Sickle Cell Disease in Cape Town: a perspective from two regional hospitals

Principal Investigator:
Dr Anisa Vahed
VHDANI001

Supervisor: Dr M.L. Cooke
Co-supervisor: Prof A. Westwood

Red Cross Memorial Children's Hospital
Department of Paediatrics and Child Health, University of Cape Town

TABLE OF CONTENTS

Declaration

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

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

Signature: ..... Signed by candidate

Date: .....1/10/2020.....

ABSTRACT

Background:
Inherited hemoglobinopathies are a global health burden. Sickle cell disease (SCD) is the most common genetic disorder of haemoglobin in Africa but is uncommon in the South African population.

Objectives
This study aimed to describe the presentation and experience managing paediatric patients with SCD at two regional hospitals in Cape Town.

Methods
This retrospective study used routine data of children aged 0-13 years with SCD managed at New Somerset and Victoria Hospitals in Cape Town from January 2010 to December 2018. Data analysed included demographics, diagnosis, out- and in-patient episodes, and the need for transfers to tertiary level.

Results
We identified 63 patients of which three did not fit the study criteria and four had missing clinical records. Of the 56 children included, most were diagnosed at the regional hospital (n=32 [58%]) and only a third (n=18 [32%]) were down-referrals from tertiary level facilities. The annual number of new patients per year varied with the most in 2009 and 2015. The median age at first presentation was 20.1 months (interquartile range [IQR] 7.1-43.9 months). There was a male predominance. The majority (n=39 [67%]) were born in South Africa, eleven were born in the Democratic Republic of Congo (DRC) and six in other African countries. None of the parents were born in South Africa. The majority of parents were from DRC (73/110) and Nigeria (11/110). Approximately one third (39%) of patients had a family history of SCD and a quarter (25%) had an affected sibling. Most children were diagnosed incidentally via full blood count findings (66%); others presented with symptomatic anaemia (28%) or were screened because of an affected sibling (11%). The mean number of hospital days was 3.0 (range 0-13). Infections, bone crises and symptomatic anaemia accounted for the majority of hospital admissions. Referral for tertiary level care occurred in 23/56 (41%) patients with most requiring specialist opinion from haematology and/or other specialist disciplines. Nine (16%) children were lost to follow-up, one was transferred to another province and one died at another institution.

Conclusion
An increasing number of children diagnosed with SCD are being seen in health facilities in Cape Town and probably other parts of South Africa due to migration and children being born to families with SCD ancestries. Recognising the presentation and complications of SCD and developing competency at all levels of care in providing appropriate, protocolised management are important to reduce morbidity and mortality among children with SCD in our setting.

Introduction:

Sickle cell disease (SCD) is the most common genetic disorder of haemoglobin in Africa but is uncommon in the local South African population.[1] An estimated 75% of the global burden of SCD is in sub-Saharan Africa (SSA) while Nigeria, India and the Democratic Republic of Congo (DRC) account for half the global burden.[2] There has been a significant increase in SCD cases seen in Cape Town due to increased migration and population movement to South Africa from other countries[3,4]

Africa faces many challenges related to obtaining accurate information. Worldwide, SCD is estimated to cause 6% of deaths in children under five years. This is expected to be higher in Africa.[3] In SSA, the current mortality rates are not up to date, with reliable data only being available from Europe and America.[2,5] There are few cohort studies describing SCD in children and there is no evidence yet that consistent standards of care are applied across SSA.[3,6] Improved management protocols and data can assist with establishing cost-effective interventions and may reduce morbidity and mortality rates amongst children with SCD in Africa.[2,3,6]

A study by Wonkham et al. from Red Cross War Memorial Children's Hospital (RCWMCH), a tertiary centre in Cape Town, highlighted the gap in identifying both the burden of SCD in Cape Town Metro and patient clinical profile.[6] This study identified the underestimation of patient numbers as many children were diagnosed and managed at regional hospital levels.

The aim of the current study was to describe the disease burden and experience managing SCD in Cape Town at two regional level hospitals to gain a more comprehensive understanding of the care of these specialised patients. Annual admission trends over a nine-year period were documented, including data on diagnosis, common presentations, complications and the need for referral/transfer to a tertiary centre.

Methodology:

Study design and setting:

A retrospective study was conducted of children with SCD managed at New Somerset Hospital (NSH) and Victoria Hospital (VH) between January 2010 and December 2018. Both are regional level hospitals in the Cape Town Metro. Supervision of patient care is by general paediatric specialists. Red Cross War Memorial Children's Hospital (RCWMCH) is the tertiary referral hospital with sub-specialist paediatric haematology service providing support to both hospitals.

Study Population:

Children younger than 13 years of age with SCD who had attended the two institutions were included in the study. These patients reside in the drainage area of the regional level hospitals. All patients noted to have sickle cells on smear and confirmed on haemoglobin electrophoresis were included. All children received the standard of inpatient and outpatient care according to the SCD protocols at each institution.

Data Collection:

Children with SCD were identified from existing outpatient clinic registers from both hospitals and Clinicom® system. Folders of the identified patients were accessed from medical records and reviewed by the principal investigator. Clinical data collected included demographics, age at first presentation, sex, anthropometry done on first admission (WHO z-scores and BMI scores), nature of first presentation, in-patient and out-patient visits (including reason for visit, number of days of admission, analgesia required), family history of SCD and country of birth of children and their parents. At each admission, acute and chronic complications and the type of analgesia used were documented. The number of patients who required blood transfusions at diagnosis and the total number of transfusions for the cohort were documented. Data on commencement and/or discontinuation of penicillin prophylaxis, folate and hydroxyurea were collected. Laboratory data at diagnosis were collected including full blood count and haemoglobin electrophoresis results. Outcomes were classified as continued care at regional level care, patients who required no admissions, transfers to tertiary level for sub-specialist management, death and lost to follow-up. Data were entered on a password-protected computer using REDCap electronic data capture tools hosted at the University of Cape Town.

Statistical Methods

Data were analysed using STATA® (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Categorical data are presented using frequencies and percentages. Continuous data are described using mean and standard deviation or median and interquartile range (IQR) for normally and non-normally distributed data, respectively.

Ethics Approval

The study was approved by the University of Cape Town Health Sciences Faculty Human Research Ethics Committee (HREC 028/2018) in line with the principles of the Declaration of Helsinki, second revision. The need for individual consent was waived as this was a medical folder review, with no risk to the patient. Approval for access to medical records was approved by the Western Cape Health Research sub-district and Superintendents of NSH and VH.

Results

Sixty-three patients were identified. Three patients were excluded as they were too old and did not meet the age criteria and four patient folders were missing, so 56 records were analysed.

Demographics

The majority of patients were diagnosed at the two regional hospitals (58%), almost a third were referred from tertiary institution and 11% diagnosed in other provinces or countries (Table 1). The median age at first presentation was 20.1 months (IQR 7.1-43.9). There was a male predominance (57%). The number of newly diagnosed patients varied between one and eight per year with the highest number of new cases diagnosed in 2009 and 2015 (Figure 1).

Table 1 shows the demographics including country of origin of patients and their parents. Most patients (39/56 [70%]) were born in South Africa with 11/56 (19%) born in DRC. The remainder were born in other African countries. The parent's country of birth was mostly from DRC and Nigeria. None of the parents were born in South Africa. There was a positive family history of SCD in 22/52 (39%) of children and 25% had a sibling affected with SCD.

Clinical and laboratory characteristics

Most patients had normal anthropometry at presentation (normal weight and height WHO z-scores for age) (51/56 [91%]), however, three were moderately stunted and two were severely wasted.

Haematological parameters at first presentation are shown in Table 2. Full blood counts done on diagnosis consistently showed a normocytic anaemia with a high white cell count. The median fetal haemoglobin (HbF) level was 13.5% (IQR 6.5-21.3%) (normal range 0.0-0.8% depending on age). High-performance liquid chromatography (HPLC) haemoglobin electrophoresis result was known for 37 (66,1%) of the patients. One patient was documented as being G6PD deficient together with SCD. Twenty-nine patients (51,7%) were known with homozygous SS and six (10,7%) with compound heterozygous SS. Beta-thalassaemia trait was noted in 9/56 (16%) of the patients and one patient had an alpha-thalassaemia trait. At diagnosis 27% (15/56) required blood transfusions for symptomatic anaemia at diagnosis.

The clinical presentation at time of diagnosis at the regional and tertiary hospital is shown in Table 3, with some children having more than one presenting feature. The most common diagnostic presentation was with an incidental full blood count finding during admission for another medical illness and/or symptomatic anaemia. Infections presenting at diagnosis included fevers of unknown source, acute gastroenteritis, respiratory tract infections, tonsillitis as well as osteitis.

Hospital admissions

Admission and outcome data are shown in Table 4. The majority (205/277 [74%]) of the non-scheduled patient visits were admissions to the paediatric ward, and the others were managed in the emergency centre. Reasons for subsequent admissions were mostly related to infections, pain crisis or symptomatic anaemia. There was generally

more than one reason for being admitted to the paediatric ward. Acute complications were related to suspected infections, pain crisis and haemolytic crisis. The only confirmed infection was one patient who tested positive for parvovirus. Infections documented included fevers of unknown source, acute gastroenteritis, respiratory tract infections, tonsillitis as well as osteitis. All blood cultures were negative. Chronic complications were seen in 17/277 (6%) of the admissions, the most common being chronic malnutrition with moderate stunting in 13/277 (5%). These admission episodes were related to the 5 patients who were noted to be malnourished on admission. The major morbidities or chronic complications noted were malnutrition, joint complications and leg ulcers.

Analgesia used to manage painful crises was mostly in oral formulations (paracetamol, NSAIDs). A combination of intravenous and oral analgesia was required in 13/274 (5%) of crisis episodes. Most painful crises were managed without the use of oral or intravenous opiates (Table 4). Twelve percent of admissions had not been compliant to hydroxyurea, folate and penicillin prophylaxis treatment prior to admission.

Blood transfusions were required in 64/277 (23%) of all admissions (at diagnosis and subsequent admissions). The mean pre-transfusion haemoglobin was 5.4g/dl (range 2,2-7,8 g/dl). Indications were haemolytic crisis and/or symptomatic anaemia. On average those who required blood transfusions had two blood transfusions during the study period but due to some being diagnosed more recently a rate per year could not be computed for the whole cohort. No children managed at regional level were on a chronic transfusion programme

Out-patient consultations

There were 955 out-patient visits during the study with an average of 2-3 visits per patient per year. Six percent of patients missed an out-patient review during the study. Management largely concentrated on issuing chronic medication (99%, 921/955), counselling regarding prevention of infection (69%, 644/955) and counselling regarding management of fever episode (53%, 497/955), pain (54%, 507/955) and danger signs (58%, 537/955). Ten percent of parents received formal genetic counselling at their out-patient visits. Concerns with treatment adherence were noted in 7% (70/955) of out-patient visits. Four of the children did not have an inpatient admission and were managed as outpatients.

Coverage of interventions to prevent infections included: pneumococcal vaccination in 98%, penicillin prophylaxis in 89% and annual influenza vaccine 85%. There were 25/56 (45%) patients receiving chronic treatment with hydroxyurea. Patients were not routinely commenced on hydroxyurea therapy due to the protocols during the study period.

Outcomes

The outcomes of the patients showed that 23/56 (30%) patients required referral to a tertiary centre for various special investigations (echo, ultrasound, micturating cystourethrogram, bone scans) or specialist opinion. Four patients were transferred to the specialist haematology service for ongoing management. One patient was transferred on day one of acute admission for specialist management and required admission to the intensive care unit; this patient died from overwhelming sepsis.

There were 9/56 (16%) children lost to follow-up with one patient transferred to another province.

Discussion

To our knowledge, this study is the first to describe SCD in children in a regional hospital setting in the South Africa Our findings complement those of the earlier study at the tertiary haematology clinic at RCWMCH in the preceding decade (2001-2010) where it was noted that the burden of disease in Cape Town was underestimated due to patients receiving care at regional level.[4] Wonkham et al., (2012) found the annual frequency of SCD patients increased by 300-400% over their study period, with up to 93% of children originally from other African countries. Most of the children in our study were not down-referrals from tertiary level and presented directly to the regional hospital where they were diagnosed and managed. Heritage was similar with no children born to South Africans and the majority from the DRC.

Our study showed variable annual number of new diagnoses with a cumulative increase in the size of the cohorts at the hospitals. This ongoing annual presentation of new cases poses a persistent demand on limited health resources since these children require regular monitoring and often require admission for investigation and management of complications. The number of newly diagnosed patients has increased during the study time, similar to the findings of the RCWMCH study.[4] This emphasises the importance of having a high index of suspicion in children whose families are from countries with a high SCD burden and to also consider SCD in the differential and work-up for normocytic anaemia in order to diagnose timeously and give appropriate care. Younger children tended to present with dactylitis and splenomegaly so SCD must be considered in the differential diagnosis of these presentations in this age group.

There is a lack of global mortality data available for children aged under five years with SCD.[1,2,7-9] In our study we documented one death related to SCD complications in a seven-year-old child. The number of deaths could be higher as nine other study patients were lost to follow-up. However, this could be due to migration back to their country of origin or to other hospitals/provinces. The global mortality rate is estimated to be 0.64 per 100 years of child observation with the highest rate in Africa at 7.3 per 100 years of observation.[5,7] This is expected because children from low-to-middle income countries with SCD may die before the age of five years and before being diagnosed.[7] We also had very few children with chronic complications or major morbidities, such as stroke.

Comprehensive SCD care programmes have been shown to improve outcomes for children. Such programmes include: neonatal screening, early diagnosis, genetic counselling, antibiotic prophylaxis, immunisations, antibiotics and hydroxyurea, as well as prompt management of complications.[10-14,16] Protocolised out-patient clinic management at both regional hospitals includes many of these recommendations. Routine newborn screening would not be a cost-effective programme in the South African setting; none of the children in our study had South African parents, so a better strategy would be screening siblings and maintaining a high index of suspicion

in children whose parents are from other parts of SSA. Twenty-five percent of children having affected siblings indicates good access to screening of siblings

Children with SCD are at risk of overwhelming pneumococcal infection due to functional asplenia.[11,15] Increased overall survival of paediatric patients with SCD was demonstrated in the Prophylactic Penicillin Study of 1986 which showed that use of prophylactic penicillin could prevent life-threatening infections.[13] Pneumococcal immunisation together with penicillin prophylaxis have increased the survival rate of children affected with SCD.[2,13,18] Our patients have access to appropriate penicillin prophylaxis and immunisation with the standard Extended Programme of Immunisation (EPI) Pneumococcal Conjugate Vaccine (PCV) as well as 23 valent polysaccharide pneumococcal vaccination in older children, and annual influenza vaccinations. In our study, 98% of patients were noted to be up-to-date with their pneumococcal vaccination. Additionally, 89% were commenced on or received during time of review penicillin VK prophylaxis. Penicillin VK prophylaxis was terminated after the age of 7 years old in some patients according to the institutional protocol.

The fifty-ninth WHO assembly report described the increasing burden of disease of SCD.[4,7,8] The report emphasised that despite resource limitations, sickle cell disorders should be covered by health-service planning in all countries where they are common, and that all components of prevention and treatment should be considered as well as institution of cost-effective measures to manage the disease. Our out-patient services and infrastructure are robust with all children having at least two out-patient visits per year and over 90% adhering to recommended prophylaxis (vaccines and penicillin).

The WHO SCD report published in 2016 includes guidelines on managing acute and chronic complications of SCD.[5] Recommendations for managing acute complications include effective analgesia for vaso-occlusive crises, hydration, and prompt empiric treatment for infections. Management of chronic complications includes attention to nutrition and rehabilitation for joint complications. There is strong evidence to screen for proliferative sickle cell retinopathy and echocardiography to evaluate for signs of pulmonary hypertension.[10,11] Neither of these interventions are routinely available in many resource limited settings including our own and expectations need to be adjusted accordingly.[8,18] A quarter of unscheduled visits were managed in the emergency centre without admission so frontline emergency colleagues also need to be educated on the same management protocols in this context. Even in countries with limited resources evidence shows that relatively simple measures like counselling about preventive health and nutrition and prompt recognition of illness can significantly reduce complications and premature deaths from SCD.[2,3,6,10,18] This is the current model we apply and the low rate of referrals for additional sub-specialty care and low chronic complication and mortality rate indicates the success of this model. Bone marrow transplantation is the only proven cure for SCD to date. This is not available in our regional hospital setting highlighting the importance of good patient care and prompt management of acute and chronic complications, and referral of those with a severe phenotype to tertiary institutions where this can be considered.[10,11]

The WHO report also proposed moderate strength evidence to suggest providing treatment with hydroxyurea to all infants, children, and adolescents with SCD at diagnosis, without specific symptom criteria. This policy was only adopted in Cape Town clinics in 2019 after the study completion. Almost half our patients were on hydroxyurea based on previous recommendations for patients who have moderate to severe disease (defined by three or more acute pain episodes requiring medical intervention).[2,11,17] This is more than the 36% noted in the study by Wonkham et al, suggesting that patients are managed equivalently at regional and tertiary level.[4]

Effective preventative strategies recommended internationally include annual transcranial Doppler examinations from the ages of 2 to 16 years and long-term transfusion therapy to prevent stroke in those children with abnormal transcranial Doppler velocity.[2,11,18] This strategy is not yet routinely available in South Africa and Dopplers have only become available in tertiary level centres recently, with screening of children over six years of age. Systematising referral criteria is an important part of regional care management to ensure complications are identified timeously and that care is equivalent. All involved in out-patient management must therefore remain informed and up to date with criteria and screening options, and this process streamlined.

Key to management is parental education regarding diagnosis, inheritance, and requirement for adherence to medication and follow-up visits. Poor adherence results in unnecessary acute admissions and potential morbidity. Genetic counsellors were not present at the majority of out-patient visits; thus most counselling was provided by medical team. The concerns are that much consultation time is spent counselling which puts an additional burden on clinicians. We did not correlate compliance with the attendance at formal genetic counselling sessions. In the future, increased availability of trained genetic counsellors may improve understanding and adherence. This will also allow for access to prenatal diagnosis and/or postnatal screening of siblings of current patients for prompt management.

Study Limitations

This study has several limitations. Its design was retrospective with a small population and was dependent on documentation in medical records with some missing data and folders. Complete electrophoresis results were not available on all patients.

Conclusions and Recommendations

Over the past two decades, there has been a consistent increase in the cohort of new SCD cases managed in hospitals in Cape Town, either due to migration of these patients from areas with high SCD burden or being born in South Africa to families with descendants of SCD. With low mortality and few patients lost to follow-up, this cumulatively represents a large cohort of patients requiring care over time; these children will need to be transitioned to adult services in time. Heightened awareness may prompt earlier diagnosis in patients of non-South African descent with severe anaemia, and facilitate early diagnosis and management and avoid complications. As many patients are now requiring transition to adult services, similar management protocols should be created to facilitate care within the adult services at regional hospital. Currently they are all transitioned to adult tertiary haematology services.

In- and out-patient management of SCD, and management of the it's complications is complex and consumes time and resources, placing significant demands on the healthcare system. However, with standardised protocols and robust referral systems and co-operation, patients can be managed equivalently at regional and tertiary level. Adherence issues are similar to those encountered in the management of other long-term health conditions. Thus, SCD should be managed with appropriate counselling, monitoring, and transition care.

Our study shows that using standardised management protocols at regional hospitals with access to tertiary opinions and care is an effective model in reducing demands on higher levels of care whilst maintaining an appropriate quality service to reduce morbidity and mortality rate among children with SCD. Increased access to hydroxyurea and transcranial Doppler screening may further improve outcomes, as would attention to growth and nutrition.

Acknowledgements & Contributions

We would like to acknowledge Dr Ann Van Eyssen for her contributions towards the initial protocol development. Dr Gill Schermbrucker and Dr Blythe Harvey from Victoria Hospital who assisted with access to patient folders at Victoria Hospital. Dr Dave le Roux currently manages the SCD service at New Somerset Hospital and assisted with manuscript review. Professor Alan Davidson is Head of Haematology Service at Red Cross Children's Hospital and assisted with manuscript review

Author contributions: Dr Anisa Vahed performed the research as part of her MMed dissertation, she was involved in protocol design and submission, database design and data collection, analysis and interpretation. Dr Kirsten Reichmuth was involved with study and database design, data analysis and editing. Dr Louise Cooke assisted as MMed supervisor involved in protocol design and submission and editing and revision of content for the dissertation and for journal submission. Prof Westwood established the SCD service at New Somerset Hospital and was involved in protocol design and manuscript review.

Funding. Internal funding was received from a Department of Education grant to the University of Cape Town for MMed students.

Conflict of Interest
The authors have no conflict of interest to disclose.

List of Tables & Figures

Figure 1: Frequency of new diagnosis per year (three patients diagnosed prior to study)

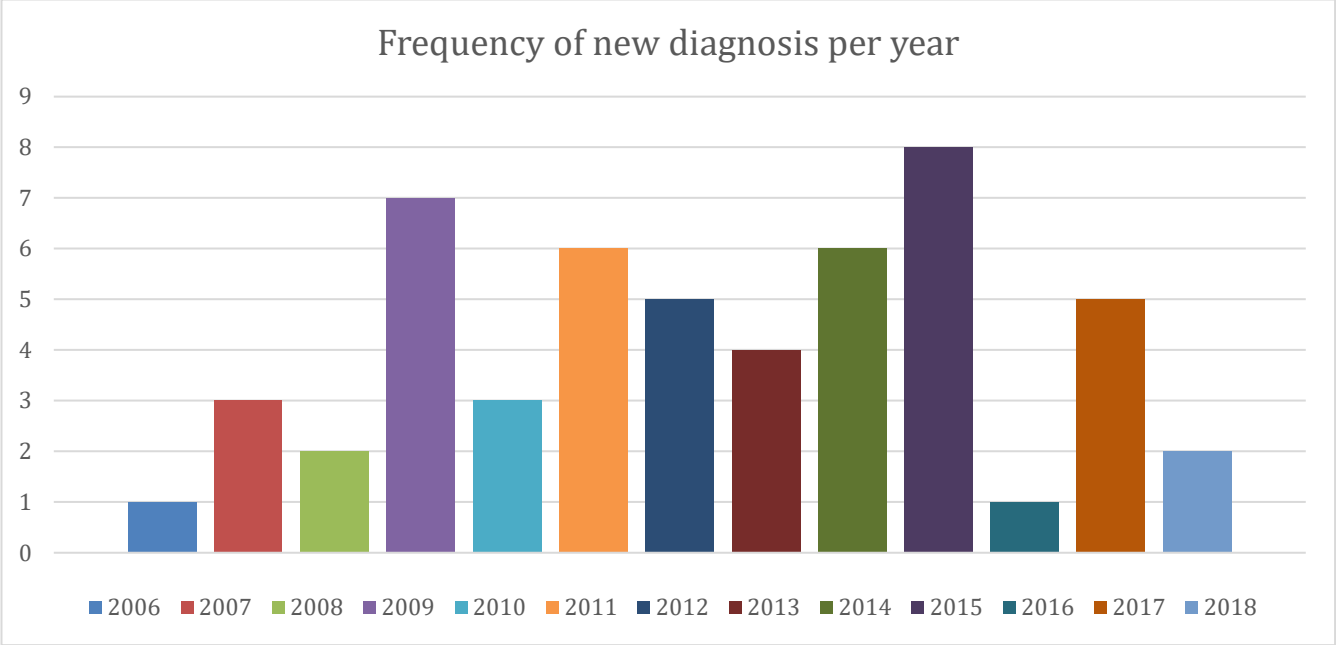


Table 1: Demographic Characteristics

Total (n=56)	**n (%)**
Age at diagnosis (months), median (IQR)	20 (7 – 44)
Sex,	
Male	32 (57%)
Female	24 (43%)
Age at diagnosis (n=53) (n, %) **(3 patients age at diagnosis unknown)**	
0-2 years	34 (63%)
2-5 years	10 (20%)
>5 years	9 (17%)
Anthropometry measures (n=56)	
WAZ, mean ± SD	-0.087 ± 1.03
WAZ, <-2, n (%)	1 (2%)
HAZ, median (IQR)	0.069 (1.51)
HAZ, <-2, n (%)	3 (6%)
WHZ, median (IQR)	-0.106 (1.49)
WHA, <-2, n (%)	2 (5%)
Place of diagnosis (n=56)	
Tertiary level (RCWMCH)	18 (31%)
NSH	21 (38%)
VH	11 (20%)
Other province/ country	6 (11%)
Patient's country of birth (n=56)	
Angola	1 (2%)
Burundi	1 (2%)
DRC	11 (18%)
Malawi	2 (4%)
Nigeria	1 (2%)
South Africa	39 (70%)
Zimbabwe	1 (2%)
Parent's country of birth (n=112)	
Angola	8 (7%)
Burundi	2 (2%)
DRC	73 (65)
Malawi	4 (4%)
Nigeria	11 (10%)
South Africa	4 (3%)
Zimbabwe	7 (6%)
Zambia	1 (1%)
Unknown	2 (2%)
Family history (n=56)	
Yes	22 (39%)
No	30 (54%)
Unknown	4 (7%)

WAZ = weight-for-age z-score, HAZ = height-for-age z-score, WHZ = weight-for-height z-score, RCWMCH = Red Cross Ward Memorial Children's Hospital, NSH = New Somerset Hospital, VH = Victoria Hospital, DRC = Democratic Republic of Congo

Table 2: Haematological parameters at time of diagnosis at regional hospital

Haematological parameters at diagnosis	**Median ± SD**	**IQR**
Hb (g/dl)	7.0±1.84	1.6-8.4
HbF (%) (range variable at age)	13.5 ± 10.89	6.5-21.3
WBC ($x10^9$/l)	16.3 ± 8.99	11.8-24.0
RBC ($x10^{12}$/l)	2.9 ± 0.83	2.5-3.4
MCV (fl)	75.5 ± 9.33	66.2-79.9
MCHC (g/dl)	33.0 ± 3.23	31.0-34.1
Platelets ($x10^9$/l)	320 ±160	213-463

Hb = haemoglobin; HbF = Fetal haemoglobin; WBC = white blood cell; RBC = red blood cell; MCV = mean corpuscular volume; MCHC = mean haemoglobin concentration

Table 3: Clinical presentation at original diagnosis at regional hospital and tertiary level hospital (Three patients age of diagnosis and initial presentation unknown, some had more than one feature)

Age at diagnosis		**incidental FBC abnormality**	**symptomatic anaemia**	**previously diagnosed**	**pain crisis**	**dactylitis**	**splenomegaly**	**screened sibling**	**other (complications)**
0-2 years	34	23	10	1	6	4	3	5	5
2-5 years	10	5	1	2	2	2	1	1	2
>5 years	9	7	1	1	2	0	0	0	0
Total	53 (3 patients unknown)	35 (66%)	12 (23%)	4 (7%)	10 (18%)	6 (11%)	4 (7%)	6 (11%)	7 (13%)

Table 4: Admission/Acute care episodes and Outcome data: includes first admission/diagnosis visit and subsequent non-scheduled admissions)

	N (%)
Admissions/ Acute care episodes	N=277
Paediatric ward admissions	205 (74%)
Emergency centre- ambulatory care	72 (26%)
Average admissions per year per child, mean (range)	2 (1-5)
Total hospital days, mean (range)	3,0 (0 – 13,0)
Acute Complications noted during admissions	N=277
Suspected Infections/ Pyrexia	178 (64%)
Vaso-occlusive Crisis	115 (41%)
Haemolytic Crisis	35 (13%)
Severe anaemia / aplastic crisis	24 (9%)
Acute splenic sequestration	20 (7%)
Dactylitis	12 (4%)
Acute chest syndrome	10 (4%)
Bone Infarction/ AVN	7 (3%)
Chronic Complications noted during admissions	n=277
Malnutrition	13 (5%)
Joint complications	3 (1%)
Leg Ulcers	1 (0.4%)
Pulmonary hypertension	0
Deep vein thrombosis	0
Vision disturbance	0
Strokes	0
Analgesia required during admission, n (%)	
Oral	242 (88%)
Intravenous	1 (11%)
None	18 (6%)
Combination	13 (5%)
Opiates required	
No	215 (80%)
Yes	54 (20%)
Blood transfusion required at time of diagnosis (n=53)	
No	38 (72%)
Yes	15 (28%)
Total number of blood transfusions required at any admission (total admissions=277)	63 (23%)
Referrals to tertiary level (total patients 23/56)	**(n=23)**
Specialist opinions from other disciplines (incl. surgical/orthopaedic)	12
Specialist haematology management	4

Special investigations	7
Lost to follow-up	9 (16%)
Patients who required no admissions	4 (7%)
Died	1 (2%)
Continued care at regional level hospital	46 (82%)

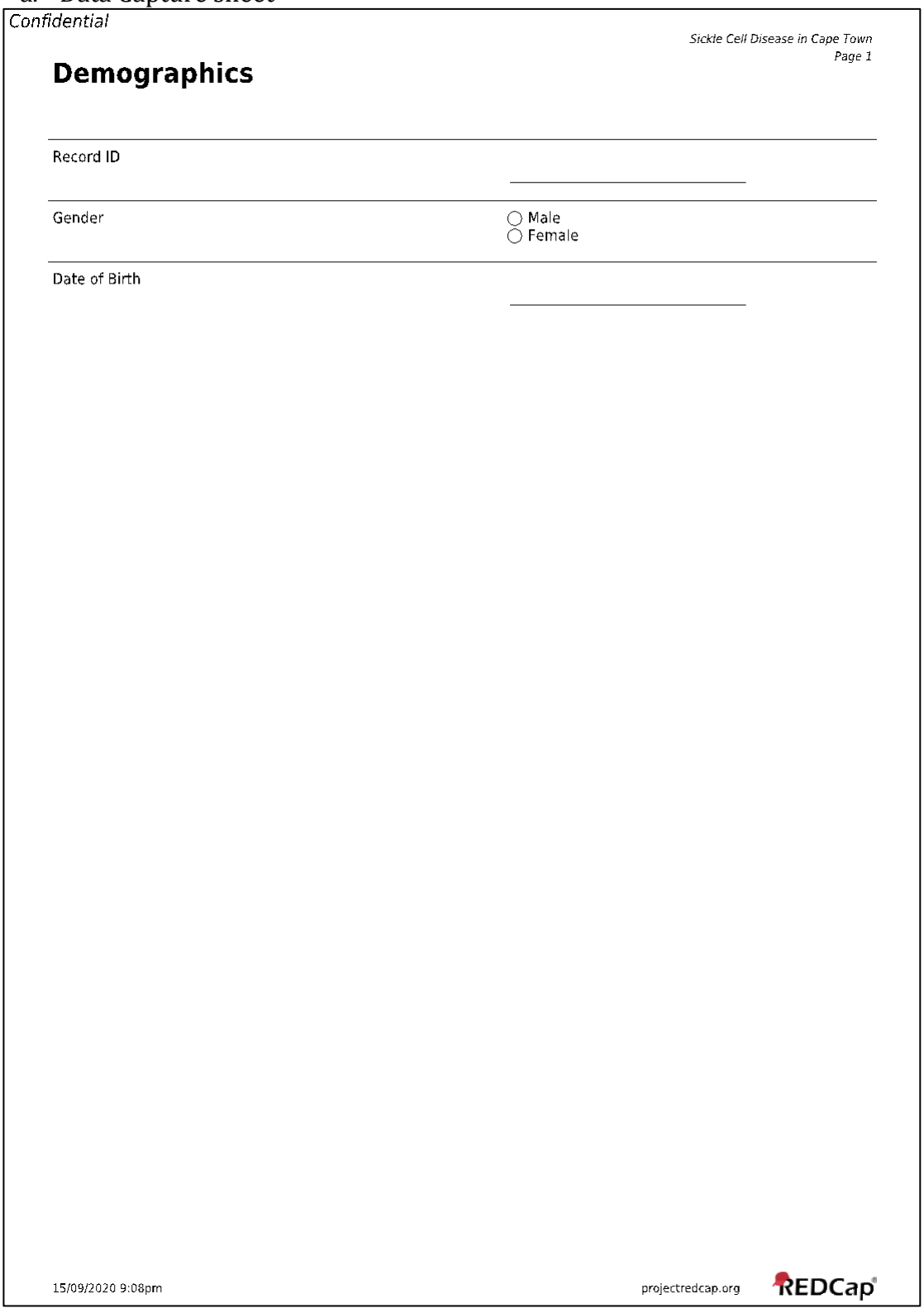
References:

1. Piel, F. B., Hay, S. I., Gupta, S. et al. Global Burden of Sickle Cell Anaemia in Children under Five, 2010-2050: Modelling Based on Demographics, Excess Mortality, and Interventions. PLoS Medicine 2013, 10(7). https://doi.org/10.1371/journal.pmed.1001484
2. M.E. Houwinga, P.J. de Pagtera, E.J. van Beersb, B.J. et al. Sickle cell disease: Clinical presentation and management of a global health Challenge. Blood reviews, Volume 37, 2019. https://doi.org/10.1016/j.blre.2019.05.004
3. Grosse, S. D., Odame, I., Atrash, H. K. et al (2011). Sickle Cell Disease in Africa- a neglected cause of early childhood mortality. AMEPRE,2011: 41(6); S398–S405. https://doi.org/10.1016/j.amepre.2011.09.013
4. Wonkam, A., Ponde, C., Nicholson, N., et al. The burden of sickle cell disease in Cape Town. South African Medical Journal. 2012;102(9):752-754. https://doi.org/10.7196/samj.5886
5. Wastnedge, E., Waters, D., Patel, S., et al. The global burden of sickle cell disease in children under five years of age: a systematic review and meta-analysis. *J Glob Health*. 2018;8(2):021103. https://doi.org/10.7189/jogh.08.021103
6. Kadima, B. T., Lambert, J., & Ehungu, G., et al. High rate of sickle cell anaemia in Sub-Saharan Africa underlines the need to screen all children with severe anaemia for the disease. Acts Paediatrics, 2015(104);1269–1273. https://doi.org/10.1111/apa.13040
7. World Health Organisation. *59th World Health Assembly*. Geneva, Switzerland: World Health Organisation; 2006. Sickle cell anaemia. Agenda item 11.4.
8. Chakravorty, S. & Williams, T. N. Sickle cell disease: a neglected chronic disease of increasing global health importance. Archives of disease in childhood 2015(100);48–53. https://doi.org/10.1136/archdischild-2013-303773
9. Makani J, Sangeda RZ, Nnodu O, et al. SickleInAfrica. *Lancet Haematol*. 2020;7(2):e98-e99. https://doi.org/10.1016/S2352-3026(20)30006-5
10. Fernandes, Q. Therapeutic strategies in Sickle Cell Anemia: The past present and future. Life Sciences, 2017;178, 100-108. https://doi.org/10.1016/j.lfs.2017.03.025
11. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of Sickle Cell Disease: Summary of the 2014 Evidence-Based Report by Expert Panel Members. *JAMA.* 2014;312(10):1033–1048. https://doi.org/10.1001/jama.2014.10517
12. Booth, C., Inusa, B., & Obaro, S. K. Infection in sickle cell disease: A review. International Journal of Infectious Diseases, Jan 2010(14); 2–12. https://doi.org/10.1016/j.ijid.2009.03.010
13. Challenge. Houwinga, M.E., de Pagtera, P.J., van Beersb, E.J., et al. Sickle cell disease: Clinical presentation and management of a global health. Blood Reviews, Vol: 37, Page: 100580. https://doi.org/10.1016/j.blre.2019.05.004
14. Rahimy, M. C., Gangbo, A., Ahouignan, G., et al. Effect of a comprehensive clinical care program on disease course in severely ill children with sickle cell anemia in a sub-Saharan African setting. Blood, 2003;102(3), 834–838. http://dx.doi.org/10.1182/blood-2002-05-1453.
15. Cober, M. P., & Phelps, S. J.. Penicillin prophylaxis in children with sickle cell disease. The Journal of Pediatric Pharmacology and Therapeutics : JPPT : The Official Journal of PPAG, 2010; 15(3), 152–9.

16. Alli, N. A., Patel, M., Alli, H. D., et al. Recommendations for the management of sickle cell disease in South Africa. South African Medical Journal, 2014;104(11), 743–751. https://doi.org/10.7196/samj.8470
17. Heeney, M. M. & Ware, R. E. Hydroxyurea for children with sickle cell disease. Hematology/oncology clinics of North America, Volume 24(1), 199–214. https://doi.org/10.1016/j.hoc.2009.11.002
18. Lughetti, L., Bigi, E., & Venturelli, D. Novel insights in the management of sickle cell disease in childhood. *World journal of clinical pediatrics*, February 2016; 8(51), 25–34. https://doi.org/10.5409/wjcp.v5.i1.25

Appendices:

a. Data Capture sheet



Confidential

Sickle Cell Disease in Cape Town
Page 1

Demographics

Record ID	_____
Gender	◯ Male ◯ Female
Date of Birth	_____

15/09/2020 9:08pm

projectredcap.org

REDCap

Diagnosis

Record ID	_____
Date of Diagnosis	_____
Place of Diagnosis	◯ New Somerset Hospital ◯ Victoria Hospital ◯ Red Cross Hospital ◯ Other Country
Electrophoresis result known	◯ Yes ◯ No
Haemaglobin S	_____
Haemaglobin F	_____
Haemaglobin A	_____
Haemaglobin A2	_____
Any trait noted on result	_____
Haemaglobin on diagnosis	_____
WBC	_____
Red Cell Count	_____
MCV	_____
MCHC	_____
Platelets	_____

Admission

Record ID	_____
Date of admission	_____
Date of discharge	_____
Diagnosis made on this admission?	◯ Yes ◯ No
Type of visit to hospital	◯ Casualty ◯ Paediatric Ward
Weight	_____ (kg)
height	_____ (cm)
Reason for admission	☐ Incidental FBC abnormality ☐ Pain Crisis ☐ Screened sibling ☐ Dactylitis ☐ Symptomatic Anaemia ☐ Previously diagnosed in another institute ☐ Infection ☐ Other
If Other, please explain	_____
If Infection, what type of infection	_____
If any infections. What were the documented cultures?	_____
Acute complications noted on this admission	☐ Dactylitis ☐ Pain Crisis ☐ Bone Infarction/ Avascular necrosis ☐ Acute splenic sequestration ☐ Severe Anaemia/Aplastic Crisis ☐ Infections ☐ Vaso-occlusive crisis ☐ Haemolytic Crisis

OPD Visit

Record ID	_____
Date of OPD visit	_____
Previous missed OPD visits	◯ Yes ◯ No
Adherence with medication	◯ Yes ◯ No
Receiving Hydroxyurea?	◯ Yes ◯ No
Receiving Folate?	◯ Yes ◯ No
Receiving Pen VK?	◯ Yes ◯ No
Symptoms noted over last period	_____
Issues discussed	☐ Management on fever episode ☐ Management of pain ☐ Danger signs/emergency care ☐ Prevention of infection ☐ Continuous medication ☐ Education ☐ Genetic counselling ☐ Family & Finance ☐ Reproduction ☐ Nutrition ☐ Travel
Issues raised at OPD visit	_____
Transfer to Tertiary	◯ Yes ◯ No
Reason for transfer	◯ Chronic Care ◯ Investigations
Reason for chronic Care?	_____
Investigation required and result	_____
Transferred back to regional hospital for OPD care	_____

Medication

Record ID	
Hydroxyurea started	
Hydroxyurea stopped	
Reason for stopping hydroxyurea	
Pen VK– date started	
PEN VK–Stopped	
Reason for stopping Pen Vk/ Not starting on Pen VK	
Folate Started	

Immunizations at time of last visit

Record ID	_____
Pneumococcal vaccine up-to-date	◯ Yes ◯ No ◯ Outstanding
Last Pneumococcal vaccine given	_____
Haemophilus vaccine up-to-date	◯ Yes ◯ No ◯ Outstanding
Last Haemophilus vaccine given	_____
Influenza Vaccine given	◯ Yes ◯ No ◯ Outstanding

b. Human Research Ethics Committee Approval:

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

31 January 2018

HREC REF: 028/2018

Dr ML Cooke
Paediatrics
5th floor
ICH Building
Red Cross Children's Hospital

Dear Dr Cooke

PROJECT TITLE: SICKLE CELL DISEASE IN CAPE TOWN: A PERSPECTIVE FROM TWO REGIONAL HOSPITALS (MMED CANDIDATE - DR A VAHED)

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

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 January 2019.

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

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.

The HREC acknowledge that the student, Dr Anisa Vahed will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

c. Annual Health Sciences Human Research Ethics Approval

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE
31 JAN 2019
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

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

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.01.2020
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	3/2/19

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	29 January 2019		
HREC REF Number	028/2018	Current Ethics Approval was granted until	30 January 2019
Protocol title	Sickle Cell Disease in Cape Town: A perspective from two regional hospitals		
Principal Investigator	Dr Melissa Louise Cooke		
Department / Office Internal Mail Address	Paediatrics- 5th floor ICH building, Red Cross Hospital		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☐ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☐	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	
Sickle Cell Disease in Cape Town: A perspective from two regional hospitals- HREC 028/2018.	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		20
Total number of records or specimens collected, reviewed or stored since last progress report		20
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	☐ No

4. Signature

Signature of PI		Date	29 January 2019

d. Annual Health Sciences Human Research Ethics Approval

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

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

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/01/2021
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	20/1/2020

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	16 January 2020		
HREC REF Number	028/2018	Current Ethics Approval was granted until	30 January 2020
Protocol title	Sickle Cell Disease in Cape Town: A perspective from two regional hospitals		
Principal Investigator	Dr Melissa Louise Cooke		
Department / Office Internal Mail Address	Paediatrics- 5th floor ICH building, Red Cross Hospital		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☑ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☑	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	
Sickle Cell Disease in Cape Town: A perspective from two regional hospitals- HREC 028/2018.	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		60
Total number of records or specimens collected, reviewed or stored since last progress report		40
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	☑ No

4. Signature

Signature of PI		Date	16 January 2020

HUMAN RESEARCH ETHICS COMMITTEE
20 JAN 2020
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

(Note: Please complete the Closure form (FHS019) if the study is completed within the approval period)

Signatures on above appendices removed

e. NSH Provincial Government Access

Western Cape Government
Health

Health impact assessment
Health research sub-directorate
Health.Research@westerncape.gov.za
Tel: +27 21 483 0866; fax: +27 21 483 9895
5th Floor, Norton Rose House, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za

REFERENCE: WC_201802_010
ENQUIRIES: Dr Sabela Petros

University of Cape Town

Anzio Road

Observatory

Cape Town

7925

For attention: Dr Anisa Vahed, Dr Melissa Louise Cooke

Re: Sickle Cell Disease in Cape Town: a perspective from two regional hospitals.

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research. Please contact following people to assist you with any further enquiries in accessing the following sites:

New Someret Hospital	**Dr Donna Stokes**	**021 402 2856**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

f. Victoria Hospital Government Access

Western Cape Government
Health

Health impact assessment
Health research sub-directorate
Health.Research@westerncape.gov.za
Tel: +27 21 483 0866; fax: +27 21 483 9895
5th Floor, Norton Rose House, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: WC_201802_010
ENQUIRIES: Dr Sabela Petros

University of Cape Town

Anzio Road

Observatory

Cape Town

7925

For attention: Dr Anisa Vahed, Dr Melissa Louise Cooke

Re: Sickle Cell Disease in Cape Town: a perspective from two regional hospitals.

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research. Please contact following people to assist you with any further enquiries in accessing the following sites:

Victoria Hospital	**Dr Graeme Dunbar**	**021 799 1211**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

g. Turnitin Report

vhdani001:Draft_10_SCD_MMed_.docx

ORIGINALITY REPORT

18%	14%	11%	8%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	hdl.handle.net Internet Source	3%
2	www.samj.org.za Internet Source	2%
3	Submitted to University of Cape Town Student Paper	1%
4	sicklecelltn.com Internet Source	1%
5	open.uct.ac.za Internet Source	1%
6	Submitted to Polk State College Student Paper	1%
7	docplayer.net Internet Source	1%