

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

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NSNSAR001

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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

South African Journal of Child Health (SAJCH), an online, quarterly, peer-reviewed medical journal. SAJCH is DoHET accredited

1 ABSTRACT

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

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

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

12 **Results:**

13 Of 119 children, 63 (53%) were male; their median age was 29.6 (IQR 14.8-76.1) months: 22
14 (18%) were under one year of age, 63 (53%) were 1-5 years, and 34 (29%) >5 years. There
15 were 31 (26%) children who were moderately-severely underweight-for-age; 5 (4%) children
16 were HIV-infected. Fifty (42%) children were known to have epilepsy of whom ten reported
17 poor compliance with their antiseizure medication, 20 (17%) children had cerebral palsy, 40
18 (34%) had developmental delay, and nine (8%) had a history of previously treated tuberculosis
19 (TB)- of whom six had pulmonary TB, one TBM, one with extrapulmonary TB and one with
20 disseminated TB. During the captured episode of CSE, 55 (51%) children were brought by
21 ambulance, the rest self-presented using private or hired transport; 33 children received a
22 benzodiazepine agent pre-hospital, 19 had aborted by the time of arrival at hospital, but 72
23 (62%) required antiseizure medication in the ED. In their seizure semiology, 82 (71%) children
24 had generalised convulsive seizures and 34 (29%) had focal seizures; with 85 (73%) being
25 prolonged events and 32 (27%) being multiple events. Aetiology according to ILAE classified
26 74 (62%) as secondary to acute infective cause, 12 (10%) had an electroclinical syndrome, 9
27 (8%) were remote and 25 (22%) were unknown. A recorded tympanic membrane temperature
28 of $\geq 38^{\circ}\text{C}$ was found in 41 (37%) of 112 children, supporting a diagnosis of febrile status
29 epilepticus in these children. Imaging was undertaken in 45/119 (38%), with 28 (62%) being
30 abnormal. Cerebral spinal fluid findings were abnormal in 7 (12%) of 57 children who had

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

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

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Chapter 1: Publication-Ready Format

41

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43 **Title page**

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

46

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85 **Abstract**

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

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

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

94 **Results:** Of 119 children, 63 (53%) were male; their median age was 29.6 (IQR 14.8-76.1)
95 months: 22 (18%) were <12-months, 63 (53%) were 1-5 years, and 34 (29%) >5years. Thirty-
96 one (26%) were moderately-severely-underweight-for-age and 5 (4%) were HIV-infected. In
97 seizure semiology, 82 (71%) had generalised convulsive seizures and 34 (29%) had focal
98 seizures; with ILAE-classified aetiology 74 (62%) were secondary to acute infective cause, 12
99 (10%) electroclinical syndrome, 9 (8%) remote and 25 (22%) were unknown. A recorded
100 tympanic membrane temperature of $\geq 38^{\circ}\text{C}$ was found in 41 (37%) of 112 children, supporting
101 the diagnosis of febrile status epilepticus in these children. Fifty (42%) were known with
102 epilepsy related breakthrough seizures. Imaging was abnormal in 28 (62%) of 45 children.
103 Cerebrospinal fluid findings were abnormal in 7 (12%) of 57 children. Most children, 87 (75%),
104 were stabilised adequately for admission in the short stay ward, however eight required
105 admission to the ICU. No deaths were recorded in the cohort.

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

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

109

110

111 INTRODUCTION

112 Convulsive Status Epilepticus (CSE) is defined as continuous seizure activity without an
113 arresting phase or recurrent seizures without regaining consciousness in between for more than
114 5 minutes.^[1] There is a variance with the estimated prevalence and mortality of paediatric CSE.
115 It has been noted that the rates tend to be higher in the first few years of life.^[2-7] Further, a
116 similarity in these rates has been observed in studies conducted across high-income countries
117 ^[8]. Paediatric CSE is considered to be a serious medical emergency worldwide associated with
118 morbidity and death.^[9,12]

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

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

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

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

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

155

156 **METHODOLOGY**

157 **Study Design and participants**

158 This retrospective descriptive study was conducted over a 24-month period (May 2016- May
159 2018) at Redcross War Memorial Children's Hospital (RWMCH), in Cape Town. All children
160 presenting in CSE were included in the study.

161 **Study Setting**

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

171

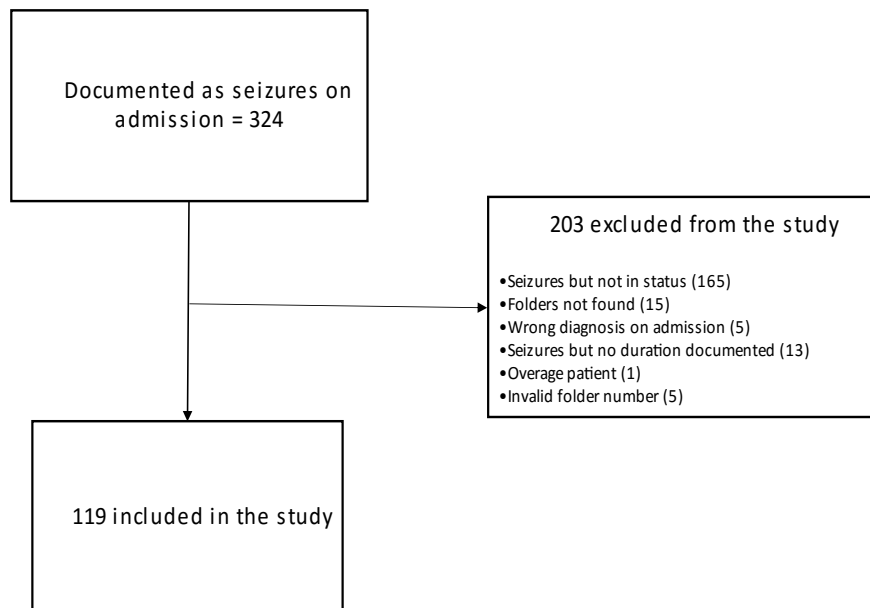
172 **Data collection**

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

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

185

186 **Figure 1: Flow diagram of the study recruitment process**



187

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

194

195 **Definitions**

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

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

203

204 **Statistical Analysis**

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

210 **Ethics and Consent**

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

215

216 **RESULTS**

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

222

223

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225

226 **Table 1: Demographics of children presenting with convulsive status epilepticus**

227

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)

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

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

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

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

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

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

255

256

257

258 **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)

259

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

261 A recorded tympanic membrane temperature of $\geq 38^{\circ}\text{C}$ was found in 41 (37%) of 112
 262 children. The final diagnosis at discharge in 74 children in CSE with an acute infectious
 263 aetiology is as illustrated in **Table 3**. Forty-seven of those with an infectious aetiology had an
 264 upper respiratory tract infection. Thirteen had a lower respiratory tract infection, 7 had a CNS
 265 infection, 5 had acute gastroenteritis and other infections included otitis media (4), urinary
 266 tract infection (1), neurocysticercosis (1) and congenital cytomegalovirus (CMV) infection
 267 (1).

268

269

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

Diagnosis associated with CSE	Number (%)
Upper respiratory tract infection (pharyngitis, tonsillitis, 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

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

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

274

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

281

282 **DISCUSSION**

283 In this study we have been able to describe the demographics and aetiologies of CSE in 119
 284 children who accessed care at a public children’s tertiary hospital in an African setting. Our
 285 study found that 22 (19%) of our child cohort were infants. This is similar to a cross-sectional
 286 study from Iran by Barzegar et al.,^[21] where 20.9% of their 43 children (under the age of 15
 287 years) were less than 12 months of age. These results support that children less than 1 year are
 288 more affected by CSE. This can be attributed to the enhanced excitation of the immature brain,
 289 which further renders the developing brain more susceptible to seizures. According to Epstein
 290 et al.,^[24] younger children have a lower threshold to seizures, especially febrile seizures at
 291 lower febrile temperatures. Gurcharran et al., in a multi-centre population-based study also
 292 noted that the peak age incidence of CSE in children in Virginia, Minnesota and London was
 293 less than one year.^[9] Other studies from Iran^[21], Taiwan^[22] and London^[23] showed that 21
 294 (46.5%), 73 (51.8%) and 76 (55%) respectively of children were in the age category of 1-5

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

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

310 A recorded tympanic membrane temperature of $\geq 38^{\circ}\text{C}$ was noted in 37% of our patients.
311 Similarly, a multicentred study of 3 785 Chinese children (aged 29 days to 18 years) reported
312 36.8% (1 385)^[27] were pyrexial, and a Kenyan study reported 48% of their confirmed CSE
313 cases presented with a fever.^[12] Though we do not routinely test for human herpes virus 6/7,
314 it has been identified as one of the common causes of fever in young children presenting with
315 febrile status epilepticus.^[24]

316 In terms of transportation and referrals, 43% of our children utilised private transport whereas
317 48% of the patients were self-referred. This gives us an indication that children who self-
318 present or use private transport are less likely to receive antiseizure medication prior to arriving
319 at a health facility and this increases the likelihood of having a prolonged seizure. This was
320 supported by the fact that only 33 out of the 119 actually received a benzodiazepine pre-
321 hospital. Though we could not calculate the exact time to intervene, we can conclude that it
322 was prolonged based on the mode of transportation, self-referrals from home and the small
323 number receiving benzodiazepines prior to hospital arrival. This is further supported by a study
324 done in South Africa^[16] in which the time to intervene was calculated at 50 minutes. In some

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

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

339 The seizure semiology (**Table 2**) was varied with generalised tonic-clonic being the most
340 common accounting for 71% of our patients. This finding was in accordance with previous
341 reports by Wang et al., from China who described 66% (2317) of their cohort aged 1 month to
342 18 years as having generalised tonic clonic seizures.^[27] In the same Chinese study, acute
343 symptomatic aetiology of SE accounted for 42.8% (1 819), with an unknown aetiology
344 accounting for more than half of their cases 58.8% (2 503), electroclinical syndrome 1.6%, and
345 progressive aetiology 0.6%. By contrast, our study had a higher number of acute symptomatic
346 aetiology at 62% and our unknown aetiology only accounted for 21%. Our electroclinical
347 syndromes and progressive aetiology cases were much higher at 10% and 8% respectively. An
348 8-year retrospective analysis of 76 South African children (aged 1 month to 13 years) admitted
349 to a tertiary paediatric intensive care unit (PICU) with CSE reported a much higher acute
350 symptomatic aetiology at 80%.^[14]

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

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

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

364 Most of our cohort with an acute infection (60 out of 74) had a diagnosis at discharge
365 documented as respiratory tract infection. This included pharyngitis, tonsillitis, sinusitis and
366 pneumonia. According to a review article by Bomwalhd et al., respiratory viral infections can
367 be associated with neurological manifestations such as seizures and status epilepticus.^[35] Viral
368 respiratory diseases are a critical health problem and account for the high rates of morbidity
369 and mortality predominantly in the immunocompromised, young children, and the elderly.^[36]
370 Acute gastroenteritis accounted for five of our patients. Similarly, a review article by Kim from
371 Korea described children with mild acute gastroenteritis who presented with both febrile and
372 afebrile seizures.^[37] Though we did not dwell on the specific aetiology of the acute
373 gastroenteritis, Higuchi et al., from Japan described the clinical features of convulsions with
374 rotavirus and norovirus gastroenteritis as similar, except for fever.^[38] A case-control study of
375 165 children aged 6 months to 5 years, conducted by Mayhar et al., in Iran showed that there
376 was a significant link between urinary tract infections and febrile seizures.^[39] Our cohort
377 reported one patient who presented in status epilepticus with a proven diagnosis of a urinary
378 tract infection.

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

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

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

405 The zero mortality rate in this study was comparable to that reported by high income settings,
406 as illustrated by an epidemiological study of 120 children (1 month to 15 years) from Japan^[44]
407 and a 5-year retrospective review of 137 children (aged 1 month to 15 years) admitted to the
408 paediatric ICU (PICU) in London.^[23] This could be attributed to the fact that our patients are
409 able to access treatment within 5 minutes of admission to the emergency ward^[16] and the
410 hospital staff are able to manage CSE appropriately. In contrast, studies from Nigeria,^[43] Kenya
411 ^[12], Pakistan ^[45] and India ^[33] have reported high mortality at 23%, 22%, 11% and 31%
412 respectively. Deaths can be attributed to the underlying cause of CSE or as a result of the
413 complications of the CSE itself ^[33] and infective causes are associated with an increased risk
414 of mortality.^[3,6,7] Increase in mortality in resource poor countries can be attributed to
415 unorthodox cultural practices where patients with CSE are taken to traditional healers prior to
416 seeking medical attention.^[28] Kumar et al., also highlighted poor literacy and the lack of
417 transport which delays accessing treatment. ^[33] This results in a prolonged time interval from

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

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

426 Based on our study findings and the above comparisons, we conclude that the aetiological
427 spectrum of CSE in resource limited countries is divergent when compared to resource
428 equipped countries. The aetiologies differ further within the sub-Saharan African setting due
429 to local endemic influences as in the case of malaria, tuberculosis and neurocysticercosis.
430 ^[3,12,40,43,45] Notably, whereas these comparisons were made within a similar population group,
431 the definitions of CSE differed and therefore we may have deviations from the methodologies
432 and the directness of the study question.

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

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

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

450 **Study limitations**

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

460

461 **RECOMMENDATIONS AND CONCLUSION**

462 **Recommendations**

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

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

475 **Conclusion:**

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

481

482 **Declarations:**

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487 patients- the children from whom we learn so much.

488 **Author contributions**

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

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498

499 **Conflicts of interest:**

500 The authors declare there are no conflicts of interest.

501

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Chapter Two: Appendices

660 **Appendix 1: Research protocol**
661 **DEMOGRAPHIC AND AETIOLOGICAL FACTORS OF PAEDIATRIC STATUS**
662 **EPILEPTICUS AT REDCROSS WAR MEMORIAL CHILDREN’S HOSPITAL**

663

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681

682 **ABBREVIATIONS**

683 CNS Central Nervous System

684 CSE Convulsive Status Epilepticus

685 EEG Electroencephalogram

686 ILAE International League Against Epilepsy

687 JICNA Journal of the International Child Neurology Association

688 LICE Italian League Against Epilepsy

689 RCWMCH Red Cross War Memorial Children's Hospital

690 SE Status Epilepticus

691 WMA World Medical Association

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704 **GLOSSARY OF TERMS**

705 **1)International League Against Epilepsy(ILAE)**

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

711 The **goals** of the ILAE are:

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

716

717 **2)Italian League Against Epilepsy(LICE)**

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

722 **3)Electroencephalogram(EEG)**

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

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Appendix 1: Synopsis

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748

749 **PURPOSE OF THE STUDY**

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

752 **BACKGROUND**

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

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

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

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

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

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

794 A hospital based retrospective study in Western Nepal by Adhikari et al., reported that CNS
795 infections and acquired epilepsy are the main cause of seizures in resource poor countries and
796 geographical variations determine common aetiology in a particular region. (11) (15) Human
797 Herpes simplex virus 6 and 7 have been highlighted as an aetiological factor in febrile status
798 epilepticus. Of 199 children evaluated, HHV-6 or HHV-7 status could be determined in 169
799 (84.9%) and it accounted for one third of the FSE cases. (12)

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

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

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

812 **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

--	--	--

813

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

815

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

818 1) Semiology

819 2) Aetiology

820 3) EEG correlates

821 4) Age

822 The purpose of the diagnostic axes is to provide a framework for clinical diagnosis,
823 investigation and therapeutic approaches for each patient. At least half of patients presenting
824 with status epilepticus do not have epilepsy or specific epilepsy syndromes but have seizures
825 due to acute or remote CNS or systemic illness hence the axes used previously in seizure
826 classification were modified for the classification of status epilepticus. (15) In a resource-
827 limited paediatric setting a different hypothesis may be drawn. Currently there is little data on
828 the aetiological and demographic factors that play a role in paediatric status epilepticus in sub-
829 Saharan Africa, specifically, South Africa. Most research undertaken is from high income
830 countries and it is not known if these trends also apply to resource limited sub-Saharan African
831 countries. The data collected will be important in that it is required for decision making
832 purposes on allocation of resources and may be used to develop preventative strategies of SE.
833 (18)

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

836 **HYPOTHESIS**

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

839 **OBJECTIVES**

840 **a) PRIMARY**

841 1) Establish the major causes of CSE in our population

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

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

845

846 **b) SECONDARY**

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

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

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

850 **Study Population**

851 Inclusion criteria:

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

854 Exclusion criteria:

- 855 • children not in status epilepticus

856

857 **METHODOLOGY**

858 **Study Design**

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

861 **Study Site**

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

867 **Sample Size**

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

869 **Data collection**

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

876 **Statistical Analysis**

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

884 **Ethics and Consent**

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

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

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

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

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

899 **Limitations**

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

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

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

907 **Risks or Benefits to participation**

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

912 **Budget**

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

914 **Table 2: Budget**

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

915

916 **Study Time Frame**

917 **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

918

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- 964
- 965
- 966

967 **Appendix 2: Data capture sheet**

968

969 *Confidential*

970 *Paediatric Convulsive Status Epilepticus Study*

971 *Page 1 of 12* **first_admission**

972 Record ID _____

973 **PROTOCOL INFORMATION**

974 Was the patient recruited into the PHB vs PHY/MDZ
975 study?

976 Yes No

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

979 _____

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

982 What treatment arm was the patient allocated to Protocol 1 - Phenobarbitone

983 Protocol 2 - Phenytoin/Midazolam

984 (The treatment patient was randomised to upon
985 pulling the study envelope.)

986 **PATIENT INFORMATION**

987 Surname _____

988 Initials _____

989 (first letter of first name(s))

990 Folder number _____

991 Sex Male Female

992 Date of birth _____

993 Postal code _____

994 (area of residence)

995 **ANTHROPOMETRY**

996 Weight (kg) _____

997 Weight-for-age (Z) 2; < 3

998 >3

999 Height / length (cm) _____

1000 Height / length for age (Z) 2; < 3

1001 >3

1002 Weight-for-height (Z) 2; < 3

1003 >3

1004 Head circumference (cm) _____

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1006 *Confidential*

1007 *Page 2 of 12*

1008 Was a MUAC recorded? Yes

1009 No

1010 If 'Yes', what was the MUAC (cm)? _____

1011 CP charts used? No

1012 Yes

1013 Unknown / not recorded

1014 Down's syndrome charts used? No

1015 Yes,

1016 Unknown / not reported

1017 **ADMISSION DETAILS**

1018 Date of admission _____

1019 Time of admission to S12 _____

1020 Referral source Unreferred (self) Private GP

1021 Level 1 hospital Level 2 hospital

1022 Other

1023 If 'Other', please explain where the patient was _____

1024 referred from

1025 How did the patient get to RXH S12? Walk in Ambulance

1026 Private vehicle Other

1027 If 'Other', please specify how the patient got to the _____

1028 S12

1029 **SEIZURE INFORMATION**

1030 Time of seizure onset _____

1031 (time first seizure started)

1032 Did the seizure start upon admission to S12? Yes

1033 No

1034 Seizure type Focal Generalised

1035 Other

1036 (type of seizure according to initial onset - if

1037 starts focal and progresses to secondary

1038 generalisation, record as focal)

1039 If 'Other', please specify the type of seizure

1040 _____

1041 Seizure nature Prolonged event Multiple / recurrent

1042 events

1043 (one prolonged event or multiple / recurrent

1044 events with no recovery to baseline cognitive

1045 function in-between)

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1048 *Page 3 of 12*

1049 Semiology

1050 _____

1051 (Comment on onset and progression of seizure.)

1052 Did this patient receive treatment prior to admission

1053 to S12?

1054 Yes No

1055 (Any treatment received before admission to S12.

1056 This includes any intervention administered by

1057 caregivers, ambulance staff or from healthcare

1058 workers at the referring centre.)

1059 If 'Yes', what anti-convulsant treatment did the

1060 patient receive prior to S12 admission?

1061 Diazepam Lorazepam

1062 Midazolam Other

1063 (If the patient has received PHB or PHY prior to

1064 admission, they are not eligible for this study.)

1065 If 'Other', please explain what anticonvulsant the _____

1066 patient received

1067 What dose of medication did the patient receive? _____

1068 (mg, ml, etc)

1069 How many doses did the patient receive before _____

1070 admission?

1071 What was the route of administration? Intravenous (IV) Per rectal (PR)

1072 Intra-muscular (IM) Sublingual (SL)

1073 Intra-nasal (IN)

1074 **ANTI-CONVULSANT MANAGEMENT IN S12**

1075 Agent 1 drug Lorazepam Diazepam

1076 Midazolam Other

1077 None

1078 (First drug given given to patient to arrest

1079 seizures)

1080 If 'Other', please specify which agent 1 was given _____

1081 Agent 1 dose given (mg) _____

1082 Agent 1 time given _____

1083 Agent 1 route of administration Intravenous (IV) Per rectal (PR)

1084 Sublingual (SL) Intra-muscular (IM)

1085 Infusion

1086 Agent 2 drug Lorazepam Diazepam

1087 Midazolam Other

1088 None

1089 If 'Other', please specify which agent 2 was given _____

1090 Agent 2 dose given (mg) _____

1091 Agent 2 time given _____

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1094 *Page 4 of 12*

1095 Agent 2 route of administration Intravenous (IV) Per rectal (PR)

1096 Sublingual (SL) Intramuscular (IM)

1097 Infusion

1098 Agent 3 drug Phenobarbitone Phenytoin

1099 Midazolam Other

1100 None

1101 If 'Other', please specify which agent 3 was given _____

1102 Agent 3 dose given (mg) _____

1103 Agent 3 time given _____

1104 Agent 3 route of administration Intravenous (IV) Per rectal (PR)

1105 Sublingual (SL) Intramuscular (IM)

1106 Infusion

1107 Agent 4 drug Phenobarbitone Phenytoin

1108 Midazolam Other

1109 None

1110 If 'Other', please specify which agent 4 was given _____

1111 Agent 4 dose given (mg) _____

1112 Agent 4 time given _____

1113 Agent 4 route of administration intravenous (IV) per rectal (PR)

1114 sublingual (SL) intramuscular (IM)

1115 infusion

1116 Agent 5 drug Phenobarbitone Phenytoin

1117 Midazolam Other

1118 None

1119 If 'Other', please specify which agent 5 was given _____

1120 Agent 5 dose given (mg) _____

1121 Agent 5 time given _____

1122 Agent 5 route of administration Intravenous (IV) Per rectal (PR)

1123 Sublingual (SL) Intramuscular (IM)

1124 Infusion

1125 Level of intervention reached level 1 (benzodiazepine)

1126 level 2 (phenytoin or phenobarbitone)

1127 level 3 (midazolam infusion)

1128 level 4 (induced coma)

1129 (What level of intervention (1-4) did this patient
1130 reach before seizure activity was fully arrested)
1131 Deviation from study protocol Yes No
1132 (Did this patient management deviate from what is
1133 prescribed in allocated protocol?)
1134 If 'yes', please explain how the patient deviated
1135 from the protocol allocated to them?
1136 _____
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1138 **Confidential**
1139 *Page 5 of 12*
1140 **PHYSIOLOGICAL PROFILE AT ADMISSION**
1141 Systolic blood pressure (SBP - mmHg) _____
1142 (SBP on arrival to S12)
1143 Diastolic blood pressure (DBP - mmHg) _____
1144 (DBP at admission to S12)
1145 Heart rate (bpm) _____
1146 (Heart rate at admission to S12)
1147 Respiratory rate (bpm) _____
1148 (RR at admission to S12)
1149 SaO2 (%) _____
1150 (First recording of SaO2 upon admission to S12)
1151 Temperature (degrees celsius) _____
1152 (Temperature at admission to s12)
1153 Blood glucose (mmol/L) _____
1154 Was a blood gas done in S12? Yes No
1155 pH _____
1156 pCO2 _____
1157 pO2 _____
1158 HCO3 _____
1159 base excess (BE) _____
1160 Lactate _____
1161 **ACUTE MANAGEMENT IN S12**
1162 Did this patient require any cardiac interventions? Yes No
1163 If yes, please select which cardiac interventions Fluid bolus
1164 this patient received Inotropes
1165 Adrenaline
1166 Other
1167 If 'Other' selected, please specify _____
1168 Did this patient require any respiratory
1169 interventions?
1170 Yes No
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1173 *Page 6 of 12*
1174 If 'Yes', please select which respiratory NPO2
1175 intervention(s) did this patient received FMO2
1176 CPAP
1177 HiFlow
1178 IPPV
1179 BMV
1180 Other
1181 If 'Other' selected, please specify _____
1182 Was the patient given sedation? Yes
1183 No

1184 If 'Yes', what sedating agent was given? Ketamine
1185 Etomidate
1186 Propofol
1187 Other
1188 If 'Other', please specify the name of the sedating agent used _____
1189 agent used
1190 Was the patient given a muscle relaxant? Yes
1191 No
1192 If 'Yes', which muscle relaxant was given to the Cisatracurium
1193 patient? Suxamethonium
1194 Other
1195 If 'Other', please specify the name of the muscle relaxant _____
1196 relaxant
1197 **SEIZURE TERMINATION**
1198 Did the seizure(s) arrest is S12? Yes No
1199 (Did the seizure arrest while the patient was
1200 being managed in S12?)
1201 If 'No', where did the patient SE terminate? _____
1202 Time of seizure arrest _____
1203 (Range within +/- 5min)
1204 Post-ictal level of consciousness (LOC) Alert
1205 Drowsy
1206 Sedated
1207 Unknown / Not recorded
1208 **POST S12 MANAGEMENT**
1209 Where was this patient referred to after S12? Discharged S11
1210 PICU High-care B1
1211 B2 E1 E2
1212 (Where was the patient taken after receiving
1213 initial management in S12?)
1214 Did they have subsequent seizures during their
1215 admission?
1216 Yes No
1217 If 'Yes', how many breakthrough events did they have? _____
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1219 *Confidential*
1220 *Page 7 of 12*
1221 Please specify the details of each breakthrough
1222 event(s)
1223 _____
1224 Please specify how the breakthrough seizure(s) was
1225 managed
1226 _____
1227 **Paediatric intensive care unit (PICU)**
1228 Was the patient admitted to the PICU during this
1229 admission?
1230 Yes No
1231 If 'Yes', what date was the patient admitted to the _____
1232 PICU?
1233 If 'Yes', what time was the patient admitted to the _____
1234 PICU?
1235 Please specify the reason for admission to the PICU
1236 _____
1237 Date of 1st PICU discharge _____
1238 Did the patient receive further anti-convulsant

1239 treatment while in PICU?
1240 Yes No
1241 If 'Yes', specify the anti-convulsant treatment given
1242 _____
1243 Where was the patient referred to after the PICU? Discharged S11
1244 PICU High-care B1
1245 B2 E1 E2 Unknown / Not
1246 recorded
1247 **DIAGNOSIS**
1248 Axis 1: Semiology Generalised convulsive
1249 Focal onset evolving into bilateral CSE
1250 Unknown focal or generalised
1251 (see ILAE 2015 Guidelines - A.1 convulsive SE)
1252 Axis 2: Aetiology Acute (infectious, stroke, etc)
1253 Remote (post-encephalitis, post-stroke, etc)
1254 Progressive (tumour, PME, etc)
1255 Electroclinical syndrome
1256 Unknown
1257 (see ILAE 2015 Guidelines)
1258 Axis 4: Age Neonatal (0 to 30 days)
1259 Infancy (1 month to 1 years)
1260 Childhood (> 1 to 12 years)
1261 Adolescence and adulthood (> 12 to 59
1262 years)
1263 (see ILAE 2015 Guidelines / WHO criteria)
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1266 *Page 8 of 12*
1267 Did the patient have a imaging done during this
1268 admission?
1269 Yes No
1270 If 'Yes', what type of imaging did this patient
1271 receive?
1272 Skull Xray Ultrasound
1273 CT MRI
1274 What were the major findings on imaging? Normal
1275 Oedema
1276 Infarction
1277 Hydrocephalus
1278 TBM
1279 Neurocysticercosis
1280 Other
1281 If 'Other', please specify
1282 _____
1283 Did the patient have a lumbar puncture done during
1284 this admission?
1285 Yes No
1286 Polymorphs _____
1287 Lymphocytes _____
1288 Red blood cells _____
1289 Glucose _____
1290 Protein _____
1291 Gram stain _____
1292 Culture result Negative Positive
1293 Unknown / Not reported

1294 Not done

1295 If culture positive, what were the findings?

1296 _____

1297 Did this patient have an EEG done during this

1298 admission?

1299 Yes No

1300 If 'Yes', when did the patient have the EEG? _____

1301 Was epileptic activity seen on the EEG?

1302 _____

1303 EEG: Location of activity Generalized (incl. bilateral synchronous

1304 patterns) Suppressed

1305 Lateralized Bilateral independent

1306 Multifocal Unknown

1307 Not described

1308 EEG: Name of pattern Periodic discharges Rhythmic delta

1309 activity Spike-and-wave/sharp-and-wave

1310 plus subtypes Unknown

1311 Not described

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1314 *Page 9 of 12*

1315 EEG: Morphology

1316 _____

1317 (sharpness, number of phases (e.g. triphasic

1318 morphology), absolute and relative amplitude,

1319 polarity, unknown, not described.)

1320 EEG: Time-related features

1321 _____

1322 (prevalence, frequency, duration, daily pattern

1323 duration and index, onset (sudden vs. gradual),

1324 and dynamics (evolving, fluctuating, or static),

1325 unknown, not described.)

1326 EEG: Modulation Stimulus-induced Spontaneous

1327 Unknown Not described

1328 EEG: Effect of intervention (medication) on EEG

1329 _____

1330 (If described.)

1331 Was a urinalysis performed at admission? Yes No

1332 (Not recorded is taken to mean not performed)

1333 If 'Yes', what were the significant results of the

1334 urinalysis?

1335 _____

1336 (Report as 'normal' if no significant findings)

1337 Was a mantoux test performed during this admission? Yes No

1338 (Not recorded is taken to mean not performed)

1339 If 'Yes', what was the result of the mantoux test? Negative Postive

1340 Unknown / Not recorded

1341 (negative if < 5mm, postitive if equal / greater

1342 than 10mm (HIV negative) or equal / greater than

1343 5mm (HIV positive))

1344 Did the patient receive a CXR during this admission? Yes No

1345 If 'Yes', what were the results of the CXR Yes No

1346 (If no significant findings, report as normal)

1347 Did this patient have blood tests done during this

1348 admission?

1349 Yes No

1350 If 'Yes', what blood test(s) were done? U&E

1351 FBC

1352 CRP

1353 LFT

1354 Blood culture

1355 Tox screen

1356 Other

1357 If 'Other', please specify which tests were done _____

1358 What were the significant results of these tests?

1359 _____

1360 (please include Mg, Ca, Pi, ALT (if available) as

1361 well as other significant results)

1362 04/08/2016 19:58 www.projectredcap.org

1363 **Confidential**

1364 *Page 10 of 12*

1365 **PAST MEDICAL HISTORY**

1366 Has this patient previously been admitted to RXH

1367 presenting with seizures or SE?

1368 Yes No

1369 If 'Yes', when was the last admission for seizures or _____

1370 SE?

1371 Is this patient a known epileptic? Yes No

1372 If 'Yes', which service is currently responsible for RXH Neurology

1373 managing this patient's epilepsy? Medical OPD

1374 Private paediatrician / paediatric neurologist

1375 Other

1376 If 'Other', please specify which service is currently

1377 responsible for this patient's epilepsy care?

1378 _____

1379 If 'Yes', what type of epilepsy does this patient

1380 have?

1381 Underlying epilepsy aetiology Genetic Structural

1382 Metabolic Immune

1383 Infectious Unknown

1384 Does this patient have an epileptic encephalopathy

1385 (EE)?

1386 Yes No

1387 If 'Yes', which category of EE does this patient fall

1388 into?

1389 Dravet Epileptic spasms

1390 Burst suppression (EOEE)

1391 Unknown

1392 Is the patient on AEDs? Yes No

1393 What AEDs is the patient on? Valproate

1394 Lamotrigine

1395 Carbamazepine

1396 Phenobarbitone

1397 Levetiracetam

1398 Vigabatrin

1399 Other

1400 If 'Other', please specify which AED(s) the patient

1401 is currently receiving

1402 _____

1403 Please specify the name, dose, route / frequency of

1404 the AED(s)
1405 _____
1406 New line for each AED
1407 EXAMPLE:
1408 valproate / 10mg / PO / BD
1409 lamotrigine / 5mg / PO / daily
1410 HIV status Positive Negative
1411 Unknown
1412 If 'Positive', what is the patient's latest viral _____
1413 load count?
1414 04/08/2016 19:58 www.projectredcap.org
1415 **Confidential**
1416 *Page 11 of 12*
1417 If HIV positive, is the patient on ART? No Yes Unknown
1418 Not recorded
1419 Is the patient HIV exposed? No Yes Unknown / Not recorded
1420 If 'Yes', please specify how the patient is HIV
1421 exposed?
1422 _____
1423 Known cerebral palsy? Yes No
1424 Known developmental delay? Yes No
1425 Has this patient ever had TB? Yes No
1426 If 'Yes', where was the main TB infection? Pulmonary
1427 Meningitis
1428 Abdominal
1429 Other
1430 If 'Other', please specify _____
1431 Previous traumatic brain injury? Yes No
1432 If 'Yes', when did the patient have the traumatic _____
1433 brain injury?
1434 Does this patient have any other neurological
1435 conditions?
1436 Yes No
1437 If 'Yes', please specify? _____
1438 Does this patient have any other chronic medical
1439 conditions?
1440 Yes No
1441 (Any other chronic medical condition.)
1442 If 'Yes', please specify? _____
1443 Is this patient on any chronic medication? Yes No
1444 If 'Yes', please specify?
1445 _____
1446 (include name, dose, route of administration,
1447 frequency)
1448 **PERINATAL HISTORY**
1449 Were there any problems during the pregnancy? Yes No
1450 If 'Yes', please specify
1451 _____
1452 Gestational age at birth Pre-term (< 37 weeks)
1453 Term (37 - 42 weeks)
1454 Post-term (>42 weeks)
1455 Unknown / lost RTHC
1456 04/08/2016 19:58 www.projectredcap.org
1457 **Confidential**
1458 *Page 12 of 12*
1459 Where was the patient born? Home

- 1460 MOU
- 1461 Level 1 hospital
- 1462 Level 2 hospital
- 1463 Level 3 hospital
- 1464 Other
- 1465 Unknown / Not recorded / Lost RTHC
- 1466 If 'Other', please specify where exactly the patient
- 1467 was born and whether they were born before arrival
- 1468 to a healthcare facility? _____
- 1469 Birth weight (kg) _____
- 1470 Mode of delivery NVD
- 1471 Assisted
- 1472 Caesarian section
- 1473 Unknown / Not recorded / Lost RTHC
- 1474 If caesarian was done, was it an elective or Elective
- 1475 emergency procedure? Emergency
- 1476 If an 'Emergency' caesarian was performed, what was _____
- 1477 the indication?
- 1478 Did this patient suffer from HIE? No
- 1479 Yes
- 1480 Unknown / lost RTHC
- 1481 If 'Yes', please specify severity (Sarnat staging) Grade I (mild)
- 1482 Grade II (moderate)
- 1483 Grade III (severe)
- 1484 Unknown
- 1485 Were their other complications during the neonatal No
- 1486 period? Yes
- 1487 Unknown / lost RTHC
- 1488 If 'Yes', please specify
- 1489 _____
- 1490 **FINAL COMMENTS**
- 1491 Final comments - any interesting / relevant features
- 1492 about this patinet
- 1493 _____
- 1494 (other health concerns; known learning
- 1495 difficulties; other routinely used medications,
- 1496 etc)
- 1497
- 1498

1499 **Appendix 3: Ethics Approval**

1500



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



Room E53-46 Old Main Building
Grote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: samayah.arietdien@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

M Burgess
PP **PROFESSOR M BLOCKMAN**
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

HREC 622/2017

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.

1502

HREC 622/2017

1503

1504

1505

1506 Ethics Renewal



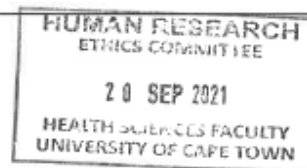
Annual Progress Report / Renewal
Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date	30.9.22
<input type="checkbox"/> Not approved	See attached comments		

Signature Chairperson of the HREC

Designee Date Signed

 21/7/22



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 Sarahlouse 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?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

2. Protocol status (tick ✓)

<input type="checkbox"/>	Research-related activities are ongoing
<input checked="" type="checkbox"/>	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.	

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.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4. Signature *SNsanta*

25 March 2020 Page 1 of 2 FHS017 (Note: Please complete the Closure form (FHS019) if the study is completed within the approval period)



UNIVERSITY OF CAPE TOWN
UNIBESITHI YOKAPATA-UNIBESITHI YOKAPATA

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee



Signature of PI		Date	16/09/2021
-----------------	--	------	------------

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

1508

1509

1510

1511

1512 **Appendix 4: Author guidelines - South African Journal of Child Health**

1513

1514 **SAJCH Author Guidelines**

1515

1516 Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

1517

1518 To submit a manuscript, please proceed to the *SAJCH* Editorial Manager website: Editorial
1519 Manager

1520 There is currently a backlog of articles in production. Authors submitting new articles should
1521 note that the earliest date for publication will be in the second quarter of 2022.

1522 To access and submit an article already in production, please see the SAJCH author
1523 guidelines here.

1524

1525 Please take the time to familiarise yourself with the policies and processes below. If you still
1526 have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281,
1527 email: submissions@hmpg.co.za).

1528

1529 **Article Processing Charges**

1530 All articles published in the South African Journal of Child Health are open access and freely
1531 available online upon publication. This is made possible by applying a business model to
1532 offset the costs of peer review management, copyediting, design and production, by charging
1533 an article-processing charge (APC) of R3 275.40 (ex Vat) for all articles published. The
1534 charge applies only to Research articles submitted after 1 Jan 2019. The APC is standard and
1535 does not vary based on length, colour, figures, or other elements.

1536

1537 When submitting a Research article to the SAJCH, the submitting author must agree to pay
1538 the APC should the article be accepted for publication. The APC is payable when your
1539 manuscript is editorially accepted and before production commences for publication. The
1540 submitting author will be notified that payment is due and given details on the available
1541 methods of payment. Prompt payment is advised; the article will not enter into production
1542 until payment is received.

1543 Queries can be directed to claudian@hmpg.co.za.

1544 Please refer to the section on ‘Sponsored Supplements’ regarding the publication of
1545 supplements, where a charge is applicable. Queries can be directed to dianes@hmpg.co.za or
1546 claudian@hmpg.co.za

1547 **Authorship**

1548 Named authors must consent to publication. Authorship should be based on: *(i)* substantial
1549 contribution to conceptualisation, design, analysis and interpretation of data; *(ii)* drafting or
1550 critical revision of important scientific content; or *(iii)* approval of the version to be
1551 published. These conditions must all be met for an individual to be included as an author
1552 (uniform requirements for manuscripts submitted to biomedical journals; refer
1553 to www.icmje.org)

1554

1555 If authors’ names are added or deleted after submission of an article, or the order of the
1556 names is changed, all authors must agree to this in writing.

1557

1558 Please note that co-authors will be requested to verify their contribution upon submission.
1559 Non-verification may lead to delays in the processing of submissions.

1560 Author contributions should be listed/described in the manuscript.

1561 **Conflicts of interest**

1562 Conflicts of interest can derive from any kind of relationship or association that may
1563 influence authors' or reviewers' opinions about the subject matter of a paper. The existence
1564 of a conflict – whether actual, perceived or potential – does not preclude publication of an
1565 article. However, we aim to ensure that, in such cases, readers have all the information they
1566 need to enable them to make an informed assessment about a publication's message and
1567 conclusions. We require that both authors and reviewers declare all sources of support for
1568 their research, any personal or financial relationships (including honoraria, speaking fees,
1569 gifts received, etc) with relevant individuals or organisations connected to the topic of the
1570 paper, and any association with a product or subject that may constitute a real, perceived or
1571 potential conflict of interest. If you are unsure whether a specific relationship constitutes a
1572 conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is
1573 later brought to the attention of the editorial team, it will be considered a serious issue
1574 prompting an investigation with the possibility of retraction.

1575

1576 **Research ethics committee approval**

1577 Authors must provide evidence of Research Ethics Committee approval of the research where
1578 relevant. Ensure the correct, full ethics committee name and reference number is included in
1579 the manuscript.

1580 If the study was carried out using data from provincial healthcare facilities, or required active
1581 data collection through facility visits or staff interviews, approval should be sought from the
1582 relevant provincial authorities. For South African authors, please refer to the guidelines for
1583 submission to the National Health Research Database. Research involving human subjects
1584 must be conducted according to the principles outlined in the Declaration of Helsinki. Please
1585 refer to the National Department of Health's guideline on Ethics in Health research:
1586 principles, processes and structures to ensure that the appropriate requirements for conducting
1587 research have been met, and that the HPCSA's General Ethical Guidelines for Health
1588 Researchers have been adhered to.

1589

1590 **Clinical trials**

1591 Since 1st December 2005, all clinical trials conducted in South Africa have been required to
1592 be registered in the South African National Clinical Trials Register. The *SAJCH* therefore
1593 requires that clinical trials be registered in the relevant public trials registry at or before the
1594 time of first patient enrollment as a condition for publication. The trial registry name and
1595 registration number must be included in the manuscript.

1596

1597 **Protection of rights to privacy**

1598 **Patient**

1599 Information that would enable identification of individual patients should not be published in
1600 written descriptions, photographs, radiographs and pedigrees unless the information is
1601 essential for scientific purposes and the patient (or parent or guardian) has given informed
1602 written consent for publication and distribution. We further recommend that the published
1603 article is disseminated not only to the involved researchers but also to the
1604 patients/participants from whom the data was drawn. Refer to Protection of Research
1605 Participants. The signed consent form should be submitted with the manuscript to enable
1606 verification by the editorial team.

1607

1608 **Other individuals**

1609 Any individual who is identifiable in an image must provide written agreement that the image
1610 may be used in that context in the *SAJCH*.

1611

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1613 Copyright remains in the Author's name. The work is licensed under a Creative Commons
1614 Attribution - Noncommercial Works License. Authors are required to complete and sign an
1615 Author Agreement form that outlines Author and Publisher rights and terms of publication.
1616 The Agreement form should be uploaded along with other submissions files and any
1617 submission will be considered incomplete without it [*forthcoming*].

1618

1619 Material submitted for publication in the *SAJCH* is accepted provided it has not been
1620 published or submitted for publication elsewhere. Please inform the editorial team if the main
1621 findings of your paper have been presented at a conference and published in abstract form, to
1622 avoid copyright infringement. The *SAJCH* does not hold itself responsible for statements
1623 made by the authors. The corresponding author should also indicate if the research forms part
1624 of a postgraduate short report, dissertation or thesis.

1625 **Previously published images**

1626 If an image/figure has been previously published, permission to reproduce or alter it must be
1627 obtained by the authors from the original publisher and the figure legend must give full credit
1628 to the original source. This credit should be accompanied by a letter indicating that
1629 permission to reproduce the image has been granted to the author/s. This letter should be
1630 uploaded as a supplementary file during submission.

1631

1632 **Privacy statement**

1633 The *SAJCH* is committed to protecting the privacy of its website and submission system
1634 users. The names, personal particulars and email addresses entered in the website or
1635 submission system will not be made available to any third party without the user's
1636 permission or due process. By registering to use the website or submission system, users
1637 consent to receive communication from the *SAJCH* or its publisher HMPG on matters
1638 relating to the journal or associated publications. Queries with regard to privacy may be
1639 directed to publishing@hmpg.co.za.

1640

1641 **Ethnic/race classification**

1642 Use of racial or ethnicity classifications in research is fraught with problems. If you choose to
1643 use a research design that involves classification of participants based on race or ethnicity, or
1644 discuss issues with reference to such classifications, please ensure that you include a detailed
1645 rationale for doing so, ensure that the categories you describe are carefully defined, and that

1646 socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities
1647 are appropriately controlled for. Please also clearly specify whether race or ethnicity is
1648 classified as reported by the patient (self-identifying) or as perceived by the investigators.
1649 Please note that it is not appropriate to use self-reported or investigator-assigned racial or
1650 ethnic categories for genetic studies.

1651

1652 **Continuing Professional Development (CPD)**

1653 *SAJCH* is an HPCSA-accredited service provider of CPD materials. Principal authors can
1654 earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors
1655 are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each
1656 month, *SAJCH* also publishes a CPD-accredited questionnaire relating to the academic
1657 content of the journal. Successful completion of the questionnaire with a pass rate of 70%
1658 will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical
1659 Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP
1660 Consulting

1661

1662 **Manuscript preparation**

1663 **Preparing an article for anonymous review**

1664

1665 To ensure a fair and unbiased review process, all submissions are to include an anonymised
1666 version of the manuscript. The exceptions to this requirement are Editorials, Correspondence,
1667 Book reviews and Obituary submissions.

1668

1669 Submitting a manuscript that needs additional blinding can slow down your review process,
1670 so please be sure to follow these simple guidelines as much as possible:

- 1671 • An anonymous version should not contain any author, affiliation or particular
1672 institutional details that will enable identification.
- 1673 • Please remove title page, acknowledgements, contact details, funding grants to a
1674 named person, and any running headers of author names.
- 1675 • Mask self-citations by referring to your own work in third person.

1676

1677 **General article format/layout**

1678 Submitted manuscripts that are not in the correct format specified in these guidelines will be
1679 returned to the author(s) for correction prior to being sent for review, which will delay
1680 publication.

1681 General:

- 1682 • Manuscripts must be written in UK English (this includes spelling).
- 1683 • The manuscript must be in Microsoft Word or RTF document format. Text must be
1684 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary
1685 formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- 1686 • Please make your article concise, even if it is below the word limit.
- 1687 • Qualifications, *full* affiliation (department, school/faculty, institution, city, country)
1688 and contact details of ALL authors must be provided in the manuscript and in the
1689 online submission process.
- 1690 • Abbreviations should be spelt out when first used and thereafter used consistently,
1691 e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- 1692 • Scientific measurements must be expressed in SI units except: blood pressure
1693 (mmHg) and haemoglobin (g/dL).
- 1694 • Litres is denoted with an uppercase L e.g. 'mL' for millilitres).

- 1695 • Units should be preceded by a space (except for % and °C), e.g. '40 kg' and '20 cm' but
1696 '50%' and '19°C'.
- 1697 • Please be sure to insert proper symbols e.g. μ not u for micro, α not a for alpha, β not
1698 B for beta, etc.
- 1699 • Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- 1700 • Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- 1701 • Round brackets (parentheses) should be used, as opposed to square brackets, which
1702 are reserved for denoting concentrations or insertions in direct quotes.
- 1703 If you wish material to be in a box, simply indicate this in the text. You may use the table
1704 format –this is the *only* exception. Please DO NOT use fill, format lines and so on.
- 1705
- 1706 *SAJCH* is a Journal on child health, therefore for articles involving genetics, it is the
1707 responsibility of authors to apply the following:
- 1708 - Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- 1709 - Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.
- 1710 ** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above,
1711 although they will raise queries where concerned.
- 1712 - Define all genes, proteins and related shorthand terms at first mention, e.g.
1713 '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- 1714 - Use the latest approved gene or protein symbol as appropriate:
- 1715 • Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- 1716 • HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- 1717 • OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions

- 1718 • Bennet et al. Standardized human pedigree nomenclature: Update and assessment of
1719 the recommendations of the National Society of Genetic Counselors. J Genet Counsel
1720 2008;17:424-433: standard human pedigree nomenclature.

1721

1722 **Preparation notes by article type**

1723

1724 **Research**

1725 *Guideline word limit: 3 000 words (excluding abstract and bibliography)*

1726 Research articles describe the background, methods, results and conclusions of an original
1727 research study. The article should contain the following sections: introduction, methods,
1728 results, discussion and conclusion, and should include a structured abstract (see below). The
1729 introduction should be concise – no more than three paragraphs – on the background to the
1730 research question, and must include references to other relevant published studies that clearly
1731 lay out the rationale for conducting the study. Some common reasons for conducting a study
1732 are: to fill a gap in the literature, a logical extension of previous work, or to answer an
1733 important clinical question. If other papers related to the same study have been published
1734 previously, please make sure to refer to them specifically. Describe the study methods in as
1735 much detail as possible so that others would be able to replicate the study should they need
1736 to. Where appropriate, sample size calculations should be included to demonstrate that the
1737 study is not underpowered. Results should describe the study sample as well as the findings
1738 from the study itself, but all interpretation of findings must be kept in the discussion section,
1739 which should consider primary outcomes first before any secondary or tertiary findings or
1740 post-hoc analyses. The conclusion should briefly summarise the main message of the paper
1741 and provide recommendations for further study.

- 1742 • May include up to 3 illustrations or tables.

- 1743 • A max of 20 - 25 references

1744

1745 *Structured abstract*

- 1746 • This should be no more than 250 words, with the following recommended headings:
- 1747 ○ **Background:** why the study is being done and how it relates to other
1748 published work.
- 1749 ○ **Objectives:** what the study intends to find out
- 1750 ○ **Methods:** must include study design, number of participants, description of
1751 the intervention, primary and secondary outcomes, any specific analyses that
1752 were done on the data.
- 1753 ○ **Results:** first sentence must be brief population and sample description;
1754 outline the results according to the methods described. Primary outcomes must
1755 be described first, even if they are not the most significant findings of the
1756 study.
- 1757 ○ **Conclusion:** must be supported by the data, include recommendations for
1758 further study/actions.
- 1759 ○ Please ensure that the structured abstract is complete, accurate and clear and
1760 has been approved by all authors. It should be able to be intelligible to the
1761 reader without referral to the main body of the article.
- 1762 ○ Do not include any references in the abstracts.

1763

1764 Here is an example of a good abstract.

1765

1766 *Scientific letters/short reports*

1767

1768 These include case reports, side effects of drugs and brief or negative research findings.

1769

1770 *Guideline word limit: 1500 words*

1771 • Abstract: unstructured, of about 100-150 words

1772 • May include only one illustration or table

1773 • A maximum of 6 references

1774

1775

1776 **Editorials**

1777 *Guideline word limit: 1 000 words*

1778 These opinion or comment articles are usually commissioned but we are happy to consider

1779 and peer review unsolicited editorials. Editorials should be accessible and interesting to

1780 readers without specialist knowledge of the subject under discussion and should have an

1781 element of topicality (why is a comment on this issue relevant now?) There should be a clear

1782 message to the piece, supported by evidence.

1783 Please make clear the type of evidence that supports each key statement, e.g.:

1784 • expert opinion

1785 • personal clinical experience

1786 • observational studies

1787 • trials

1788 • systematic reviews.

1789

1790 **Review articles**

1791 Review articles should always be discussed with the Editor prior to submission.

1792

1793 *Guideline word limit: 4 000 words*

1794

1795 These are welcome, but should be either commissioned or discussed with the Editor before
1796 submission. A review article should provide a clear, up-to-date account of the topic and be
1797 aimed at non-specialist hospital doctors and general practitioners. They should be aligned to
1798 practice in South and/or sub-Saharan Africa and not a precis of reviews published in the
1799 international literature

1800 Please ensure that your article includes:

- 1801 • Abstract: unstructured, of about 100-150 words, explaining the review and why it is
1802 important
- 1803 • Methods: Outline the sources and selection methods, including search strategy and
1804 keywords used for identifying references from online bibliographic databases. Discuss
1805 the quality of evidence.
- 1806 • When writing: clarify the evidence you used for key statements and the strength of the
1807 evidence. Do not present statements or opinions without such evidence, or if you have
1808 to, say that there is little or no evidence and that this is opinion. Avoid specialist
1809 jargon and abbreviations, and provide advice specific to southern Africa.
- 1810 • Personal details: Please supply your qualifications, position and affiliations and MP
1811 number (used for CPD points); address, telephone number and fax number, and your
1812 e-mail address; and a short personal profile (50 words) and a few words about your
1813 current fields of interest.

1814

1815

1816 **Correspondence (Letters to the Editor)**

1817 *Guideline word limit: 400 words*

1818 Letters to the editor should relate either to a paper or article published by the SAJCH or to a
1819 topical issue of particular relevance to the journal's readership

1820 • May include only one illustration or table

1821 • Must include a correspondence address.

1822

1823 **Obituaries**

1824 *Guideline word limit: 400 words*

1825 Should be offered within the first year of the practitioner's death, and may be accompanied
1826 by a photograph.

1827

1828 **Illustrations/photos/scans**

1829 • If illustrations submitted have been published elsewhere, the author(s) should provide
1830 evidence of consent to republication obtained from the copyright holder.

1831 • Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.

1832 • Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in
1833 full).

1834 • All images must be of high enough resolution/quality for print.

1835 • All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.

1836 • Ensure all graph axes are labelled appropriately, with a heading/description and units
1837 (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0;
1838 2.0; 3.0; 4.0 etc.

1839 • Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph*
1840 *of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include
1841 an arrow to show the tumour.

1842 • Each image must be attached individually as a 'supplementary file' upon submission
1843 (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

1844

1845 **Tables**

1846 • Tables should be constructed carefully and simply for intelligible data representation.
1847 Unnecessarily complicated tables are strongly discouraged.

1848 • Large tables will generally not be accepted for publication in their entirety. Please
1849 consider shortening and using the text to highlight specific important sections, or offer
1850 a large table as an addendum to the publication, but available in full on request from
1851 the author.

1852 • Embed/include each table in the manuscript Word file - do not provide separately as
1853 supplementary files.

1854 • Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they
1855 are referred to in the text.

1856 • Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.

1857 • Ensure each table has a concise title and column headings, and include units where
1858 necessary.

1859 • Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶
1860 || then ** †† ‡‡ etc.

1861

1862 **Do not:** Use [Enter] within a row to make 'new rows':

1863

1864 *Rather:*

1865 Each row of data must have its own proper row:

1866

1867 **Do not:** use separate columns for *n* and %:

1868

1869 *Rather:*

1870 Combine into one column, *n* (%):

1871

1872 **Do not:** have overlapping categories, e.g.:

1873

1874 *Rather:*

1875 Use \diamond symbols or numbers that don't overlap:

1876

1877

1878 **References**

1879 **NB:** *Only complete, correctly formatted reference lists in Vancouver style will be accepted.*

1880 *If reference manager software is used, the reference list and citations in text are to be*

1881 *unformatted to plain text before submitting..*

1882

- Authors must verify references from original sources.

1883

- Citations should be inserted in the text as superscript numbers between square

1884 brackets, e.g. These regulations are endorsed by the World Health Organization,^[2] and

1885 others.^[3,4-6]

- 1886 • All references should be listed at the end of the article in numerical order of
1887 appearance in the Vancouver style (not alphabetical order).
- 1888 • Approved abbreviations of journal titles must be used; see the List of Journals in
1889 Index Medicus.
- 1890 • Names and initials of all authors should be given; if there are more than six authors,
1891 the first three names should be given followed by et al.
- 1892 • Volume and issue numbers should be given.
- 1893 • First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- 1894 • Wherever possible, references must be accompanied by a digital object identifier
1895 (DOI) link). Authors are encouraged to use the DOI lookup service offered
1896 by CrossRef:
- 1897 ○ On the Crossref homepage, paste the article title into the ‘Metadata search’
1898 box.
 - 1899 ○ Look for the correct, matching article in the list of results.
 - 1900 ○ Click Actions > Cite
 - 1901 ○ Alongside 'url =' copy the URL between { }.
 - 1902 ○ Provide as follows, e.g.: <https://doi.org/10.7196/07294.937.98x>
- 1903
- 1904 **Some examples:**
- 1905 • *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking
1906 about glaucoma. Stat Med 1998;289(1):350-355. <http://dx.doi.org/10.1000/hgjr.182>
 - 1907 • *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London:
1908 Butterworth, 1975:96-101.

- 1909 • *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of
 1910 Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic
 1911 Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- 1912 • *Internet references:* World Health Organization. The World Health Report 2002 -
 1913 Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002.
 1914 <http://www.who.int/whr/2002> (accessed 16 January 2010).
- 1915 • Legal references
- 1916 • Government Gazettes:
- 1917 National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No.
 1918 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.
- 1919 In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice
 1920 number in this Gazette.
- 1921 • Provincial Gazettes:
- 1922 Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and
 1923 Land Affairs. Publication of the Gauteng health care waste management draft regulations.
 1924 Gauteng Provincial Gazette No. 373:3003, 2003.
- 1925 • Acts:
- 1926 South Africa. National Health Act No. 61 of 2003.
- 1927 • Regulations to an Act:
- 1928 South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic
 1929 medicine services. Government Gazette No. 35099, 2012. (Published under Government
 1930 Notice R176).
- 1931 • Bills:
- 1932 South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.
- 1933 • Green/white papers:

1934 South Africa. Department of Health Green Paper: National Health Insurance in South Africa.
1935 2011.

1936 • Case law:

1937 Rex v Jopp and Another 1949 (4) SA 11 (N)

1938 Rex v Jopp and Another: Name of the parties concerned

1939 1949: Date of decision (or when the case was heard)

1940 (4): Volume number

1941 SA: SA Law Reports

1942 11: Page or section number

1943 (N): In this case Natal - where the case was heard. Similarly, (C) would indicate Cape, (G)

1944 Gauteng, and so on.

1945 NOTE: no . after the v

1946 • *Other references (e.g. reports) should follow the same format: Author(s). Title.*

1947 *Publisher place: Publisher name, year; pages.*

1948 • Cited manuscripts that have been accepted but not yet published can be included as
1949 references followed by '(in press)'.

1950 • Unpublished observations and personal communications in the text must **not** appear
1951 in the reference list. The full name of the source person must be provided for personal
1952 communications e.g. '...(Prof. Michael Jones, personal communication)'.

1953

1954 **From submission to acceptance**

1955 **Submission and peer-review**

1956 To submit an article:

- 1957 • Please ensure that you have prepared your manuscript in line with
1958 the *SAJCH* requirements.
- 1959 • All submissions should be submitted via Editorial Manager
- 1960 • The following are required for your submission to be complete:
- 1961 ○ Anonymous manuscript (unless otherwise stated)
- 1962 ○ Author Agreement form [forthcoming]
- 1963 ○ Manuscript
- 1964 ○ Any supplementary files: figures, datasets, patient consent form, permissions
1965 for published images, etc.
- 1966 ○ Once the submission has been successfully processed on Editorial Manager, it
1967 will undergo a technical check by the Editorial Office before it will be
1968 assigned to an editor who will handle the review process. If the author
1969 guidelines have not been appropriately followed, the manuscript may be sent
1970 back to the author for correcting.

1971

1972 **Peer Review Process**

1973

1974 All manuscripts are reviewed initially by the Editor-in-Chief and only those that meet the
1975 scientific and editorial standards of the journal, and fit within the aims and scope of the
1976 journal, will be sent for external peer review. Each manuscript is reviewed by either one or
1977 two reviewers selected on the basis of their expertise in the field. A double blind review
1978 process is followed at SAJCH.

1979 Authors are expected to receive feedback from reviewers and an editorial decision within
1980 approximately 6 weeks of submission. The time period of the entire review process may vary
1981 however depending upon the quality of the manuscript submitted, reviewers' responses and
1982 the time taken by the authors to submit the revised manuscript.

1983 Manuscripts from review may be accepted, rejected or returned to the author for revision or
1984 resubmission for review. Authors will be directed to submit revised manuscripts within two
1985 months of receiving the editor's decision, and are requested to submit a point by point
1986 response to the reviewers' comments. Manuscripts which authors are requested to revise and
1987 resubmit will be sent for a second round of peer review, often to the original set of reviewers.
1988 All final decisions on a manuscript are at the Editor's discretion.

1989

1990 **Production process**

- 1991 1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor
1992 (CE).
- 1993 2. The CE copyedits in Word, working on house style, format,
1994 spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
- 1995 3. If the CE has an author queries, he/she will contact the corresponding author and send
1996 them the copyedited Word doc, asking them to solve the queries by means of track
1997 changes or comment boxes.
- 1998 4. The authors are typically asked to respond within 1-3 days. Any comments/changes
1999 must be clearly indicated e.g. by means of track changes. Do not work in the original
2000 manuscript - work in the copyedited file sent to you and make your changes clear.
- 2001 5. The CE will finalise the article and then it will be typeset.
- 2002 6. Once typeset, the CE will send a PDF of the file to the authors to complete their final
2003 check, while simultaneously sending to the 2nd-eye proofreader.
- 2004 7. The authors are typically asked to complete their final check and sign-off within 1-2
2005 days. No major additional changes can be accommodated at this point.
- 2006 8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and
2007 prepares it for the upcoming issue.

2008

2009 **Changing contact details or authorship**

2010 Please notify the Editorial Department of any contact detail changes, including email, to
2011 facilitate communication.

2012

2013 **Errata and retractions**

2014 **Errata**

2015 Should you become aware of an error or inaccuracy in yours or someone else's contribution
2016 after it has been published, please inform us as soon as possible via an email
2017 to publishing@hmpg.co.za, including the following details:

2018 • Journal, volume and issue in which published

2019 • Article title and authors

2020 • Description of error and details of where it appears in the published article

2021 • Full detail of proposed correction and rationale

2022

2023 We will investigate the issue and provide feedback. If appropriate, we will correct the web
2024 version immediately, and will publish an erratum in the next issue. All investigations will be
2025 conducted in accordance with guidelines provided by the Committee on Publication Ethics
2026 (COPE).

2027

2028 **Retractions**

2029 Retraction of an article is the prerogative of either the original authors or the editorial team of
2030 HMPG. Should you wish to withdraw your article before publication, we need a signed
2031 statement from all the authors.

2032

2033 Should you wish to retract your published article, all authors have to agree in writing before
2034 publication of the retraction.

2035 Send an email to publishing@hmpg.co.za, including the following details:

2036 • Journal, volume and issue to which article was submitted/in which article was
2037 published

2038 • Article title and authors

2039 • Description of reason for withdrawal/retraction.

2040 We will make a decision on a case-by-case basis upon review by the editorial committee in
2041 line with international best practices. Comprehensive feedback will be communicated with
2042 the authors with regard to the process. In case where there is any suspected fraud or
2043 professional misconduct, we will follow due process as recommended by the Committee on
2044 Publication Ethics (COPE), and in liaison with any relevant institutions.

2045

2046 When a retraction is published, it will be linked to the original article.

2047

2048

2049 **Appendix 5: Turnitin Report**

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