Use of Patient-Reported Outcomes for Sickle-Sell Disease in Clinical Trials: Do they match with consensus-based core outcomes sets recommendations?

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Key findings:

- **Comparison of a recent Core Outcome Set (COS) in Sickle Cell Disease (SCD) with clinical trials shows gaps in Patient-Reported Outcome (PRO) assessed**
- **The review process has also identified potential PRO measures that could be included within the COS to facilitate its usage in clinical research Only diaries for pain and hospitalizations were included in labels for SCD, suggesting the need for further evaluation of fit-for-purpose instruments**

Background and Objective

"A *COS is an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care*." (Core Outcome Measures in Effectiveness Trials; COMET, https://www.comet-initiative.org/). Use of COS in clinical research and drug development is believed to increase measurement of relevant outcomes, increase consistency across trials, reduce the risk of outcome-reporting bias and produce usable information for decision-makers from all the trials targeting a specific condition.

Recently, COS for SCD (coreSCD), one each for Disease modifying therapy (DMT) and Acute intervention (**Figure 1**), have been suggested by a panel of patients and experts using COMET Initiative methodology (*Tambor et al. 2021*).

This empirical study investigated whether previously registered clinical trials assessed outcomes from coreSCD.

Core Outcome Sets for Sickle Cell Disease	
Disease Modifying Therapy (DMT)	**Acute interventions**
Acute sickle cell pain frequency	**Acute sickle cell pain frequency**
Acute chest syndrome	Acute chest syndrome
Stroke or cerebrovascular accident	**Ability to return to usual activities**
Neurocognitive function	**Frequency of hospitalization**
Health-related quality of life	Emergency department/acute care visit
Frequency of hospitalization	Cause-specific survival/mortality
Emergency department/acute care visit	
Need for blood transfusion	
Cause-specific survival/mortality	
Event-free survival	

Figure 1. CoreSCD from *Tambor et al. 2021*

The figure lists the outcomes included in the final core sets described in *Tambor et al. 2021.*

Methods

To obtain information on PROs in SCD, we searched in Clinicaltrials.gov for on-going and recently completed phase II-IV clinical trials in adolescent and adult SCD population (First posted: Nov-2015 to Nov-2022). Screening was based on participants (adolescent and adult patients with SCD) and the presence of PRO measures in trials' endpoints, while information on PRO was extracted for further analysis.

Concepts assessed with PRO measures were compared with coreSCD to highlight possible gaps in concepts assessed in clinical trials.

PROLABELS™ database (https://eprovide.mapi-trust.org) was searched to obtain information on drugs approved for use in patients with SCD and respective list of PROs were extracted.

Results

173 SCD trials were retrieved among which 54 included at least one PRO measure and thus considered for data extraction. The top three concepts assessed by PROs were: Pain (mostly intensity), Health-Related Quality of Life (HRQOL) and Fatigue/Tiredness/Sleep impact. 73.3% of PROs were secondary endpoints, while primary and exploratory endpoints accounted for 13.3% each.

Considering only DMT and Acute intervention trials that included at least one PRO measure, 23 and 14 trials were identified, respectively. For DMT trials, several concepts identified by the review of clinical trials could be included within the coreSCD, with 'HRQOL' and 'Pain' (mostly assessed as intensity of pain in the endpoints reviewed) outcomes being the most represented. For Acute trials, 'Absence from School/Work' and 'Pain' were the only concepts identified that could be included within the coreSCD. Moreover, additional concepts were identified in the clinical trials that are not considered under any of the suggested outcomes in the coreSCD (**Table 1**).

Table 1. Concepts measured in SCD clinical trials

Concepts measured	Number of trials (frequency)	CoreSCD category
Pain*	22	Acute and DMT coreSCD
Quality of Life/Health status	20	DMT coreSCD
Fatigue/Tiredness/Sleep impact	6	DMT coreSCD
Physical functioning/Exercise capacity	3	DMT coreSCD
Absence from School/Work	3	Acute coreSCD
Adherence	2	-
Analgesic/Substances use	2	-
Palatability	2	-
Anxiety/depression	2	DMT coreSCD
Treatment efficacy	1	-
Self-efficacy/Self-management	1	-
Appetite/Nausea/Constipation	1	-
Bruising	1	-
Respiratory symptoms	1	-
Social functioning	1	DMT coreSCD
Emotional functioning	1	DMT coreSCD
Pain interference	1	DMT coreSCD

Table 1 shows the concepts measured by PROs instruments and their frequencies, as well as the category of coreSCD in which they were recommended, if applicable. Only DMT and Acute intervention trials were considered, accounting for 37 (23 and 14, respectively) out of the 54 trials including a PRO measure in the endpoints. (* Pain was mostly assessed as intensity in the endpoints reviewed)

There was a high variability in terms of measures to assess HRQOL, including both disease-specific and generic PRO measures. Pain frequency and AtR (i.e., Absence from School/Work), which were assessed in a lower share of trials, were always assessed using patient diaries (**Table 2**).

Table 2. PRO measures for HRQOL, Pain frequency and AtR in clinical trials

Concepts	Endpoint position	PRO measure acronym	Frequency
HRQOL	Secondary	ASCQ-Me	5
	Secondary / Exploratory	PedsQL Generic Core Scales	5
	Secondary	PedsQL Sickle Cell Disease Module	4
	Secondary	EQ-5D	4
	Secondary	SF-36 / SF-36v2	3
	Exploratory	PGI-C	3
	Secondary	PROMIS-57 Profile v2.1	3
Pain frequency	Primary	Diary – Pain quantity	1
	Exploratory	eDiary – Pain intensity scale	1
	Secondary	eDiary – Pain	1
AtR	Secondary	eDiary - Absence from School/Work	1
	Secondary	eDevice - Absence from School/Work	1
	Exploratory	eDiary - Absence from School	1

This table lists the PRO measures, with relative endpoint positioning and frequency of use to assess the outcomes suggested in the coreSCD. For HRQOL, we limited the list to the top 7 (frequency>2).
Note: HRQOL: Health-Related Quality Of Life; AtR: Ability to Return to usual activities; ASCQ-Me: Adult Sickle Cell Quality of Life Measurement Information System; EQ-5D: EuroQol 5-Dimension; SF-36: SF-36 Health Survey; PGI-C: Patient Global Impression of Change; PROMIS: Patient Reported Outcomes Measurement Information System

Three products have been approved in SCD by the FDA and the EMA with PRO mentioned in their labels. From the PRO identified so far, only pain frequency and hospitalization were identified in the labels, and patient diaries were used for the assessment (**Table 3**).

Limitations

- PROs not listed in ClinicalTrials.gov (e.g., from published clinical studies) were not available for extraction and may have aligned with coreSCD.
- In coreSCD publication, the authors acknowledge that 'pain' is an important, yet complex and multidimensional outcome without a unique way to address it. Many trials did capture pain outcomes (e.g., pain intensity, pain duration) that were important, but measurement challenges may have ruled them out, and they were not included in the final coreSCD.

Table 3. Drugs approved for use in SCD with PROs as endpoints and respective mentions in labeling claims

Brand name	INN	Regulatory agency / Year of approval	Endpoint positioning	Endpoint definition	COA mentioned in label
Drug mechanism of action: Amino acids					
Endari	L-glutamine	FDA / 2017	Primary	number of occurrences of protocol-defined sickle cell crises	Diary – Sickle cell crises (dose interruption, medications, medical facility visits and adverse events)
Drug mechanism of action: Other antineoplastic agents					
Xromi	hydroxycarbamide	EMA / 2019	Not specified	frequency and duration of pain crisis	Not specified
Droxia (previously Hydrea)	hydroxyurea	FDA / 1967	Not specified	yearly rate of painful crises, yearly rate of painful crises requiring hospitalization	Diary – Painful crises

Source: PROLABELS™

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References

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