Reviewer’s report

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

Version: 0 Date: 03 Jan 2019

Reviewer: Carlton Dampier

Reviewer's report:

This is an important study to help us understand the impact of SCD in a low/middle income country (LMIC) where SCD is much more prevalent than in Western countries. The cross-sectional study design is appropriate for an initial study of HRQOL measures in SCD. The qualitative studies with focus groups provide valuable information to provide context to the quantitative data, and is an important addition. My questions, comments, suggestions are divided by section and are listed below:

Methods:
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 patients were visiting clinic for routine care and were in their usual state of health or whether some/many were being seen for acute care, typically pain, that might impact HRQOL?
2. Page 3 line 31-32 has a typo-"asses" should be "assess"
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 day recall period?
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?
5. The established cutoff scores referenced are for healthy US populations and may not be a relevant comparator; 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.
6. These HRQOL domain values can often be skewed so medians rather than means may be more appropriate, was this issue addressed?

Results:
1. Means and standard deviations for age for the entire sample would be useful to allow comparison to other published studies
2. While I assume this sample was entirely homozygous SS, it would be important to report the sickle cell diagnoses for comparison to other studies.
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, lifetime?? How was pain or fever defined?
4. Information on several aspects of local clinical practice is needed to better understand results in Table 2. For example, what was the typical indication and age for the use of hydroxyurea; what were
the indications for blood transfusion; what was the practice for usage of folic acid; and what was the age/indication for pneumococcal vaccines.

5. Table 3 has the most important results and should be expanded with relevant known group comparisons (e.g. age groups 8-12/>12yrs; male/female; pain/no pain; fever/no fever; malaria/no malaria; stroke/no stroke; etc)

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

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 covariates, most of the reported results may be spurious. For example, are those receiving pneumococcal vaccine younger and thus would have higher HRQOL scores? Similarly the folic acid effects don't make physiologic/clinical sense.

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

Discussion:
1. In a number of places in the discussion section, for example last sentence on page 7, results from the qualitative study are discussed but were not presented in result section
2. Page 8, line 12—the MSH study was done in the US and not Canada; Dr Ballas was the author of the referenced manuscript rather than the leader of the clinical trial
3. Interpretation of the effects of blood transfusion makes clinical sense
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
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
6. Folic acid effect makes no sense

References:
1. References after reference #7 are not available in the copy of the manuscript available for my review—please provide

Tables:
1. Table 5 would be easier to understand if data was presented in table format similar to Table III in reference #3

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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