RESEARCH ARTICLE

Characterising demographics, knowledge, practices and clinical care among patients attending sickle cell disease clinics in Eastern Uganda [version 2; peer review: 2 approved]

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Abstract

Background: In Uganda to date, there are neither established registries nor descriptions of facility-based sickle cell disease (SCD) patient characteristics beyond the central region. Here, we summarize data on the baseline clinical characteristics and routine care available to patients at four clinics in Eastern Uganda as a prelude to a clinical trial.

Methods: Between February and August 2018, we conducted a cross-sectional survey of patients attending four SCD clinics in Mbale, Soroti, Atutur and Ngora, all in Eastern Uganda, the planned sites for an upcoming clinical trial (H-PRIME: ISRCTN15724013). Data on socio-demographic characteristics, diagnostic methods, clinic schedules, the use of prophylactic and therapeutic drugs, clinical complications and patient understanding of SCD were collected using a structured questionnaire.

Results: Data were collected on 1829 patients. Their ages ranged from 0 to 64 years with a median (IQR) of 6 (3-11) years. 49.1% of participants were male. The majority (1151; 62.9%) reported a positive family history for SCD. Approximately half knew that SCD is inherited from both parents but a substantial proportion did not know how SCD is transmitted and small numbers believed that it is acquired by either transfusion or from other people. Only 118/1819 (6.5%) participants...
had heard about or were using hydroxyurea while 356/1794 (19.8%) reported stigmatization. Participants reported a median of three (IQR 1-4) hospital admissions during the preceding 12 months; 80.8% had been admitted at least once, while 14.2% had been admitted more than five times. Pain was the most common symptom, while 83.9% of those admitted had received at least one blood transfusion.

**Conclusion:** The majority of patients attending SCD clinics in Eastern Uganda are children and few are currently being treated with hydroxyurea. The data collected through this facility-based survey will provide background data that will be useful in planning for the H-PRIME trial.

**Keywords**
Sickle Cell Disease, knowledge, care, wellbeing, Eastern Uganda

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Introduction

Following years of neglect in many parts of sub-Saharan Africa (SSA), sickle cell disease (SCD) is increasingly being recognized as a disease of major public health significance. Nevertheless, the lack of universal newborn screening, SCD registries and SCD surveillance programmes mean that accurate data on the total numbers living with the disease and its clinical consequences remain rather limited. Globally, approximately 330,000 children are born with the most common form of SCD (HbSS) every year, the majority (>80%) in SSA where carrier frequencies of 10–20% are common, and up to 2% of all births are affected. Typically, SCD causes chronic ill health that is interposed by acute complications, which result in cumulative damage to multiple end-organs. It has been estimated that in many parts of SSA between 5 and 16% of all under-five mortality is attributable to SCD.

Uganda is ranked as the country with the fifth highest birth rate of children with SCD globally and the highest in Eastern Africa. Throughout much of the country, the carrier frequency is between 9 and 21% and an estimated 10–15,000 babies are born with SCD every year. Nevertheless, few facility-based studies have been published that describe the characteristics of cases, their clinical care or patterns of disease awareness in Uganda. In the current study, we present the results of a descriptive study that documents these parameters from SCD clinics within the Eastern Region of the country in preparation for an upcoming clinical trial that will investigate potential options for the pragmatic treatment of SCD in low resource settings.

Methods

Ethical statement

Ethical approval for the study was obtained from the Mbale Regional Referral Hospital Research & Ethics Committee (MRRH-REC; approval number MRRH-REC IN-COM 007/2018) while written permission to conduct the survey was also obtained from each of the health facilities individually. Written informed consent to administer the questionnaire was obtained from all participants or their parents who were approached directly and individually in the study clinics. Participants were also informed about the plans for data sharing and publication. The Mbale Clinical Research Institute, a research entity affiliated to the Uganda National Health Research Organization (UNHRO), permits the publication of this manuscript.

Study design and site

Our study was conducted in the Elgon and Teso sub-regions of Eastern Uganda where the prevalence rates of SCD is high. There are 24 district level health facilities within these regions that offer general care for all patients, including subjects with SCD. However, only five of these facilities have dedicated SCD clinics. In the current study, we collected data from four of these clinics, one in Elgon and three in the Teso sub regions, selected on the basis that all will contribute participants for the upcoming H-PRIME trial. Between February and August 2018, we conducted a cross-sectional survey at our four target clinics at (1) Mbale Regional Referral Hospital; (2) Atutur District Hospital; (3) Ngora Health Centre IV; and (4) Soroti Regional Referral Hospital. Details of these government-aided not-for-profit, charge-free facilities are summarized in the Supplementary Table (see Extended data). Following a process of informed consent, all patients attending the SCD clinics held at these hospitals on survey days were invited to participate in the survey. Each was approached individually by a member of the study team who administered the consenting materials and sought individual informed consent. The only inclusion criteria were attendance at one of the study clinics on one of the surveillance days plus consent to participate while any patient declining consent was excluded. Before finalizing, the questionnaire was first piloted in a small group of SCD patients with their families who were attending the SCD clinic within the four health facilities. The pilot involved testing the wording, the order of questions, the range of possible answers and the clarity of the instructions for both the whole questionnaire and the individual questions.

Data collection

A questionnaire was designed to address a range of issues including the socio-demographic characteristics of patients, the method of diagnosis, the frequency of clinic attendance, knowledge and understanding of SCD, the use of therapeutic and prophylactic drugs and the frequency of SCD-specific crises, inpatient admissions and blood transfusions. In addition, data were collected on disease complications, and awareness of hydroxyurea (see Extended data). The questions on the study questionnaire were read to the study participants by study personnel in their preferred language, who then completed the questionnaire on behalf of study participants. Responses were deferred to parents or carers of those <18 years and to the participant themselves if ≥18 years. The whole process took an average of 20–30 minutes / participant interviewed.

Statistical analysis

The sampling approach was pragmatic, and no sample-size calculation was considered. Data were analyzed using the R statistical package V3.6.0. Categorical variables were analyzed as frequencies, while continuous variables were computed as medians with interquartile ranges (IQR). Participants were stratified into the age groups ≤5 years and >5 years. Between-group differences were assessed using the χ² test. P-values of <0.05 were considered significant.
Results
While clinic records were not computerised and were somewhat incomplete, the total number of patients who were registered at these 4 SCD clinics was 2257. When conducting the survey, we noticed that some of the clinics had registered fewer patients than they were actually handling. All 1829 patients who were in attendance during the study period and who were invited to participate gave their consent and were included in the study, so at minimum, 428 (19%) of the registered participants did not attend their clinics during the course of the survey.

Characteristics of respondents
The social and demographic characteristics of the 1829 study participants are summarized in Table 1. Their age range was 0 to 64 years with a median (IQR) of 6 (3–11) years, while 858/1744 (49.1%) were females. More than half (1006/1820; 55.3%) were >5 years, only 371 (20.3%) being children <2 years and 92 (5.1%) being adults >18 years. Three of the four study sites were located in the Teso sub-region of Eastern Uganda and as a result, the majority of participants (1319/1826; 72.2%) were Iteso, followed by 204 (11.2%) from the Bagisu ethnic group, the balance being Kumam, Bagwere and others. The majority of subjects (1588/1782; 89.1%) were Christian, while 155 (8.7%) and 39 (2.2%) were either Muslim or from other religions, respectively. A majority (1151; 62.9%) had another family member with SCD, of whom 298 (16.3%) had died. Of these deaths, 69.9% were among children <5 years old. Around half (920/176; 52.2%) of participants reported visiting the SCD clinic at least once every month and 629/1761 (35.7%) at least once every 3 months. A total of 143/1761 (8.1%) reported that they had never previously attended the SCD clinic for their treatment or care.

Hospitalizations
The median number of hospitalizations within the preceding twelve-month period was three (IQR 1–4). Of 1707 participants with data on hospitalization, 1380 (80.8%) had been admitted at least once, while 243 (14.2%) had been admitted more than five times (Table 1). The most common symptoms at admission are summarized in Table 2. Overall, pain was present in 1261 of 1342 (91.8%) admissions, while other common syndromes included severe anaemia, hand-foot syndrome and malaria. In general, patterns of clinical illness were similar across age-groups, although hand-foot syndrome and pneumonia were significantly more common (P<0.0001), while pain was significantly less common (p=0.0002) among children <5 years old. Of the participants who had been admitted to hospital during the preceding year, 951/1133 (83.9%) had received at least one blood transfusion, while 151 (13.3%) had received five or more (Table 3).

Knowledge of SCD
The perceptions of participants with regard to SCD are summarized in Table 4. More than half (934/1729; 54.0%) understood that SCD is inherited from both parents although small proportions believed that it was acquired through either a blood transfusion (17; 1%) or through personal contact (3; 0.2%). Almost half of all participants (775; 45%) had no understanding of how the disease is acquired. The metabisulphite sickling test and haemoglobin electrophoresis were reported as the two most common methods of diagnosis. Feelings of stigmatization were reported by 356/1794 participants (19.8%).

Table 1. Socio-demographic characteristics of respondents.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>858 (49.1)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>≤5 years</td>
<td>814 (44.7)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>1006 (55.3)</td>
</tr>
<tr>
<td>Tribe</td>
<td></td>
</tr>
<tr>
<td>Iteso</td>
<td>1319 (72.2)</td>
</tr>
<tr>
<td>Gishu</td>
<td>204 (11.2)</td>
</tr>
<tr>
<td>Kumam</td>
<td>114 (6.2)</td>
</tr>
<tr>
<td>Bagwere</td>
<td>78 (4.3)</td>
</tr>
<tr>
<td>Others</td>
<td>111 (6.1)</td>
</tr>
<tr>
<td>Religion</td>
<td></td>
</tr>
<tr>
<td>Christians</td>
<td>1588/1782 (89.1)</td>
</tr>
<tr>
<td>Muslims</td>
<td>155/1782 (8.7)</td>
</tr>
<tr>
<td>Others</td>
<td>39/1782 (2.2)</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>Relative with SCD</td>
<td>1151/1829 (62.9)</td>
</tr>
<tr>
<td>Siblings died of SCD</td>
<td>298/1829 (16.2)</td>
</tr>
<tr>
<td>Self-reported clinic visits</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>143/1761 (8.1)</td>
</tr>
<tr>
<td>Bi-weekly</td>
<td>21/1761 (1.2)</td>
</tr>
<tr>
<td>Monthly</td>
<td>920/1761 (52.2)</td>
</tr>
<tr>
<td>Bi-monthly</td>
<td>39/1761 (2.2)</td>
</tr>
<tr>
<td>Every 3 months</td>
<td>629/1761 (35.7)</td>
</tr>
<tr>
<td>Every 6 months</td>
<td>1/1761 (0.1)</td>
</tr>
<tr>
<td>Once a year</td>
<td>8/1761 (0.5)</td>
</tr>
</tbody>
</table>

SCD, sickle cell disease.

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Table 2. Features present during the most recent hospitalization among respondents who were admitted within the preceding 12 months.

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Overall, N (%)</th>
<th>≤5 years (%)</th>
<th>&gt;5 year (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totals</td>
<td>1374</td>
<td>656</td>
<td>718</td>
<td>n/a</td>
</tr>
<tr>
<td>Painful crisis</td>
<td>1261 (91.8)</td>
<td>583 (88.8)</td>
<td>678 (94.4)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Fever</td>
<td>949 (69.1)</td>
<td>463 (70.5)</td>
<td>486 (67.6)</td>
<td>0.24</td>
</tr>
<tr>
<td>Anaemia</td>
<td>852 (62.0)</td>
<td>409 (62.3)</td>
<td>443 (61.6)</td>
<td>0.80</td>
</tr>
<tr>
<td>Hand foot syndrome</td>
<td>697 (50.7)</td>
<td>391 (59.6)</td>
<td>306 (42.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Malaria</td>
<td>622 (45.3)</td>
<td>288 (43.9)</td>
<td>334 (46.5)</td>
<td>0.33</td>
</tr>
<tr>
<td>Convulsions</td>
<td>20 (1.5)</td>
<td>11 (1.6)</td>
<td>9 (1.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>Very large spleen</td>
<td>83 (6.0)</td>
<td>39 (5.9)</td>
<td>44 (6.1)</td>
<td>0.88</td>
</tr>
<tr>
<td>Bone infection</td>
<td>22 (1.6)</td>
<td>11 (1.7)</td>
<td>11 (1.5)</td>
<td>0.83</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>109 (7.9)</td>
<td>73 (11.1)</td>
<td>36 (5.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>25 (1.8)</td>
<td>9 (1.4)</td>
<td>16 (2.2)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

* Clinical features are self-reported rather than being based on hospital records. Most participants reported more than one clinical syndrome.

Table 3. The number of blood transfusions received by study participants during the preceding 12 months.

<table>
<thead>
<tr>
<th>Number of blood transfusions (self reported)</th>
<th>Totals</th>
<th>Age in years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤5</td>
<td>&gt;5</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>0</td>
<td>182 (16.1)</td>
<td>86 (16.1)</td>
<td>96 (16.0)</td>
</tr>
<tr>
<td>1</td>
<td>352 (31.0%)</td>
<td>194 (36.3)</td>
<td>158 (26.4)</td>
</tr>
<tr>
<td>2</td>
<td>235 (20.7%)</td>
<td>117 (21.9)</td>
<td>118 (19.7)</td>
</tr>
<tr>
<td>3</td>
<td>137 (12.1%)</td>
<td>59 (11.0)</td>
<td>78 (13.0)</td>
</tr>
<tr>
<td>4</td>
<td>76 (6.7%)</td>
<td>34 (6.4)</td>
<td>42 (7.0)</td>
</tr>
<tr>
<td>5</td>
<td>38 (3.5%)</td>
<td>11 (2.1)</td>
<td>27 (4.5)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>113 (9.8%)</td>
<td>33 (6.2)</td>
<td>80 (13.4)</td>
</tr>
</tbody>
</table>

Table 4. Participant knowledge of sickle disease and awareness of hydroxyurea.

<table>
<thead>
<tr>
<th>Question</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the cause of SCD?</td>
<td></td>
</tr>
<tr>
<td>Inherited</td>
<td>934/1729 (54.0)</td>
</tr>
<tr>
<td>Acquired from blood transfusion</td>
<td>17/1729 (1.0)</td>
</tr>
<tr>
<td>Acquired from body contact</td>
<td>3/1729 (0.2)</td>
</tr>
<tr>
<td>Don’t know</td>
<td>775/1729 (44.8)</td>
</tr>
<tr>
<td>Have you heard about hydroxyurea?</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1711/1829 (93.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>118/1829 (6.5)</td>
</tr>
<tr>
<td>Patient or a family member are using hydroxyurea</td>
<td>41/1829 (2.2)</td>
</tr>
<tr>
<td>If using hydroxyurea, where do you get the drug?</td>
<td></td>
</tr>
<tr>
<td>Private pharmacy</td>
<td>15/41(36.5)</td>
</tr>
<tr>
<td>Private clinic/hospital</td>
<td>13/41(31.7)</td>
</tr>
<tr>
<td>Projects</td>
<td>4/41 (9.7)</td>
</tr>
<tr>
<td>Government hospital</td>
<td>0/41 (0)</td>
</tr>
</tbody>
</table>

SCD, sickle cell disease.
Awareness and use of hydroxyurea

In total, 118/1829 (6.5%) of study participants had heard about hydroxyurea. None were taking it personally but 41 (2.2%) reported that a relative was using it (Table 4). The main sources of hydroxyurea for relatives using the drug were either private clinics or community pharmacies (Table 4).

Antibiotics and immunization

The routine treatments received by participants are summarised in Table 5. It was found that 777/1820 participants (42%) were receiving antimalarial prophylaxis with sulphadoxine/pyrimethamine, the current standard of care for children with SCD in Uganda\(^1\), while 940 (51.6%) were taking chloroquine. Overall rates of immunization with BCG, measles, polio and DPT vaccines were >90%, while that for the PCV10 pneumococcal vaccine was 626/1820 (34.4%). A significant proportion of those >5 years, in whom penicillin prophylaxis is not part of the Ugandan standard of care\(^1\), were receiving either oral penicillin-V (105/1006; 10.4%) or intramuscular benzathine penicillin (49/1006; 4.9%).

Laboratory capacity

Tests that were commonly conducted on SCD patients at the study facilities are summarised in Table 6. Varying levels of

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Overall, N (%)</th>
<th>Age group &lt;=5 years (%)</th>
<th>&gt;5 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1820 (100)</td>
<td>814 (100)</td>
<td>1006 (100)</td>
</tr>
<tr>
<td>Antimalarial prophylaxis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulphadoxine/pyrimethamine</td>
<td>777 (42.7)</td>
<td>340 (41.8)</td>
<td>437 (43.4)</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>940 (51.6)</td>
<td>399 (49.0)</td>
<td>541 (53.8)</td>
</tr>
<tr>
<td>Proguanil</td>
<td>2 (0.1)</td>
<td>0 (0.0)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Use of antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin V</td>
<td>211 (11.6)</td>
<td>106 (13.0)</td>
<td>105 (10.4)</td>
</tr>
<tr>
<td>Benzathine Penicillin</td>
<td>155 (8.5)</td>
<td>106 (13.0)</td>
<td>49 (4.9)</td>
</tr>
<tr>
<td>Immunizations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG</td>
<td>1796 (98.7)</td>
<td>805 (98.9)</td>
<td>991 (98.5)</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>626 (34.4)</td>
<td>422 (51.8)</td>
<td>204 (20.3)</td>
</tr>
<tr>
<td>Measles</td>
<td>1742 (95.7)</td>
<td>765 (94.0)</td>
<td>977 (97.1)</td>
</tr>
<tr>
<td>Polio</td>
<td>1568 (86.2)</td>
<td>700 (86.0)</td>
<td>868 (86.3)</td>
</tr>
<tr>
<td>DPT</td>
<td>1770 (97.3)</td>
<td>789 (96.9)</td>
<td>981 (97.5)</td>
</tr>
</tbody>
</table>

Table 6. Laboratory tests available by facility.

<table>
<thead>
<tr>
<th>Laboratory tests commonly performed</th>
<th>Facility Mbale</th>
<th>Soroti</th>
<th>Atutur</th>
<th>Ngora</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete blood count</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Red cell indices</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Haemoglobin F concentration</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sickle diagnostics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb electrophoresis/analysis</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sickling test</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Malaria diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral blood film</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rapid diagnostic tests</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum biochemistry tests</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Microbiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood culture</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Culture and sensitivity</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
laboratory capacity were available at these health facilities for investigations related to the management of SCD. For example, although all had the capacity to perform complete blood counts and tests for malaria, only Mbale and Soroti Regional Referral Hospitals were able to conduct clinical chemistry assays such as renal and liver function tests. Neither Mbale nor Soroti Regional Referral Hospitals had facilities for measuring levels of haemoglobin F (HbF), but the other sites had access to HbF measurements through referral to the Central Public Health Laboratory in Kampala. None of the clinics had direct access to haemoglobin electrophoresis. Whenever laboratory services were not available, patients at all four clinics were sent to private laboratories.

Discussion

Through this survey we have investigated the demographics, knowledge, practices and a range of factors relating to clinical care of patients attending four SCD clinics in Eastern Uganda as a prelude to the upcoming H-PRIME clinical trial. All four clinics are in an area with a high prevalence of SCD and have treated patients with SCD for many years.

In contrast to clinics in Europe and North America, where the frequency of attendance at SCD clinics is typically tailored to patient needs, more than half of respondents were attending clinic on a monthly basis. To the best of our knowledge, there have been no evaluations of the relative effectiveness of different clinic schedules. Although transport costs have been cited as a potential barrier to adherence, more than 90% of patients at the Mbale clinic comply with their monthly visits (PO-O, unpublished report). Nevertheless, it seems likely that such regular attendance must represent a significant challenge for patients, their families and the medical staff involved and that if safe, a less frequent schedule would be of benefit to all.

The poor understanding by participants of even some of the most basic facts about SCD, including its mode of acquisition, was striking. Almost half of respondents did not know how the disease is acquired, and small proportions believed that it could be caught through either blood transfusion or personal contact. Similarly, many participants reported that they felt stigmatized, a finding that accords with observations from other studies. The need for education about SCD, both in these clinics and within the wider society, are clear priorities for these clinics going forwards.

Previous studies have highlighted the high rate of mortality within Africa among children with undiagnosed SCD, with one suggesting that historically this may have been as high as 90% in those <5 years. While a large proportion of the patients attending these SCD clinics were <5 years old, the age range of respondents was wide (0 to 64 years), and almost half were >5 years old. This observation supports one recent study, conducted in Kenya, which concluded that mortality can be substantially improved by the introduction of just a handful of simple interventions that include education and measures to prevent both malaria and bacterial infections. Nevertheless, it is also clear from our survey that irrespective of improved survival, many respondents were facing significant health challenges, exemplified by a high rate of admission to hospital. More than 80% had been admitted to hospital in the preceding year and almost one fifth had been admitted five times or more. Pain was a common feature during those admissions, occurring at a substantially higher prevalence than that reported in several recent studies. While the reason for this difference is unknown, we hypothesize that it might reflect socio-economic issues and the local epidemiology of conditions such as bacterial diseases or malaria. A further observation was the high rate of transfusion among study participants. More than 80% of those who had been admitted to hospital during the preceding year had received at least one blood transfusion, and 13.3% had received five transfusions or more. This reinforces the message from a number of recent studies that have reported the heavy demand that patients with SCD place on blood transfusion services in a number of African settings. For example, in the recently reported multi-centre Transfusion and Treatment of Severe Anaemia in African Children Trial (TRACT), 33% of those recruited with severe and complicated anaemia had SCD, of whom almost half had not been previously diagnosed.

Our study had a number of limitations, not least the fact that our questionnaire was administered over a limited period of time, meaning that it was not possible for us to capture questions such as the seasonal patterns of specific complications. Nevertheless, taken together, the results of our survey suggest that many of the participants could potentially stand to benefit from access to disease-modifying therapies. Of those that are commonly available, all are either too complex to administer or too expensive to be realistic options, with one exception - hydroxyurea. Hydroxyurea is an orally-administered drug that is included for the treatment of SCD in the WHO list of essential medicines for children. Where it has been used in resource-rich countries with regular monitoring, the safety record of hydroxyurea has been excellent. Nevertheless, experience in the use of hydroxyurea in Africa is limited, where a number of potential safety concerns have been raised. Perhaps most importantly, one of the mechanisms of action is through the induction of some degree of immunosuppression. That necessitates the careful supervision of treatment and regular laboratory monitoring when hydroxyurea is used. In two recent studies it has been shown that hydroxyurea can be safely used in Africa when accompanied by regular laboratory monitoring. However, our current survey shows that the laboratory services that are currently available at our study sites would not be adequate to support the use of hydroxyurea in a similar way. Indeed, not all clinicians even have access to reliable diagnostic tests and as a result, we cannot even be sure that all those attending these clinics definitely have SCD. In Uganda, most patients with SCD live in rural settings where both laboratory capacity and specialist support are limited. In our survey, none of the patients were receiving hydroxyurea, although a small proportion had a relative who was using it. Further studies that evaluate the use of hydroxyurea in resource-poor settings such as these - a major aim of the H-PRIME trial - are urgently needed.

Finally, our study shows that the standards of care, as laid out in The Uganda Clinical Guidelines 2016, with regard to the prevention of infections in children with SCD are not...
being followed systematically. While these guidelines recommend the use of daily penicillin V for bacterial prophylaxis in children <5 years and monthly sulphadoxine/pyrimethamine for the prevention of malaria, we found that a high proportion of older participants were still taking penicillin and that more than half were using chloroquine instead of sulphadoxine/pyrimethamine. Further studies regarding the optimal treatments for both are also needed.

**Conclusions**

Our survey illustrates some of the problems faced by those affected by SCD, and by their health-care providers. Although the results of our study should be interpreted with caution, given that many of our observations relied on patient recall rather than observed events, they do allow us to make some important deductions. First, patient and caregiver knowledge of SCD within this cohort was very low. There is high morbidity in SCD patients represented by frequent clinic visits, frequent admissions, and frequent blood transfusions. Hydroxyurea is not in use in the setting of this study, yet it has been found to reduce morbidities in SCD. There remains much to be done to improve the lives of people living with SCD in low income countries. Locally appropriate interventions need to be based on research conducted locally, the central aim of the H-PRIME trial.

**Data availability**

**Underlying data**

Harvard Dataverse: Data for: Characterising demographics, knowledge, practices and clinical care among patients attending sickle cell disease clinics in Eastern Uganda. [https://doi.org/10.7910/DVN/AIDNOV](https://doi.org/10.7910/DVN/AIDNOV)

This project contains the following underlying data:

- SCD_Manuscript_data26042020.xlsx (questionnaire answers and sociodemographic characteristics for all participants)
- SCD_Manuscript_data dictionary.tab (data dictionary)

**Extended data**

Harvard Dataverse: Data for: Characterising demographics, knowledge, practices and clinical care among patients attending sickle cell disease clinics in Eastern Uganda. [https://doi.org/10.7910/DVN/AIDNOV](https://doi.org/10.7910/DVN/AIDNOV)

- Sickle cell questionnaire.pdf
- SCD Informed Consent Form.df
- Extended data.docx (Supplementary Table)

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

**Acknowledgements**

We thank the study sites at Mbale, Atutur, Ngora and Soroti Hospitals for their support during the study.

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**References**


8. H-PRIME: A clinical trial with three separate randomisations aimed at investigating the benefits of hydroxyurea, used pragmatically with only clinically-based monitoring, Antimalarial prophylaxis with dihydroartemisinin-piperaquine and antibacterial prophylaxis with cotrimoxazole as potential improvements in the standard care of children living in Africa with sickle cell disease. 2020. Reference Source


Open Peer Review

Current Peer Review Status: ✔️ ✔️

Version 2

Reviewer Report 05 August 2020

https://doi.org/10.21956/wellcomeopenres.17639.r39440

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Baba Inusa
Department of Paediatric Haematology, Evelina London Children's Hospital, Guy's and St Thomas NHS Foundation Trust, London, UK

I am happy that this paper reads a lot better and it highlights the real life scenario looking at a less urban setting where the majority of people with sickle cell may seek medical attention. It is also the case that patients in these settings may also attend the health facility because of a medical emergency rather than just a routine clinic visit follow up. It is not surprising that pain is such a prevalent feature.

It is worth noting the high proportion who indicated they do not know the cause of sickle cell disease. This is a short survey and therefore did not have the capacity to explore further. It would be interesting if the respondents were able to indicate their own hypotheses about possible causes. This would be an important entry point for education and awareness. SCD in Africa calls for community based programmes to address the not only the diagnosis but address myths as much as the introduction of penicillin V and hydroxyurea therapy.

It is not possible to address the issue of survival from this survey, I do not think the study design and implementation supports that in any way. It is, however, interesting that a high proportion of patients above age 5 were surveyed.

It is also difficult to be certain about the diagnosis based on solubility test alone and probably based on clinical features alone. While this may be correct in the majority of cases the risk is that some individuals with HbAS may pass as SCD and may in fact be living with a presumed diagnosis while some with SCD may also be thought to be sickle cell trait (HBAS). This calls for urgency improvement in diagnostic capacity of a community hospital or at least a twinning with the specialist centers. The authors may wish to say something about the verification of the diagnosis, whether all these cases were actually SCD.

Competing Interests: No competing interests were disclosed.
Reviewer Expertise: Sickle cell disease including global haematology work I am particularly interested in Africa and currently lead projects in Africa.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 07 July 2020
https://doi.org/10.21956/wellcomeopenres.17639.r39439

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Simon Dyson
Unit for the Social Study of Thalassaemia and Sickle Cell, School of Allied Health Sciences, De Montfort University, Leicester, UK

No further comments

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Sociologist

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 11 May 2020
https://doi.org/10.21956/wellcomeopenres.17383.r38631

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Baba Inusa
Department of Paediatric Haematology, Evelina London Children’s Hospital, Guy’s and St Thomas NHS Foundation Trust, London, UK

This is an interesting paper. It is very relevant to describe the context of the proposed H-PRIME study. It is also important to describe the current situation in the areas where sickle cell services are lacking. It seems to be ambitious to administer such wide-ranging questions to the
respondents within 20-30 minutes. More time would be needed if further work is required in order to introduce education sessions for the clients. It is not clear how the information about diagnostic methods was collected. Was the sodium metabisulphite test used as diagnostic or screening or confirmatory following initial testing, in which case it could be used to confirm the variant haemoglobin as HbS? It is questionable to rely on the solubility test for diagnosis. How do you know that these are all sickle cell disease patients especially for those in Soroti locations?

The limitation of research based at a health facility was mentioned in the introduction, yet this work seems to have done exactly that. The fact that the sample was not done all year round may have missed important pattern of clinic attendance.

Some of the key messages were not supported by references - frequency of clinics in the developed countries as stated between 3-6 monthly. The clinic frequencies are usually related to the therapies that patients are receiving e.g. Hydroxyurea which requires regular follow up and both UK and NIH management do have management guidelines with varying degrees of supportive evidence.

I can not see the socioeconomic information, if any was collected.

It is desirable to provide more information on the reason for high rate of blood transfusion in his patient group

The language generally could be improved.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Sickle cell disease including global haematology work I am particular
interested in Africa and currently lead projects in Africa.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 05 May 2020

https://doi.org/10.21956/wellcomeopenres.17383.r38633

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Simon Dyson

Unit for the Social Study of Thalassaemia and Sickle Cell, School of Allied Health Sciences, De Montfort University, Leicester, UK

The study is a cross-sectional (2018) descriptive survey of sickle cell disease (SCD) patients, principally children across four clinics in Eastern Uganda, encompassing description of reported symptoms, hospitalizations, patient knowledge of SCD and laboratory capabilities of the four SCD clinics. It describes the reported use of and awareness of the drug hydroxyurea (hydroxycarbamide) prior to implementation of a clinical trial of hydroxyurea in that setting.

Overall, the study is soundly conducted and meticulously reported and with a few minor amendments is ready to be published in my view. It could very readily be published “as-is” so my notes are suggestions rather than requirements.

My comments are as a sociologist and so may, therefore, differ in content and focus from those of medical reviewers.

1. A major tension between disciplines is the widespread medical/public health/WHO use of the term “burden” (line 6 and passim). To a sociologist, this reads as disabling (discrimination in terms of disability rights). It is arguably a short step from recognizing the challenge of SCD to the person living with SCD, and/or the challenge to the health services of a country, to say that the person’s disease is a burden to them and/or that they are a burden on the health services of their country. The authors later note the stigmatization that can affect people living with SCD and, to a sociologist, the use of burden in the medical lexicon is part of that very stigmatization. Is there not a less pejorative way in which the ideas might be expressed? For example, the person living with SCD might be said to “face challenges of living with SCD” rather than have the burden of SCD. SCD may create pressure for health services or demand for health services rather than be a burden on health services.

2. In paragraph 2, Introduction would it be an idea to tell the reader if the four SCD clinics represent ALL the clinics in eastern Uganda or are there others not included (or are there
other hospitals in the region without an SCD clinic?)

3. Given that the participants were mainly children, the methods should ideally report that the questionnaire was read to a parent/carer/person accompanying the young person. This then raises the question of at what age did the researchers defer to the answer of the person with SCD themselves rather than to an accompanying person?

4. In paragraph 1 of Results, might it be possible to know what per cent of all clinic patients with SCD registered at the respective clinics are represented by the pragmatic sample recruited?

5. In terms of economy of presentation the authors present Male per cent. Again just to note that in terms of challenging sexism in official statistics (Ann Oakley, circa 1979) sociologists have encouraged reporting of female statistics before male statistics. It would be possible here to report female per cent and leave male per cent implied rather than the other way around?

6. For most of the data, it is not a leap of faith to record reported answers (tribe, religion) as representing the actuality. However, where other potential evidence exists (in clinic or hospital records) I think it would be wise to emphasise that some information is reported information rather than hospital records? This would apply to the number of hospitalizations, the number of blood transfusions, use of penicillin/malaria prophylaxis etc, and even to the regularity of clinic visits. Presumably, there might be some discrepancies if answers provided to a structured interview were compared with hospital records?

7. There may not be space to open this issue up but presumably the skewing of the clinic attendees to young children tells us something about the age structure of the SCD population in rural Uganda (always presuming numerous older SCD people are not living without any contact with health services, which seems highly unlikely). It may have to wait for another paper but presumably, a comparison could be made between the age structure of SCD clinic attendees and all hospital attendees? In the absence of newborn SCD screening this could tell us something about under-fives SCD mortality in Uganda before implementation of treatment with hydroxyurea?

8. The fact that symptoms appear to be reported symptoms rather than medically documented symptoms may be the reason the authors do not comment more on Table 2. Two classic child-focussed symptoms of SCD I am aware of are splenic sequestration and hand-foot syndrome. Given high rates of the latter and low level of reported enlarged spleens, I wonder if this is indicative of high mortality from splenic sequestration in the under-fives? The reported levels of stroke are very low but I don't know if blood transfusions are being used to manage this?

9. In Table 6, it is noted that only two of the four centres have the capability to undertake haemoglobin electrophoresis. This may be my lack of knowledge but other than the sickle cell solubility test (which does not distinguish HbSS, HbAS and compound heterozygous forms of SCD?) how do we know the people in the study definitively had SCD? Perhaps the diagnosis is based on sickle cell solubility test plus characteristic SCD symptoms? Or is the range of tests available at any one centre sufficient to be confident in an SCD diagnosis?
10. With regard to stigma, the authors may care to look at https://doi.org/10.1016/j.socscimed.2016.05.029 for two reasons. (1) To understand what stigma is and is not and (2) To see ways in which stigma can be challenged through research as well as described in research.

11. Page 7, fourth paragraph: higher prevalence of pain is noted compared to studies in Saudi Arabia and Tanzania. The former is clearly more affluent (even, I suspect, the population in the Eastern Saudi Arabia provinces where SCD is most common) and the latter has a higher mean per capita income compared to Uganda, so perhaps socio-economic circumstances might also play a role?

12. Finally, as I suspect the authors know only too well with regards to their intended study of hydroxyurea in Uganda, the fact that it operates through "a degree of immunosuppression" has implications for starting a trial when those who are immunosuppressed may be being given advice to shield from COVID-19.

I wish the authors every success with their future work.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Sociologist

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 05 May 2020
Thomas N. Williams, Mbale Clinical Research Institute, Mbale, Uganda
Thank you for these very helpful and constructive comments. Given that we anticipate receiving additional reviews we will defer our response until all reviews are in so we can deal with the reviews holistically.

Tom Williams on behalf of all authors

**Competing Interests:** No competing interests were disclosed.

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**Comments on this article**

**Version 1**

Author Response 16 Jun 2020

**Thomas N. Williams**, Mbale Clinical Research Institute, Mbale, Uganda

**Simon Dyson**

The study is a cross-sectional (2018) descriptive survey of sickle cell disease (SCD) patients, principally children across four clinics in Eastern Uganda, encompassing description of reported symptoms, hospitalizations, patient knowledge of SCD and laboratory capabilities of the four SCD clinics. It describes the reported use of and awareness of the drug hydroxyurea (hydroxycarbamide) prior to implementation of a clinical trial of hydroxyurea in that setting.

Overall, the study is soundly conducted and meticulously reported and with a few minor amendments is ready to be published in my view. It could very readily be published “as-is” so my notes are suggestions rather than requirements.

My comments are as a sociologist and so may, therefore, differ in content and focus from those of medical reviewers.

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Thank you. This point is well made, and much appreciated. We have deleted all use of the word “burden” throughout the article and replaced with more appropriate language.

2) In paragraph 2, Introduction would it be an idea to tell the reader if the four SCD clinics represent ALL the clinics in eastern Uganda or are there others not included (or are there other hospitals in the region without an SCD clinic?)

In response to this question we have updated the Methods section with the following text: Our study was conducted in the Elgon and Teso sub-regions of Eastern Uganda where the prevalence rates of SCD is high [7]. There are 24 district level health facilities within these regions that offer general care for all patients, including subjects with SCD. However, only five of these facilities have dedicated SCD clinics. In the current study, we collected data from four of these clinics, one in Elgon and three in the Teso sub regions, selected on the basis that all will contribute participants for the upcoming H-PRIME trial.

3) Given that the participants were mainly children, the methods should ideally report that the questionnaire was read to a parent/carer/person accompanying the young person. This then raises the question of at what age did the researchers defer to the answer of the person with SCD themselves rather than to an accompanying person?

Thank you. We have amended the methods section to state this clearly as follows: Responses to the questionnaire were deferred to parents or carers of those <18 years and to the participant themselves if ≥18 years.

4) In paragraph 1 of Results, might it be possible to know what per cent of all clinic patients with SCD registered at the respective clinics are represented by the pragmatic sample recruited?

We have addressed this point altering the first paragraph of the results to read as follows:

While clinic records were not computerised and were somewhat incomplete, the total number of patients who were registered at these 4 SCD clinics was 2257. When conducting the survey, we noticed that some of the clinics had registered fewer patients than they were actually handling. All 1829 patients who were in attendance during the study period and who were invited to participate gave their consent and were included in the study, so at minimum, 428 (19%) of the registered participants did not attend their clinics during the course of the survey.

5) In terms of economy of presentation, the authors present Male per cent. Again, just to note that in terms of challenging sexism in official statistics (Ann Oakley, circa 1979) sociologists have encouraged reporting of female statistics before male statistics. It would be possible here to report female per cent and leave male per cent implied rather than the other way around?

Thank you. We have amended as suggested.

6) For most of the data, it is not a leap of faith to record reported answers (tribe, religion) as representing the actuality. However, where other potential evidence exists (in clinic or hospital records) I think it would be wise to emphasise that some information is reported information rather
than hospital records? This would apply to the number of hospitalizations, the number of blood transfusions, use of penicillin/malaria prophylaxis etc, and even to the regularity of clinic visits. Presumably, there might be some discrepancies if answers provided to a structured interview were compared with hospital records?

Thank you for making this point. We have amended the tables to make this clearer and have added a sentence of caution in the conclusions.

7) There may not be space to open this issue up but presumably the skewing of the clinic attendees to young children tells us something about the age structure of the SCD population in rural Uganda (always presuming numerous older SCD people are not living without any contact with health services, which seems highly unlikely). It may have to wait for another paper but presumably, a comparison could be made between the age structure of SCD clinic attendees and all hospital attendees? In the absence of newborn SCD screening this could tell us something about under-fives SCD mortality in Uganda before implementation of treatment with hydroxyurea?

In our view this goes beyond the scope of current paper and comes with significant interpretative challenges. We have not amended the paper in the light of this comment.

8) The fact that symptoms appear to be reported symptoms rather than medically documented symptoms may be the reason the authors do not comment more on Table 2. Two classic child-focussed symptoms of SCD I am aware of are splenic sequestration and hand-foot syndrome. Given high rates of the latter and low level of reported enlarged spleens, I wonder if this is indicative of high mortality from splenic sequestration in the under-fives? The reported levels of stroke are very low but I don't know if blood transfusions are being used to manage this?

The reviewer is correct. These self-reported symptoms must be treated with caution. We anticipate capturing the medically documented facts during the course of our up-coming study. We do not believe that these current questionnaire-based data are sufficiently robust to make definitive statements. We have not made any changes in the light of this comment.

9) In Table 6, it is noted that only two of the four centres have the capability to undertake haemoglobin electrophoresis. This may be my lack of knowledge but other than the sickle cell solubility test (which does not distinguish HbSS, HbAS and compound heterozygous forms of SCD?) how do we know the people in the study definitively had SCD? Perhaps the diagnosis is based on sickle cell solubility test plus characteristic SCD symptoms? Or is the range of tests available at any one centre sufficient to be confident in an SCD diagnosis?

Thank you for bringing this up. The lack of access to reliable laboratory services is a major issue. As a result, even the diagnosis is not always confirmed using a reliable method. We have reinforced this point in the discussion section under the section that focuses on laboratory access by including the following sentence:

“Indeed, not all clinicians even have access to reliable diagnostic tests and as a result, we cannot even be sure that all those attending these clinics definitely have SCD.” We hope this now captures this more accurately.
10) With regard to stigma, the authors may care to look at https://doi.org/10.1016/j.socscimed.2016.05.029 for two reasons. (1) To understand what stigma is and is not and (2) To see ways in which stigma can be challenged through research as well as described in research.

Thank you for pointing us to this interesting article which we will take on board in our future work.

11) Page 7, fourth paragraph: higher prevalence of pain is noted compared to studies in Saudi Arabia and Tanzania. The former is clearly more affluent (even, I suspect, the population in the Eastern Saudi Arabia provinces where SCD is most common) and the latter has a higher mean per capita income compared to Uganda, so perhaps socio-economic circumstances might also play a role?

Thank you. We have altered the sentence dealing with this in the discussion to now read: “While the reason for this difference is unknown, we hypothesize that it might reflect socio-economic issues or the local epidemiology of conditions such as bacterial diseases or malaria.”

12) Finally, as I suspect the authors know only too well with regards to their intended study of hydroxyurea in Uganda, the fact that it operates through “a degree of immunosuppression” has implications for starting a trial when those who are immunosuppressed may be being given advice to shield from COVID-19.

Thank you. Indeed, this adds a further level of complication to our study which we will need to take into account in due course!

***************************************************************************

Baba Inusa

This is an interesting paper. It is very relevant to describe the context of the proposed H-PRIME study. It is also important to describe the current situation in the areas where sickle cell services are lacking.

1) It seems to be ambitious to administer such wide-ranging questions to the respondents within 20-30 minutes. More time would be needed if further work is required in order to introduce education sessions for the clients. It is not clear how the information about diagnostic methods was collected.

Indeed, administering the questionnaire did prompt some participants to ask additional questions. The interviewers did not ration their time but the average interview did take 20-30 minutes. We have not amended the paper in response to this observation.

2) Was the sodium metabisulphite test used as diagnostic or screening or confirmatory following initial testing, in which case it could be used to confirm the variant haemoglobin as HbS? It is questionable to rely on the solubility test for diagnosis. How do you know that these are all
sickle cell disease patients especially for those in Soroti locations?

Thank you for this which we have already addressed in response to Question 9 from reviewer #1.

3) The limitation of research based at a health facility was mentioned in the introduction, yet this work seems to have done exactly that. The fact that the sample was not done all year round may have missed important patter of clinic attendance.

We accept this criticism and have added a sentence in our penultimate paragraph to reflect this limitation as follows: “Our study had a number of limitations, not least the fact that our questionnaire was administered over a limited period of time, meaning that it was not possible for us to capture questions such as the seasonal patterns of specific complications. Nevertheless, taken…..”

4) Some of the key messages were not supported by references - frequency of clinics in the developed countries as stated between 3-6 monthly. The clinic frequencies are usually related to the therapies that patients are receiving e.g. Hydroxyurea which requires regular follow up and both UK and NIH management do have management guidelines with varying degrees of supportive evidence.

Thank you. In response to this observation we have altered the relevant sentence in the discussion to read as follows: “In contrast to clinics in Europe and North America, where the frequency of attendance at SCD clinics is typically tailored to patient needs [11],……..”

5) I can not see the socioeconomic information, if any was collected.

None was collected. No changes made.

6) It is desirable to provide more information on the reason for high rate of blood transfusion in his patient group.

We agree this would be desirable, but it is not possible to determine this from this questionnaire-based study. We hope that this will emerge from our much more detailed future work. No changes made.

7) The language generally could be improved.

Many thanks for this comment. We would be very happy to amend if provided with specific examples.

**Competing Interests:** No competing interests were disclosed.