS OF PAEDIATRIC STATUS EPILEPTICUS AT REDCROSS WAR MEMORIAL CHILDREN'S HOSPITAL

INVESTIGATORS:

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UCT MBChB student

ABBREVIATIONS

CNS	Central Nervous System
CSE	Convulsive Status Epilepticus
EEG	Electroencephalogram
ILAE	International League Against Epilepsy
JICNA	Journal of the International Child Neurology Association
LICE	Italian League Against Epilepsy
RCWMCH	Red Cross War Memorial Children's Hospital
SE	Status Epilepticus
WMA	World Medical Association

GLOSSARY OF TERMS

1)International League Against Epilepsy(ILAE)

The **International League Against Epilepsy** (**ILAE**) is the world's preeminent association of physicians and other health professionals working toward a world where no person's life is limited by epilepsy. ILAE's mission is to ensure that health professionals, patients and their care providers, governments, and the public world-wide have the educational and research resources that are essential in understanding, diagnosing and treating persons with epilepsy.

The **goals** of the ILAE are:

- To advance and disseminate knowledge about epilepsy
- To promote research, education and training
- To improve services and care for patients, especially by prevention, diagnosis and treatment

2)Italian League Against Epilepsy(LICE)

The Italian League Against Epilepsy is a scientific society with the statutory objective of contributing to the treatment and assistance of patients with epilepsy and to their integration into society at large, by promoting and pursuing all kinds of activities designed to achieve those aims.

3)Electroencephalogram(EEG)

An EEG, or electroencephalogram is a measure of electrical activity of the brain detected by electrodes attached to the scalp.

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PURPOSE OF THE STUDY

To determine the aetiology and demographics of paediatric patients presenting in convulsive status epilepticus in a sub-Saharan setting.

BACKGROUND

Status epilepticus (SE) is a common medical neurological emergency in childhood which is serious and often life threatening.

Convulsive status epilepticus (CSE) is defined as a convulsive seizure lasting 30minutes or longer or where there is failure to regain consciousness between seizures in a 30minute period. Outcome of these seizures is influenced by the duration of the seizure such that the longer it takes to arrest seizure activity, the worse the neurological outcome. (1) (2) Underlying aetiology is another factor that influences outcome. (3) (17). Rapid identification of the underlying aetiology is key for treatment and prognosis. (1). The longer the duration of convulsive status epilepticus continues the more significant the subsequent neurological morbidity and mortality. Adverse outcomes after convulsive status epilepticus include death, cognitive impairment, permanent neurological deficits and subsequent epilepsy.(21) It is therefore important that the disorder is recognised rapidly and treatment instituted as soon as possible. Although the outcome is dependent on aetiology, it is believed that appropriate early management may reduce some of the morbidity associated with CSE. Future therapeutic and neuroprotective interventions need to be investigated in the light of our current understanding of the mechanisms of seizure termination and neuronal death. Furthermore, the incidence of CSE is highest in childhood and therefore neuroprotective strategies may ultimately be most usefully carried out in children. (4)

CSE is common in sub-Saharan Africa and especially so in children. (5) A study in rural Kenya, found that children who present to hospitals in sub –Saharan Africa commonly have fever-related seizures, mostly due to malaria (5) (6) (15) (17). This may have a regional bias but other infective causes could also result in seizures in similar resource poor settings. The prevention of infections and appropriate early intervention might reduce the incidence and improve the outcome of convulsive status epilepticus. A retrospective review of Chinese children admitted

to Queen Mary Hospital in Hong Kong found that patients with normal neurological status before an episode of SE and without acute central nervous system(CNS) insult or progressive encephalopathy had a favourable outcome. (7)

Hakala I *et al* (J Child Neurology ,2016) described 381 children with status epilepticus, 81.6% were due to prolonged febrile seizure,6.6% to encephalopathy/encephalitis,0.8% to meningitis and 7.6% to epilepsy. However, the study was a febrile status study and the limitation is that data was not reported on the non-febrile cases. (8) A convulsive status epilepticus study in Thai children at Ramathibodi Hospital (J Med Assoc Thailand 2006) revealed that status epilepticus in the infantile period was more frequent in children with pre-existing epilepsy or neurological disorder. In this group, acute febrile illness and infection were the commonest precipitating causes. (9)

Based on the findings of Hesdorffer et al., on the risk factors for subsequent febrile seizures in the FEBSTAT study, children with a first febrile status epilepticus episode are more likely to experience subsequent febrile status epilepticus than simple febrile seizures. The group reported that children have a lower seizure threshold indexed by younger age of onset of first febrile seizure, lower temperature at first febrile status epilepticus and impaired ability to stop a prolonged seizure. (10)

A hospital based retrospective study in Western Nepal by Adhikari et al., reported that CNS infections and acquired epilepsy are the main cause of seizures in resource poor countries and geographical variations determine common aetiology in a particular region. (11) (15) Human Herpes simplex virus 6 and 7 have been highlighted as an aetiological factor in febrile status epilepticus. Of 199 children evaluated, HHV-6 or HHV-7 status could be determined in 169 (84.9%) and it accounted for one third of the FSE cases. (12)

In resource-limited settings such as South Africa where neuroinfections are so prevalent, the underlying aetiologies of CSE are expected to vary from those of resource equipped settings. Access to antiepileptic drugs which is also a challenge in sub-Saharan Africa has a significant impact on the morbidity and mortality. (1) (13). The incidence of status epilepticus appears to be higher in resource poor countries than in the high income countries as can be seen from a study by Sadarangani et al. (17) According to the National trend survey of hospitalised patients with febrile seizure in the United States (February 2017), children with very -low household

income levels were more likely to be hospitalized. This relationship between low socioeconomic status and hospitalization due to febrile seizures may reflect parental anxiety and family dysfunction in families of low socioeconomic status. (22) (23).

Below is a simple table that can be used to illustrate the differences between resource poor countries and high-income countries as regards aetiology, incidence and outcomes of CSE.

Table1: Comparison of Aetiology, Incidence and Outcomes of SE

	Resource Poor countries	**High income countries**
Aetiology of CSE	Febrile Seizures: associated with respiratory tract infections, gastroenteritis, neonatal, Malaria (malaria endemic) (6)	CNS infections, Epilepsy, breakthrough seizures, low levels of AED (20)
Incidence of CSE	Higher(46/100,000/year) (6),(17),(18)	Lower(18-20/100,000/year) (6)
Outcomes	Worse due to poor facilities, worse infections, unavailability of drugs, long distances from healthcare facilities (6), (17),(18)(1)	Better: related to access to facilities and more remedial underlying aetiologies

CSE: Convulsive status epilepticus, anti-epileptic drugs AED, Central nervous system CNS

According to the report of the Italian League Against Epilepsy Task Force on classification of status epilepticus the following axes have been proposed:

1) Semiology

2) Aetiology

3) EEG correlates

4) Age

The purpose of the diagnostic axes is to provide a framework for clinical diagnosis, investigation and therapeutic approaches for each patient. At least half of patients presenting with status epilepticus do not have epilepsy or specific epilepsy syndromes but have seizures due to acute or remote CNS or systemic illness hence the axes used previously in seizure classification were modified for the classification of status epilepticus. (15) In a resource-limited paediatric setting a different hypothesis may be drawn. Currently there is little data on the aetiological and demographic factors that play a role in paediatric status epilepticus in sub-Saharan Africa, specifically, South Africa. Most research undertaken is from high income countries and it is not known if these trends also apply to resource limited sub-Saharan African countries. The data collected will be important in that it is required for decision making purposes on allocation of resources and may be used to develop preventative strategies of SE. (18)

Our study aims to identify the epidemiological and aetiological factors of convulsive status epilepticus in South Africa

HYPOTHESIS

We can therefore hypothesise that aetiological and demographic factors have regional variations.

OBJECTIVES

a) PRIMARY

1)Establish the major causes of CSE in our population

2)To understand the demographics of the population group who present with convulsive status epilepticus

3) Determine the number of patients who presented with status epilepticus

b) SECONDARY

1) To classify the aetiology of convulsive status epilepticus according to ILAE criteria.

2) To ascertain the median age and age range of presentation of Paediatric SE.

3) To ascertain if dermographic variation plays a role in aetiology.

METHODOLOGY

Study Population

Inclusion criteria:

- All children presenting to the medical emergency unit at Red Cross War Memorial Children's Hospital (RCWMCH) in CSE

Exclusion criteria:

- children not in status epilepticus

Study Design

An retrospective study of children presenting to the medical emergency unit at Red Cross War Memorial Children's Hospital(RCWMCH) in CSE.

Study Site

The study will be carried out in the medical emergency unit and Department of Neurology at RCWMCH. Red Cross War Memorial Children's Hospital is the largest children's hospital in sub-Saharan Africa and provides healthcare to a wide sector of the population, local and from wider afield. The study aims to provide information which will eventually be published and available for the rest of Africa as a reference.

Sample Size

The study will comprise of a sample size of about 200.

Data collection

Clinical data will be captured onto a proforma and then uploaded into an electronic data base using a secure online platform i.e. REDCAP. Data to be collected includes demographic data, anthropometry, seizure information, physiological profile, duration of hospital stay, past medical history, drug history, comorbidities, investigation carried out and adherence to antiepileptic drugs. Aetiology will be classified according to the ILAE classification. Attached is a copy of the proforma. (appendix 1)

Statistical Analysis

The main outcome of interest is the aetiology of CSE. Other variables are age at presentation, investigations, seizure type and co-morbidities. Descriptive statistics based on multiple variables such as age, aetiology, demographic regions, nutritional status, socioeconomic status(using area postal codes) will be analysed using multivariant regression analysis. Data will also be assessed graphically using histograms. Categories will be cross tabulated to estimate associations and tested for statistical significance using the X^2 test. The continuous variable will be compared across categories with the non-parametric Kruskal-Wallis test.

Ethics and Consent

Confidentiality and anonymity will be maintained at all times as the data will be accessed by the investigators via a password protected computer. The de-identified data will be used for data analysis by the statistician.

Deferred consent will be obtained for inclusion in the study after treatment because of the urgent nature of the level of intervention required.

All the children in the study will receive the standard of care according to the status epilepticus protocol at RCWMCH.

The data to be captured as part of this study is already approved through the study "Childhood Convulsive Status Epilepticus- In Search of Optimal Drug Management in A Resource Limited Setting ref rec :297/2005

Approval for this MMed component of the study will be sought from the Human Research Ethics Committee of the University of Cape Town and it will also be run in accordance with the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, 2015.

Limitations

1)The study has a retrospective aspect and therefore inherent limitations such as inaccurate documentation may occur due to the fact that we are relying on other medical personnel accurately entering demographic data into the medical folders

2) The limited published data on aetiology and epidemiological factors of CSE in Africa is a challenge because the comparison is being made with high income countries.

3)In some cases history may need to be obtained from care givers who struggle to provide very accurate information relating to the events prior to the child's arrival in a healthcare facility.

Risks or Benefits to participation

There will be no risk posed to the patients for the duration of the study. Patients, caregivers, the paediatric population from which they come and clinicians may benefit from the study because a data base will be created as a reference point not only for RCWMCH but for sub-Saharan Africa.

Budget

The costs of the study are estimated to be R4000. Requirements include:

Table 2: Budget

Stationary/ printing/posters/pens	R1,000
Ink cartridges + Calls to parents	R1,000 + R500
Biostatician (UCT)	R150+VAT/hr (2016 rates)
TOTAL	R4,000

Study Time Frame

Table 3: Study Time Frame

Activity	**Time-frame**
Protocol development	12-14weeks
Ethics approval	8weeks
MMed processing	6weeks
Collection of data	12-24weeks
Data analysis	8weeks
Report write up	20weeks

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Appendix 2: Data capture sheet

Confidential
Paediatric Convulsive Status Epilepticus Study

Page 1 of 12 **first_admission**

Record ID _____

PROTOCOL INFORMATION

Was the patient recruited into the PHB vs PHY/MDZ study?
Yes No

If 'No', please explain why the patient was not recruited?
_____

If 'Yes', what was the protocol number _____
(seen in top right of brown envelope)

What treatment arm was the patient allocated to Protocol 1 - Phenobarbitone Protocol 2 - Phenytoin/Midazolam
(The treatment patient was randomised to upon pulling the study envelope.)

PATIENT INFORMATION

Surname _____
Initials _____
(first letter of first name(s))
Folder number _____
Sex Male Female
Date of birth _____
Postal code _____
(area of residence)

ANTHROPOMETRY

Weight (kg) _____
Weight-for-age (Z) 2; < 3
>3
Height / length (cm) _____
Height / length for age (Z) 2; < 3
>3
Weight-for-height (Z) 2; < 3
>3
Head circumference (cm) _____

04/08/2016 19:58 www.projectredcap.org

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Page 2 of 12

Was a MUAC recorded? Yes
No
If 'Yes', what was the MUAC (cm)? _____
CP charts used? No
Yes
Unknown / not recorded
Down's syndrome charts used? No
Yes,
Unknown / not reported

ADMISSION DETAILS

Date of admission _____

Time of admission to S12 _____
Referral source Unrefered (self) Private GP
Level 1 hospital Level 2 hospital
Other
If 'Other', please explain where the patient was _____
referred from
How did the patient get to RXH S12? Walk in Ambulance
Private vehicle Other
If 'Other', please specify how the patient got to the _____
S12

SEIZURE INFORMATION

Time of seizure onset _____
(time first seizure started)
Did the seizure start upon admission to S12? Yes
No
Seizure type Focal Generalised
Other
(type of seizure according to initial onset - if
starts focal and progresses to secondary
generalisation, record as focal)
If 'Other', please specify the type of seizure
_____
Seizure nature Prolonged event Multiple / recurrent
events
(one prolonged event or multiple / recurrent
events with no recovery to baseline cognitive
function in-between)

Semiology
_____
(Comment on onset and progression of seizure.)
Did this patient receive treatment prior to admission
to S12?
Yes No
(Any treatment received before admission to S12.
This includes any intervention administered by
caregivers, ambulance staff or from healthcare
workers at the referring centre.)
If 'Yes', what anti-convulsant treatment did the
patient receive prior to S12 admission?
Diazepam Lorazepam
Midazolam Other
(If the patient has received PHB or PHY prior to
admission, they are not eligible for this study.)
If 'Other', please explain what anticonvulsant the _____
patient received
What dose of medication did the patient receive? _____
(mg, ml, etc)
How many doses did the patient receive before _____
admission?
What was the route of administration? Intravenous (IV) Per rectal (PR)
Intra-muscular (IM) Sublingual (SL)
Intra-nasal (IN)

ANTI-CONVULSANT MANAGEMENT IN S12

Agent 1 drug Lorazepam Diazepam
Midazolam Other
None
(First drug given given to patient to arrest
seizures)
If 'Other', please specify which agent 1 was given _____
Agent 1 dose given (mg) _____
Agent 1 time given _____
Agent 1 route of administration Intravenous (IV) Per rectal (PR)
Sublingual (SL) Intra-muscular (IM)
Infusion
Agent 2 drug Lorazepam Diazepam
Midazolam Other
None
If 'Other', please specify which agent 2 was given _____
Agent 2 dose given (mg) _____
Agent 2 time given _____

Agent 2 route of administration Intravenous (IV) Per rectal (PR)
Sublingual (SL) Intramuscular (IM)
Infusion
Agent 3 drug Phenobarbitone Phenytoin
Midazolam Other
None
If 'Other', please specify which agent 3 was given _____
Agent 3 dose given (mg) _____
Agent 3 time given _____
Agent 3 route of administration Intravenous (IV) Per rectal (PR)
Sublingual (SL) Intramuscular (IM)
Infusion
Agent 4 drug Phenobarbitone Phenytoin
Midazolam Other
None
If 'Other', please specify which agent 4 was given _____
Agent 4 dose given (mg) _____
Agent 4 time given _____
Agent 4 route of administration intravenous (IV) per rectal (PR)
sublingual (SL) intramuscular (IM)
infusion
Agent 5 drug Phenobarbitone Phenytoin
Midazolam Other
None
If 'Other', please specify which agent 5 was given _____
Agent 5 dose given (mg) _____
Agent 5 time given _____
Agent 5 route of administration Intravenous (IV) Per rectal (PR)
Sublingual (SL) Intramuscular (IM)
Infusion
Level of intervention reached level 1 (benzodiazepine)
level 2 (phenytoin or phenobarbitone)
level 3 (midazolam infusion)
level 4 (induced coma)

(What level of intervention (1-4) did this patient reach before seizure activity was fully arrested)

Deviation from study protocol Yes No

(Did this patient management deviate from what is prescribed in allocated protocol?)

If 'yes', please explain how the patient deviated from the protocol allocated to them?

_____

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PHYSIOLOGICAL PROFILE AT ADMISSION

Systolic blood pressure (SBP - mmHg) _____

(SBP on arrival to S12)

Diastolic blood pressure (DBP - mmHg) _____

(DBP at admission to S12)

Heart rate (bpm) _____

(Heart rate at admission to S12)

Respiratory rate (bpm) _____

(RR at admission to S12)

SaO2 (%) _____

(First recording of SaO2 upon admission to S12)

Temperature (degrees celsius) _____

(Temperature at admission to s12)

Blood glucose (mmol/L) _____

Was a blood gas done in S12? Yes No

pH _____

pCO2 _____

pO2 _____

HCO3 _____

base excess (BE) _____

Lactate _____

ACUTE MANAGEMENT IN S12

Did this patient require any cardiac interventions? Yes No

If yes, please select which cardiac interventions Fluid bolus

this patient received Inotropes

Adrenaline

Other

If 'Other' selected, please specify _____

Did this patient require any respiratory interventions?

Yes No

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If 'Yes', please select which respiratory NPO2 intervention(s) did this patient received FMO2

CPAP

HiFlow

IPPV

BMV

Other

If 'Other' selected, please specify _____

Was the patient given sedation? Yes

No

If 'Yes', what sedating agent was given? Ketamine
Etomidate
Propofol
Other
If 'Other', please specify the name of the sedating _____
agent used
Was the patient given a muscle relaxant? Yes
No
If 'Yes', which muscle relaxant was given to the Cisatracurium
patient? Suxamethonium
Other
If 'Other', please specify the name of the muscle _____
relaxant

SEIZURE TERMINATION

Did the seizure(s) arrest is S12? Yes No
(Did the seizure arrest while the patient was
being managed in S12?)
If 'No', where did the patient SE terminate? _____
Time of seizure arrest _____
(Range within +/- 5min)
Post-ictal level of consciousness (LOC) Alert
Drowsy
Sedated
Unknown / Not recorded

POST S12 MANAGEMENT

Where was this patient referred to after S12? Discharged S11
PICU High-care B1
B2 E1 E2
(Where was the patient taken after receiving
initial management in S12?)
Did they have subsequent seizures during their
admission?
Yes No
If 'Yes', how many breakthrough events did they have? _____

Please specify the details of each breakthrough
event(s)
_____
Please specify how the breakthrough seizure(s) was
managed
_____

Paediatric intensive care unit (PICU)

Was the patient admitted to the PICU during this
admission?
Yes No
If 'Yes', what date was the patient admitted to the _____
PICU?
If 'Yes', what time was the patient admitted to the _____
PICU?
Please specify the reason for admission to the PICU
_____
Date of 1st PICU discharge _____
Did the patient receive further anti-convulsant

treatment while in PICU?
Yes No
If 'Yes', specify the anti-convulsant treatment given
_____
Where was the patient referred to after the PICU? Discharged S11
PICU High-care B1
B2 E1 E2 Unknown / Not
recorded
DIAGNOSIS
Axis 1: Semiology Generalised convulsive
Focal onset evolving into bilateral CSE
Unknown focal or generalised
(see ILAE 2015 Guildelines - A.1 convulsive SE)
Axis 2: Aetiology Acute (infectious, stroke, etc)
Remote (post-encephalitis, post-stroke, etc)
Progressive (tumour, PME, etc)
Electroclinical syndrome
Unknown
(see ILAE 2015 Guidelines)
Axis 4: Age Neonatal (0 to 30 days)
Infancy (1 month to 1 years)
Childhood (> 1 to 12 years)
Adolescence and adulthood (> 12 to 59
years)
(see ILAE 2015 Guidelines / WHO criteria)

Did the patient have a imaging done during this
admission?
Yes No
If 'Yes', what type of imaging did this patient
receive?
Skull Xray Ultrsound
CT MRI
What were the major findings on imaging? Normal
Oedema
Infarction
Hydrocephalus
TBM
Neurocysticercosis
Other
If 'Other', please specify
_____
Did the patient have a lumbar puncture done during
this admission?
Yes No
Polymorphs _____
Lymphocytes _____
Red blood cells _____
Glucose _____
Protein _____
Gram stain _____
Culture result Negative Positive
Unknown / Not reported

Not done
If culture positive, what were the findings?
_____
Did this patient have an EEG done during this admission?
Yes No
If 'Yes', when did the patient have the EEG? _____
Was epileptic activity seen on the EEG?
_____
EEG: Location of activity Generalized (incl. bilateral synchronous patterns) Surpressed
Lateralized Bilateral independent
Multifocal Unknown
Not described
EEG: Name of pattern Periodic discharges Rhythmic delta activity Spike-and-wave/sharp-and-wave
plus subtypes Unknown
Not described

EEG: Morphology
_____
(sharpness, number of phases (e.g. triphasic morphology), absolute and relative amplitude, polarity, unknown, not described.)
EEG: Time-related features
_____
(prevalence, frequency, duration, daily pattern duration and index, onset (sudden vs. gradual), and dynamics (evolving, fluctuating, or static), unknown, not described.)
EEG: Modulation Stimulus-induced Spontaneous
Unknown Not described
EEG: Effect of intervention (medication) on EEG
_____
(If described.)
Was a urinalysis performed at admission? Yes No
(Not recorded is taken to mean not performed)
If 'Yes', what were the significant results of the urinalysis?
_____
(Report as 'normal' if no significant findings)
Was a mantoux test performed during this admission? Yes No
(Not recorded is taken to mean not performed)
If 'Yes', what was the result of the mantoux test? Negative Postive
Unknown / Not recorded
(negative if < 5mm, postitive if equal / greater than 10mm (HIV negative) or equal / greater than 5mm (HIV positive))
Did the patient receive a CXR during this admission? Yes No
If 'Yes', what were the results of the CXR Yes No
(If no significant findings, report as normal)
Did this patient have blood tests done during this admission?

Yes No
If 'Yes', what blood test(s) where done? U&E
FBC
CRP
LFT
Blood culture
Tox screen
Other
If 'Other', please specify which tests were done _____
What were the significant results of these tests?
_____
(please include Mg, Ca, Pi, ALT (if available) as
well as other significant results)

PAST MEDICAL HISTORY
Has this patient previously been admitted to RXH
presenting with seizures or SE?
Yes No
If 'Yes', when was the last admission for seizures or _____
SE?
Is this patient a known epileptic? Yes No
If 'Yes', which service is currently responsible for RXH Neurology
managing this patient's epilepsy? Medical OPD
Private paediatrician / paediatric neurologist
Other
If 'Other', please specify which service is currently
responsible for this patient's epilepsy care?
_____
If 'Yes', what type of epilepsy does this patient
have?
Underlying epilepsy aetiology Genetic Structural
Metabolic Immune
Infectious Unknown
Does this patient have an epileptic encephalopathy
(EE)?
Yes No
If 'Yes', which category of EE does this patient fall
into?
Dravet Epileptic spasms
Burst surpression (EOEE)
Unknown
Is the patient on AEDs? Yes No
What AEDs is the patient on? Valproate
Lamotrigine
Carbamazepine
Phenobarbitone
Levetiracetam
Vigabatrin
Other
If 'Other', please specify which AED(s) the patient
is currently receiving
_____
Please specify the name, dose, route / frequency of

the AED(s)
_____
New line for each AED
EXAMPLE:
valproate / 10mg / PO / BD
lamotrigine / 5mg / PO / daily
HIV status Positive Negative
Unknown
If 'Positive', what is the patient's latest viral _____
load count?

If HIV positive, is the patient on ART? No Yes Unknown
Not recorded
Is the patient HIV exposed? No Yes Unknown / Not recorded
If 'Yes', please specify how the patient is HIV
exposed?
_____
Known cerebral palsy? Yes No
Known developmental delay? Yes No
Has this patient ever had TB? Yes No
If 'Yes', where was the main TB infection? Pulmonary
Meningitis
Abdominal
Other
If 'Other', please specify _____
Previous traumatic brain injury? Yes No
If 'Yes', when did the patient have the traumatic _____
brain injury?
Does this have patient have any other neurological
conditions?
Yes No
If 'Yes', please specify? _____
Does this patient have any other chronic medical
conditions?
Yes No
(Any other chronic medical condition.)
If 'Yes', please specify? _____
Is this patient on any chronic medication? Yes No
If 'Yes', please specify?
_____
(include name, dose, route of administration,
frequency)
PERINATAL HISTORY
Were there any problems during the pregnancy? Yes No
If 'Yes', please specify
_____
Gestational age at birth Pre-term (< 37 weeks)
Term (37 - 42 weeks)
Post-term (>42 weeks)
Unknown / lost RTHC

Where was the patient born? Home

MOU
Level 1 hospital
Level 2 hospital
Level 3 hospital
Other
Unknown / Not recorded / Lost RTHC
If 'Other', please specify where exactly the patient was born and whether they were born before arrival to a healthcare facility? _____
Birth weight (kg) _____
Mode of delivery NVD
Assisted
Caesarian section
Unknown / Not recorded / Lost RTHC
If caesarian was done, was it an elective or Elective emergency procedure? Emergency
If an 'Emergency' caesarian was performed, what was _____ the indication?
Did this patient suffer from HIE? No
Yes
Unknown / lost RTHC
If 'Yes', please specify severity (Sarnat staging) Grade I (mild)
Grade II (moderate)
Grade III (severe)
Unknown
Were their other complications during the neonatal No period? Yes
Unknown / lost RTHC
If 'Yes', please specify
_____

FINAL COMMENTS

Final comments - any interesting / relevant features about this patinet
_____
(other health concerns; known learning difficulties; other routinely used medications, etc)

Appendix 3: 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.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

05 September 2017

HREC REF: 622/2017

Prof J Wilmshurst
Department of Paediatric Neurology
5th Floor, ICH Building
School of Child & Adolescent Health
Red Cross Children's Hospital

Dear Prof Wilmshurst

PROJECT TITLE: DEMOGRAPHIC AND AETIOLOGICAL FACTORS OF PAEDIATRIC STATUS EPILEPTICUS AT REDCROSS WAR MEMORIAL CHILDREN'S HOSPITAL- LINKED TO 297/2005 (MMED CANDIDATE- SARAH NSANTA)

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 September 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: S Nsanta 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 HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

TBurgess

pp **PROFESSOR M BLOCKMAN**
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

1501

Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 622/2017

1502

1503

Ethics Renewal

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017:

Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.9.22
☐ Not approved	See attached comments		

HUMAN RESEARCH ETHICS COMMITTEE
20 SEP 2021
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Signature Chairperson of the HREC/
Designee Date Signed 21/7/2021

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	16 September 2021		
HREC REF Number	622/2017	Current Ethics Approval was granted until	31/07/2021
Protocol title	Demographic and aetiology of paediatric status epilepticus at Red Cross War Memorial Children's hospital- linked to 297/2005(MMED candidate Sarahlouise Nsanta)		
Principal Investigator	Professor J.M Wilmshurst		
Department / Office Internal Mail Address	Department of Paediatric Neurology,5th Floor ICH Building, School of Child and Adolescent Health, Red Cross Hospital		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☐ ✓ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☐✓	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	

1507

NIL

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		283
Total number of records or specimens collected, reviewed or stored since last progress report		283
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	✓ □ Yes	□ No

4. Signature *SNsanta*

Signature of PI		Date	16/09/2021

Research day abstract presented on 30th October ,2019 is attached.

Appendix 4: Author guidelines - South African Journal of Child Health

SAJCH Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

To submit a manuscript, please proceed to the *SAJCH* Editorial Manager website: Editorial Manager

There is currently a backlog of articles in production. Authors submitting new articles should note that the earliest date for publication will be in the second quarter of 2022.

To access and submit an article already in production, please see the SAJCH author guidelines here.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

Article Processing Charges

All articles published in the South African Journal of Child Health are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging an article-processing charge (APC) of R3 275.40 (ex Vat) for all articles published. The charge applies only to Research articles submitted after 1 Jan 2019. The APC is standard and does not vary based on length, colour, figures, or other elements.

When submitting a Research article to the SAJCH, the submitting author must agree to pay the APC should the article be accepted for publication. The APC is payable when your manuscript is editorially accepted and before production commences for publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received.

Queries can be directed to claudian@hmpg.co.za.

Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is applicable. Queries can be directed to dianes@hmpg.co.za or claudian@hmpg.co.za

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met for an individual to be included as an author (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Clinical trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAJCH* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Protection of rights to privacy

Patient

Information that would enable identification of individual patients should not be published in written descriptions, photographs, radiographs and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

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Privacy statement

The *SAJCH* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to any third party without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAJCH* or its publisher HMPG on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that

socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note thatit is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAJCH is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAJCH* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this requirement are Editorials, Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).

- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAJCH is a Journal on child health, therefore for articles involving genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions

- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

- May include up to 3 illustrations or tables.
- A max of 20 - 25references

Structured abstract

- This should be no more than 250words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
    - Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
    - Do not include any references in the abstracts.

Here is an example of a good abstract.

***Scientific letters*/short reports**

These include case reports, side effects of drugs and brief or negative research findings.

Guideline word limit: 1500 words

- Abstract: unstructured, of about 100-150 words
- May include only one illustration or table
- A maximum of 6 references

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

Review articles

Review articlesshould always be discussed with the Editor prior to submission.

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners. They should be aligned to practice in South and/or sub-Saharan Africa and not a precis of reviews published in the international literature

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 400 words

Letters to the editor should relate either to a paper or article published by the SAJCH or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.

- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.

- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.

- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.

- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.

- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.

- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.

- Ensure each table has a concise title and column headings, and include units where necessary.

- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make ‘new rows’:

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting..*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]

- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'url =' copy the URL between { }.
    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx/doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.

- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

- Legal references

- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.

- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.

- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the *SAJCH* requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
    - Anonymous manuscript (unless otherwise stated)
    - Author Agreement form [forthcoming]
    - Manuscript
    - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
    - Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer Review Process

All manuscripts are reviewed initially by the Editor-in-Chief and only those that meet the scientific and editorial standards of the journal, and fit within the aims and scope of the journal, will be sent for external peer review. Each manuscript is reviewed by either one or two reviewers selected on the basis of their expertise in the field. A double blind review process is followed at SAJCH.

Authors are expected to receive feedback from reviewers and an editorial decision within approximately 6 weeks of submission. The time period of the entire review process may vary however depending upon the quality of the manuscript submitted, reviewers' responses and the time taken by the authors to submit the revised manuscript.

Manuscripts from review may be accepted, rejected or returned to the author for revision or resubmission for review. Authors will be directed to submit revised manuscripts within two months of receiving the editor's decision, and are requested to submit a point by point response to the reviewers' comments. Manuscripts which authors are requested to revise and resubmit will be sent for a second round of peer review, often to the original set of reviewers. All final decisions on a manuscript are at the Editor's discretion.

Production process

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).

2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.

3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.

4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.

5. The CE will finalise the article and then it will be typeset.

6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.

7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.

8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish anerratum in the next issue. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of HMPG. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Appendix 5: Turnitin Report