Author’s response to reviews

Title: HEALTH-RELATED QUALITY OF LIFE OF ADOLESCENTS WITH SICKLE CELL DISEASE IN SUB-SAHARAN AFRICA: A CROSS-SECTIONAL STUDY

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EDITOR COMMENTS

1. Please include a title page as the first page of your manuscript where you list the full name, institutional addresses and email addresses for all authors. The corresponding author should be indicated. First page added.

2. Please note the role of funding body in the design of the study and collection, analysis and interpretation of data and in writing the manuscript should be declared in the funding section. They have no role in the process of the study.

3. Please specify in the Ethic approval and consent to participate section whether the consent was written or verbal. If verbal, please specify why the written consent was not taken, and if this was approved by the ethics committee. The consent was written. This has been added in the Ethic approval section.

4. Please include the ethics approval code in the Ethics approval and consent to participate section, if applicable. REC REF 2018-032

5. Please include more information in the Consent for Publication section, was this consent written or verbal, and who consented on behalf of minors (those under 18). Please also specify what they consented to be published, e.g. medical information, quotes, images, video, etc. Thank you. Information have been added.

FIRST REVIEWER REPORTS

METHODOLOGY

1. Question 1: Some further description of the participant recruitment would be helpful. It appears
that recruitment was from an outpatient clinic but it was unclear whether patient were visiting clinic for routine care and they were in their usual state of health or whether some/many were been seen for acute care, typically pain, that might impact HRQoL.

Answer to question 1: We did a consecutive sampling. This process was continued until sample size was reached. Many of our participants were visiting for acute pain and few were in their usual state of health. That might impact HRQoL. Please find this comment added in the methodology and limitation section.

2. Question 2: Page 3 line 31-32 has a typo-’assess” should be “assess”
Answer to question 2: We have corrected asses to assess. Thank you for that.

3. Question 3: Which version of the PedsQL was used in this study- was the recall period 7 days (acute version) or the traditional version with a 30 days recall period?
Answer to question 3: The version of the PedsQL used was the traditional version with a 30 days recall period. Please find the correction on methodology section subheading: Evaluation of health Quality of life.

4. Question 4: Was the Peds QL translated into local languages/dialects? If so how was the translation done and validated? If the English version was used, how was reading comprehension assessed? There are translators within the ethnic committee of Makerere University who assisted us to translate in local languages. However a trained nurse was assisting the participant to have better understanding whenever possible

5. Question 5: The established cutoff score referenced are for healthy US population and may not be a relevant comparison; a more appropriate reference is (Varni et al. Ambul Pediatr 2003; 3; 329-341). While not ideal, comparison to values for US SCD children are more relevant (eg Panepinto et al J Pediatr Hematol Oncol. 2008;30:666-673).
Answer to question 5: Thank you for your comment. Fewer studies have been done in our setting. It was difficult for us to find a cutoff reference applicable for low income country like Uganda.

6. These HRQOL domain values can often be skewed so medians rather than means may be more appropriate, was this issue addressed?. Yes. The HRQoL was normally distributed reason why we used mean as an estimate.

RESULT

1. Means and standard deviations for age for the entire sample would be used to allow comparison to other published studies. We have added mean age.

2. While I assume this sample was entirely homozygous SS, it would be important to report the sickle cell diagnoses for comparison to others studies.
Answer: The diagnoses was done using electrophoresis, the sample size was entirely homozygous SS. This precision has been included in result section subheading demographic and disease factors.

3. Page 5 line 12-15: The information provided on incidence of pain or fever requires further information. What time period was reviewed for occurrence of these events? Is this information for the previous month, year, and lifetime?? How was pain or fever defined?
Answer: The time period reviewed for pain and fever was information within the 30 days. Fever was defined as axillary temperature equal or more than 38 C (101.3 F). Pain: constant cry restlessness, facial expression and verbal report of pain. Kindly find added this comment in the methodology section.

4. Information on several aspects of local clinical practice is needed to better understand result in table 2. For example, what was the typical indication and age for use of Hydroxyurea; what were the indications for blood transfusion; what was the practice for use of folic acid and what was the age /indication for pneumococcal vaccine. We offer hydroxyurea to all adolescent with
SCA regardless of clinical severity to reduce SCD related complication. However many of them are not able to afford; and those who are able, are the very sick patients. The indications of blood transfusion were priapism, acute haemolytic, aplastic or sequestration crisis. In Uganda Pneumococcal vaccine is given in the routine immunization services; at 6 weeks, 10 weeks and 14 weeks of age which is the younger age.

5. Table 3 has the most important results and should be expended with relevant known group comparison (eg. Age groups 8-12/>12yrs; male/female; pain/no pain; fever/no fever; malaria/no malaria; stroke/no stroke; etc). Table have been added. Please find it on tables section.

6. Compare to reports from US sickle cell studies the child/parent reported value for physical functioning is remarkably low( most values are in the low to mid 70s); emotional functioning are somewhat lower than US SCD values-please point this out and provide explanation in discussion section. Where a significant number of participants recently or currently in pain at the time of assessment as pain has the largest impact on physical functioning?

Answer: This may be explained by the nature of the study population where these children were enrolled from an ongoing cohort where the level of care is high. Besides, USA is a high income country likely to have better care for children with SCD unlike Uganda where our study was conducted characterized by health system challenges. These findings can also be explained by cultural differences where level of social support, coping styles and perceptions of illness is different as compared to developed countries. This discussion has been added.

7. The multiple linear regression analyses need to be redone controlling for age and gender as they likely impact all HRQOL values; genotype may need to be controlled for as well if this a heterogeneous population. Without controlling for these covariate, most of the reported results may be spurious. For example, are those receiving pneumococcal vaccine younger and thus would have higher HRQOL score? Similarly the folic acid effects don’t make physiological/clinical sense. Thank you for your relevant comment. We have redone the multiple linear regressions; still we didn’t find any impact for age and gender.

8. Please provide the important themes from the high HRQOL focus group-understanding resilience can be as important as understanding deficits.

Answer: In our study we found that Initiation of treatment and adherence to it was the major theme with reduced pain frequency, intensity and clinic visits as sub-them. Please find the table added in the table section.

DISCUSSION:

1. In a number of place in the discussion section, for example last sentence on page 7, result from the qualitative study are discussed but were not presented in result section. We have reviewed and made a correction.

2. Page 8, line 12-the MSH study was done in the US and not Canada; Dr Ballas was the author of the reference manuscript rather than the leader of the clinic trial. Correction has been done.

3. Interpretation of the effects of blood transfusion makes clinical sense We have noted your comment.

4. Hydroxyurea effects might be better understood with description of local clinical practice, for example in some studies Hydroxyurea has been associated with worse HRQOL as it was typically used only in very symptomatic adolescents. This question has been addressed in method section. Hydroxyurea was used in very sick patients.

5. Pneumococcal vaccine effect is not likely due to reduced infections as these are relatively rare and often fatal; more likely due to younger patient age or better access to care. Thank you for this comment. In our setting we have many patients with pulmonary infections because of the
sanitation problem, education and poverty.
6. Folic acid makes no sense. Thank you. We routinely give folic acid to our patients but we have no evidence of efficacy. We need more study for that.

REFERENCES
1. References after #7 are not available in the copy of the manuscript available for my review-please provide. Sorry for that. Correction has been done.

TABLES
1. Table 5 would be easier to understand if data was presented in table format similar to Table III in reference #3 .Thank you. We have done the correction.

We have reviewed the manuscript. Your detailed was fruitful for us.

SECOND REVIEWER

ABSTRACT
1. The others should include study inclusion criteria and describe the sample in terms of age and gender. Thank you. We have made the correction.
2. The authors should also include actual data with number value in the abstract (e.g. PedsQl score and correlations) with p-values indicating statistical significance rather than just non-specific statements. Number values with p-value have been added in abstract section.

BACKGROUND
1. The authors should include additional reference for impairment of HRQOL in SCD( Panepinto and Bonner. PBC 2012. Thank you
2. The authors should include their a priori hypotheses to be clearly stated with study objectives. We have added it.

METHODS:
1. The others should revise the study design description as “Mixed-Methods study” rather than “cross-sectional study” since it has both qualitative and quantitative components. Correction done
2. The study inclusion criteria need to be clarified in the population section regarding genotypes, chronic pain, steady state versus acute pain episode at the time of enrolment, Hydroxyurea therapy exposure and chronic transfusion. All these are important variables that would affect HRQOL scores and would be important to consider while interpreting study findings. We recruited the homozygous patient symptomatic and asymptomatic who attended the clinic for at least one year. Kindly find the correction done in the methods section
3. For the Qualitative analysis, the authors should specify if they used inductive or deductive coding, or both, and should also include codebook and interview guide as a supplemental file, how many coders analyse the data and what was the inter-rater reliability. Methodology references would be helpful. We used inductive coding. For more information, kindly find added supplemental file.
Key themes and sub-themes on factors influencing HRQoL for children with SCD

Factors for low HRQoL for children (theme)
- Sickle Cell Disease related factors (pain, negative effect on growth)
- Treatment related (adherence, inability to afford cost of treatment, mistrust of treatment from other clinics)
- School related (missing school, poor performance)
- Stigma at school by peers
- Limited physical participation (sports and domestic work)
- Emotional stress

Factors for high HRQoL for children (Theme)
- Initiation and adherence to treatment (reduced pain frequency, intensity and clinic visits)

Comments of themes/sub-themes:

From the quantitative result, we classified children with SCD and their caretakers into 2 groups: One group of those who rated the HRQoL as high (they are in the theme “High HRQoL) and another group of those who rated the HRQoL as low (they are in the theme low). They were invited separately. The subthemes derived from the different voices we got after discussion with the participants

FOCUS GROUP DISCUSSION GUIDE FOR CHILDREN WITH SICKLE CELL
I am…………………………., We are conducting a study on Health related quality of life and associated factors in children with sickle cell disease, at Mulago National Referral Hospital. I would like to request you to participate in a group discussion about your health and the factors effecting your health (Obtain assent for the FGD and to record the discussion)

1. Identification information for each FGD participant
   Sex: Male-------                             Female-------
   How old are you in years? -----------
   What is the highest level of education you attended?
   How would you describe your relationship with your caregiver?
   What treatment are you receiving for SCD: On hydroxyurea---------, Folic acid-----, Malaria prophylaxis--------, Penicillin V--------?
1. Can you tell me about your health now? (Probe for good or not good and why?)
2. How was your health before you were found to have sickle cell?
3. Has your health changed now that you were found to have sickle cell? If yes how? If it has not changed why?
4. What are the major things that influence your health now?
5. Can you tell me how sickle cell has affected your health and life in general? Probe for
   • Effect on physical activities
   • Effect on children’s feeling/emotions (feeling, thought…)
   • Effects on how children relate or interact with others( at home and in school)
   • Effect on children’s schooling
   • How has sickle cell treatment affected children’s lives? Probe for positive and negative effects
   • Effect on physical activities
   .Some children with sickle cell experience different problems which affect their life. Which major
problem have you experienced since you were found to have sickle cell?

Pain
Nausea (feeling like you want to vomit)
Worry about pain crisis, anemia or other complications

Any other thing you would like to talk to us about in relation to your health and life

- Now
- When you started receiving treatment

Thank you for your time and for sharing with us your experience

FOCUS GROUP DISCUSSION GUIDE FOR CARETAKERS OF CHILDREN WITH SICKLE CELL
I am …………………….., We are conducting a study on Health related quality of life and associated factors in children with sickle cell disease, at Mulago National Referral Hospital. I would like to talk to you about the health of your child. (Obtain consent for the FGDs).

1. Identification information for each FGD participant
   Sex: Male-------- Female--------
   How old are you in years? ---------
   What is your level of education?
   What is your relationship with the child?
   Treatment status: On hydroxyurea--------, Folic acid------, Malaria prophylaxis--------, Penicillin V--------

2. Can you tell me about the health of your child now?
3. How was the health of your child before he/she was found to have sickle cell?
4. What are the major things that influence the health of your child now?
5. Can you tell me how sickle cell has affected the life of your child? Probe for
   • Effect on physical activities
   • Effect on child feeling/emotions (feeling, thought…)
   • Effects on how the child relates or interacts with others (at home and in school)
   • Effect on child’s schooling
   • How has sickle cell treatment affected your child? Probe for positive or negative effects
   • Effect on physical activities

Some children with sickle cell experience different problems which affect their life. Which major problem has your child experienced since he or she was found to have sickle cell?

Pain
Nausea (feeling like you want to vomit)
Worry about pain crisis, anemia or other complications

Any other thing you would like to talk to us about in relation to your child

- Now
- When he/she started receiving treatment

Thank you for your time and for sharing with us your experience

RESULTS
1. The authors should include section subheadings to better organize their data. Thank you for that orientation. Correction done.
2. The authors should mention statistical methods only in the methods section not results. Kindly find the correction done in the result section.
3. What is the scientific rationale for evaluating the relationship between HRQOL and folic acid or pneumococcal vaccine? Is there a plausible physiological relationship? How? Publish data? That is why
a priori hypothesis is important rather than just trying examining every possible relationship with no clear scientific rationale and justification. Thank you for having raised an important point. In our setting, we routinely give folic acid to our patients with sickle cell. So, we would like to see if it influences the HRQoL or no.

We thought that by preventing the encapsulated infection by giving Pneumococcal vaccine, the quality of life would be positively affected, raison why we put it as a variable, I thing more studies have to be done. Three trials of conjugate vaccine showed increased antibody response compared to control group in people of all age. But they did not show if the vaccine prevent infection or reduces death rate.

DISCUSSION

1. The authors should not repeat detailed results in the discussion. Thank you. The correction has been done in the discussion section.

2. The authors should include recent papers that focussed on evaluating different aspects of HRQOL in adolescents with SCD, such as Hydroxyurea treatment, perception and beliefs and barriers to adherence. These recent key references would strengthen the study argument and help to better understand HRQOL in this population. The recent papers have been included. Kindly find it in discussion section.

Reference: …

3. References 8-19 are missing from the manuscript. Sorry for that. Correction has been done.