Sickle Cell Disease and Quality of Life: An Evaluation of Reporting of Patient-Reported Outcomes in Randomized Controlled Trials

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ABSTRACT
Sickle cell disease significantly impacts one’s quality of life (QOL); thus, randomized controlled trials (RCTs) have integrated patient-reported outcomes (PROs) to assess patients’ health from their perspective. We aim to evaluate the completeness of reporting of PROs included in sickle cell disease RCTs. We searched MEDLINE, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) for published sickle cell disease RCTs with at least one PRO measure from 2006 to 2021. In a masked, duplicate fashion, two investigators evaluated RCTs using the Consolidated Standards of Reporting in Trials (CONSORT)-PRO adaptation and Cochrane Collaboration Risk of Bias (RoB) 2.0 tool. The primary objective was mean percent completeness of the CONSORT-PRO adaptation. Additional relationships between trial characteristics and completeness of reporting were evaluated. Mean completeness of reporting of RCTs was 41.49% (SD = 20.90). Randomized controlled trials with primary outcomes were more complete (57.50%, SD = 8.33) than RCTs with secondary PROs (33.48%, SD = 20.91). We did not find a significant difference in completion between trials with primary PROs and secondary PROs (t1 = 2.07, p = 0.06). Our secondary objectives included factors that may be associated with completeness of PRO reporting. Of the 12 included studies, five were considered to be overall ‘high’ RoB (41.67%). In each of the five domains, the majority of studies received ‘low’ RoB evaluations. Incomplete PRO reporting was common within sickle cell RCTs. Therefore, we recommend future RCTs including PROs should take measures to increase completeness of reporting.

Patients with sickle cell disease are at risk of experiencing pain crises, sleep disturbances, depression, deficits in cognitive function and fatigue, all indicators of quality of life (QOL) [1]. Quality of life, as defined by the World Health Organization, is ‘an individual’s perception of their position in life in the context of the culture and value systems in which they live’ [2]. Furthermore, prior research has shown that patients with sickle cell disease are not only prone to depression, but suicidal ideation and attempts [3], indicating the need to evaluate patient-reported outcomes (PROs) of sickle cell disease. Despite progress in sickle cell disease treatment and evaluation [4], concerns surrounding physical and psychosocial effects warrant that PROs be included in randomized controlled trials (RCTs) investigating the disease.

The inclusion of PROs and QOL measures in RCTs may be critical to fully weigh the benefits/risks of an intervention, especially in cases where efficacy between trial arms are indistinguishable. Therefore, it is important that PROs be included as outcome measures and receive clinical consideration in a given trial. As the use of PROs in RCTs become more prevalent, issues in reporting of the PRO necessitated the development of the Task Force of The International Society of Quality of Life Research (ISOQOL) to develop the first standards for PRO reporting in 2013 [5].

In conjunction, the Consolidated Standards of Reporting in Trials (CONSORT)-patient-reported outcome (PRO) group has provided standards for how PROs should be reported within RCTs via an extension, the CONSORT-PRO [5,6]. While the CONSORT-PRO checklist is thorough in guidance of PRO reporting, current studies have shown that RCTs still inadequately adhere to its recommendations [7–9]. Given the inconsistency in reporting of PROs, and the lack of studies regarding PRO reporting of sickle cell disease trials, we aim to examine the completeness of PRO reporting in sickle cell disease RCTs according to the CONSORT-PRO guidelines.

To foster transparency, reproducibility, and reliability our study protocol, data sheets, analysis scripts, data dictionary and extraction forms were uploaded to Open Science Framework (DOI: 10.17605/OSF.IO/V7RC6). Following the reporting guidelines for meta-epidemiological studies [10], our study was conducted over published RCTs concerning
sickle cell disease. Our investigation was conducted in concert with other studies assessing completeness of reporting in several fields of medicine using related methodology. Additions to the uploaded protocol are as follows: for the data collection process, extraction was performed in a masked, duplicate fashion using trained investigators and Google-forms.

For the risk of bias (RoB) assessment, two investigators (M. Love, E. Garrett) were trained using materials provided by Cochrane RoB 2.0 [11]. The RoB final assessment was done in the same manner with a third investigator (B. Heigle) available for questions and disagreements. Following data extraction, the investigators reconciled discrepancies. For data analysis, a \( t \)-test was also performed to explore a significant difference in the mean percent completeness between RCTs that have a PRO as a primary outcome and RCTs with a PRO as a secondary outcome.

### General characteristics

Our systematic search returned 527 records with 435 remaining after deduplication. Following title and abstract review, 87 studies were included for full-text review. After full-text evaluation, 12 published RCTs were included for data extraction. Rationales for excluded studies can be found in Figure 1.

Of the 12 included RCTs, four included PROs as a primary outcome and eight included PROs as a secondary outcome. Eight (of 12; 66.66%; Supplementary Table 1) trials evaluated a drug intervention. Five (of 12, 41.67%) RCTs were published in journals that did not endorse CONSORT reporting guidelines and no RCT cited CONSORT guidelines within the study. The mean sample size of included RCTs was 77.92 (SD = 62.93).

### Completeness of reporting according to the Consolidated Standards of Reporting in Trials-Patient-Reported Outcomes Adaptation

The overall mean completeness of reporting of RCTs in our sample was 41.49% (SD = 20.90). Randomized controlled trials with primary outcomes had a mean percent completion of 56.67% (SD = 9.81) and were more complete than RCTs with secondary PRO 33.48% (SD = 20.91). We did not find a significant difference in completion between outcome categories (\( t_1 = 2.07; p = 0.06 \)). When recategorized based on completion percent, 75.0% (3/4) trials with a primary PRO were of 'moderate' completion compared to 12.5% (1/8) of those with PROs as a secondary endpoint, with all trials remaining being of 'low' completeness.

Across all RCTs in our sample, Item 22: PROs interpreted in relation to clinical outcomes, was the most consistently reported item (10/12; 83.33%; Supplementary Table 2). No RCT in our sample reported item P1b: PRO listed as a primary or secondary outcome in the abstract, nor item P2bii: PRO domains specified in the hypothesis. Only one RCT (1/12, 0.83%) reported item P18: results of any subgroup/adjusted/exploratory analyses.

Of the four RCTs with a PRO as a primary outcome, five items were consistently reported: rationale for including PRO (P2a), evidence of PRO validity (P6ai), sample size determination (P7a), implications of PRO results for generalizability, clinical practice (P21), and PROs interpreted in relation to clinical practice (P22) (4/4, 100.0%). No RCTs with a PRO as a primary outcome reported the following: PRO domains specified in the hypothesis (P2bii), statistical approach for missing data (P12a), and results of any subgroup/adjusted/exploratory analyses [12]. For RCTs with a PRO as a secondary outcome, no item was consistently reported across these studies; however, PROs interpreted in relation to clinical practice (P22), was most frequently reported (6/8; 75.0%).

### Risk of bias

Of the 12 included RCTs, five were considered as 'high' risk of bias (41.67%; Supplementary Table 3), two had 'some concerns' for bias (16.67%), and five were considered 'low' risk of bias (41.67%). Four (of 12; 33.33%) RCTs were found to have a 'high' risk bias in domain 4 (RoB in measurement of the outcome). In 11 (of 12; 91.67%), we found no association between risk of bias and completeness of reporting (Supplementary Table 3).
**Associations between patient-reported outcomes reporting completeness and trial characteristics**

Lastly, we found no significance between PROs being a primary or secondary outcome and any trial characteristic, or completion of PRO checklist (Supplementary Table 1). Furthermore, we found no statistically significant relationship in RoB, or any RoB domains (Supplementary Table 3).

Randomized controlled trials of sickle cell disease containing PROs were incomplete in PRO reporting and were prone to bias. No RCT in our sample was considered to have ‘good’ CONSORT-PRO completeness of reporting, and twice as many were found to have ‘poor’ reporting than ‘moderate,’ most of which were RCTs with PROs as primary outcomes. Of the CONSORT-PRO adaptation items, P1b was one of the least commonly reported, and our most consistently reported item was P22. In the following discussion, we elaborate on our findings within the context of current research, highlight the significance of the CONSORT-PRO items, and address the clinical relevance of our results for patients with sickle cell disease.

Importantly, we found that RCTs in our sample had a mean completeness of PRO reporting near 41.0%. In oncology, several studies highlight a lack of completeness of reporting of PROs with mean completeness ranging from 5.0 to 66.0%, all of which found that RCTs with PROs as primary outcomes had higher completion than those with PROs as secondary outcomes [8,9,13]. When there was a failure to sufficiently report PROs, the dissemination of PRO findings to clinical practice was impeded by insufficient quantitative information advocating for patient QOL [14].

Consider a trial from our sample in which investigators randomly assigned 74 patients with sickle cell disease to receive either sildenafil or placebo for treatment of pain episodes, a PRO. The results from this trial state, ‘At week 10, sildenafil subjects had higher pain-related scores than placebo subjects (p = 0.04) on all but the pain relief scale’ [15]. This result is interpreted in the discussion: ‘Administration of sildenafil was unexpectedly associated with an increased rate of hospitalizations for pain episodes compared with placebo. The National Heart, Lung, and Blood Institute (NHLBI) stopped the study for safety reasons because a greater proportion of subjects experienced serious adverse events in the sildenafil arm and based on a futility analysis of estimated efficacy results. This observation of an increased rate of subjects experiencing serious sickle cell disease pain episodes was not reported previously in two open-label studies [16,17], most likely due to the absence of control groups or to differences in patient selection. In one of the prior studies, subjects underwent maximization of sickle cell disease-specific therapy with hydroxyurea and/or red blood cell transfusions before initiation of sildenafil’ [15].

Within the context of this discussion, the authors clearly account for an unexpected finding, report the adverse events resulting from the treatment, and discuss how this finding fits within the larger context. Such interpretations are vital to a reader’s understanding and for accurate clinical interpretation. We commend authors of trials pertaining to sickle cell disease for accurate interpretations of findings and highlight this trial report as an exemplar for others to follow.

**Recommendations**

Previous literature has advocated for responsive, valid, and interpretable instruments measuring patient experience to guide clinical decision-making [17,18]. However, many providers feel hesitant using PRO data to make clinical decisions due to poor reporting of results [14]. CONSORT-PRO guidelines, if effectively implemented in RCTs, can strengthen the reporting of PROs and expand clinically relevant literature [19,20]. Therefore, we agree with the recommendations of Calvert et al. [6] and Mercieca-Bebber et al. [7] that future RCTs including PROs, should adopt CONSORT-PRO guidelines to increase completeness of PRO reporting and journals publishing RCTs should endorse the CONSORT-PRO guidelines in their instructions for authors.

**Strengths and limitations**

The strengths of our study include: the use of CONSORT-PRO and Cochrane RoB 2.0 tools, the proper training of investigators using these tools, the establishment of our protocol a priori, and the extraction of data in a masked, duplicate fashion. A limitation of our study is the small sample size, which makes the generalization of our findings to hematology and other medical fields difficult. While our study was representative of sickle cell disease trials published in 2006 or later, it could be missing RCTs published prior to 2006. Thus, future studies are warranted.

**Conclusions**

We found incomplete reporting of PROs included in sickle cell disease RCTs coupled with inconsistent RoB. Incomplete reporting may reduce the reliability of PROs and may hinder PRO translation into clinical practice. Properly reported PROs can help clinicians understand the patient’s perspective, and support the person-centered approach to healthcare.

**Acknowledgments**

In memoriam of Abbey Renner (Oklahoma State University Center for Health Sciences Ringgold Standard Institution, College of Osteopathic Medicine, Tulsa, OK, USA); we are grateful for her leadership and expertise during the drafting of this manuscript. We are grateful to April Schweikhard (University of Oklahoma-Tulsa, Schusterman Library, Tulsa, OK, USA), who assisted in the development of our search string and the Oklahoma State University Medical Library, Tulsa, OK, USA, for their procurement of relevant literature.

**Disclosure statement**

No financial or other sources of support were provided during the development of this manuscript. Dr. M. Hartwell reports receiving funding from the National Institute of Justice for work unrelated to the current subject. Dr. M. Vassar reports receipt of funding from the National Institute on Drug Abuse, the National Institute on Alcohol...
Abuse and Alcoholism, the US Office of Research Integrity, Oklahoma Center for Advancement of Science and Technology, and internal grants from Oklahoma State University Center for Health Sciences, all outside of the present study.

**Funding**

Development of this study was funded by the Oklahoma State University Center for Health Sciences Presidential Mentor-Mentee Research Fellowship Grant.

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**Data availability statement**

Data are available upon reasonable request from the corresponding author.

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