



A STRATEGY FOR THE MEASUREMENT OF SICKLE CELL DISEASE SYMPTOMS FROM THE PATIENT PERSPECTIVE

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Introduction

- Sickle cell disease (SCD), an inherited blood disorder, impacts multiple organs leading to variable clinical presentations.
- In addition to severe pain episodes, patients may experience chronic symptoms (e.g., pain, tiredness) that can be associated with a wide range of health-related quality of life impacts.
- Assessing treatment benefit using a patient-reported outcome (PRO) measurement strategy is important in SCD research.

Goal

- To develop a PRO measurement strategy in SCD to assess daily symptoms in a patients 16 years of age and older in the context of a regulated clinical trial.

Methods

Conceptual research

- Symptom and impact concepts relevant to SCD were identified from multiple sources:
 - Concept elicitation interviews with individuals with SCD, patients 16 years of age and older (N=20)
 - SCD concept focused articles via targeted search of the peer-reviewed literature databases (N=12 articles)
 - Telephone interviews with clinical experts (N=5)
- Results were synthesized in an SCD conceptual model.

Review of conceptual research

- The SCD conceptual model was compared to the concepts measured by existing instruments used previously in SCD research (N=5) to assess the conceptual coverage of each.

Review of measurement properties and context of use

- Best practices for developing an SCD PRO measurement strategy (e.g., item structure, recall period, and context of use) were reviewed.

Results

Conceptual research

- Patients representing HbSS and HbSC SCD subtypes reported a total of 22 signs and symptoms and 29 impact concepts across nine domains.
 - Impact domains include, activities of daily living (ADLs), physical, emotional, cognitive, financial, leisure, social, sleep, and work/school impacts.
- Patients described the daily variability of SCD symptoms (i.e., occurrence, frequency, and severity), and impacts on their lives (Figure 1).
 - Pain and fatigue/tiredness were rated as highly bothersome, impactful and/or worrisome.
 - Other SCD signs and symptoms (e.g., numbness/tingling, swelling, and headache) were also highly rated.
 - Participants most commonly identified pain (N=16, 80%) and fatigue/tiredness (N=10, 50%) as the important symptoms that an effective treatment would improve.
- Most symptoms and impacts were corroborated by the literature and/or clinical experts. See Figure 2 for the harmonized SCD conceptual model.

Figure 1. Patient quotes describing SCD symptoms and impacts

Pain

"...it appears to be **extremely random**...It'll **show up out of nowhere** in any particular body part, and the pain can be really not that intense to where it's **barely noticeable**, or it can be **extremely painful**, it can **last seconds**, but **other times**, it can **last hours**, it's like no, there's no guidebook or rulebook..."

Fatigue

"I get **fatigued and tired fast**. I have to **pace myself and know what my limits are**...but if I'm like doing chores around the house I can get it done but ... I get **exhausted really quick**, so fatigue is a big, **big deal** ... I just feel drained."

Difficulty concentrating

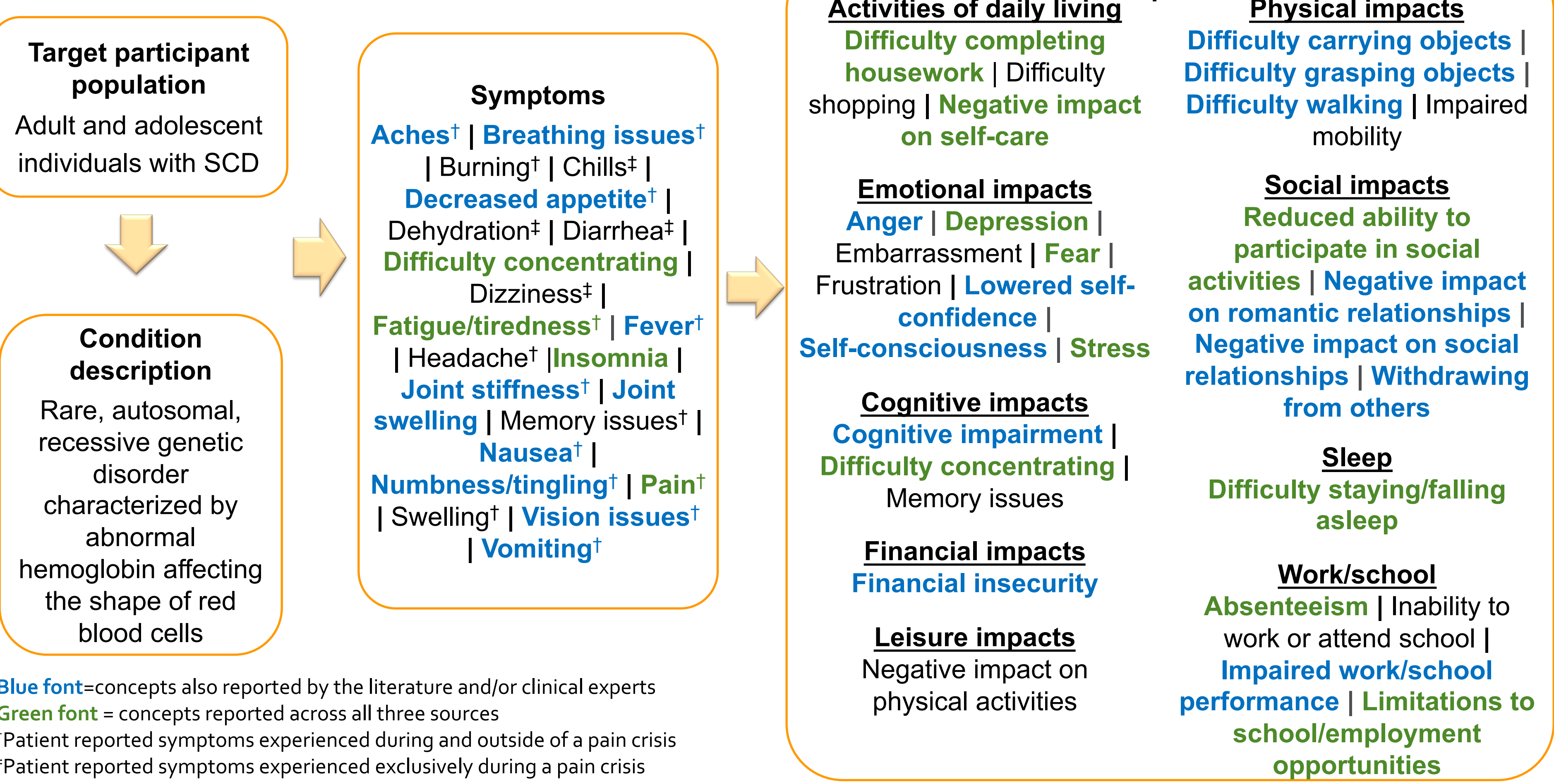
"...it's just **hard for me to focus** in...because **my brain becomes scattered**...it's just **all over the place**...I **have to remind myself** to come back, even in **conversation**...that's **day to day** for me."

Social impact

"It affects me, um, by I may **not be able to enjoy**, um, **family time, going out at times**, um, **having fun with friends**, um, or **activities with my boyfriend**.... I **can't because I'm so tired** or, um, uh, they want to clean up or cook something, but I can't, because I'm so tired."

Results cont'd

Figure 2. Sickle cell disease conceptual model from the perspective of patients, the literature, and clinical experts



Review of conceptual coverage

- Adult Sickle Cell Quality of Life Measurement Information System (ASCO-Me®); Pediatric Quality of Life Inventory (PedsQL™) sickle cell disease module; the Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue and Pediatric Pain Interference (PPI) measures; and Scribe Sickle Cell Record of Daily Symptom Burden™ (SSCRDSB) were reviewed. See Table 1.
- None assessed more than 5 symptoms from our SCD conceptual model, although each measured other symptoms and impacts not included in the model.
 - The PedsQL™ sickle cell disease module, the PROMIS-Fatigue, and the PROMIS-Pain Interference assessed one specific symptom or impact experience (fatigue or pain/pain interference).
- Pain was the most frequently measured symptom and physical impacts were the most frequently measured impact domain.
- Questionnaires with greater amounts of SCD impact coverage include the PedsQL™ sickle cell disease module, PROMIS-Pediatric Pain Interference, and ASCO-MeSM.

Table 1. Conceptual coverage of PRO questionnaires as compared to patient-reported sign/symptoms and impact domains

	ASCO-MeSM	PedsQL™ SCD module	PROMIS-Fatigue	PROMIS-PPI	SSCRDSB
Sign or symptom*					
Aches	--	--	--	--	✓
Breathing issues	--	--	--	--	✓
Difficulty concentrating	--	--	--	--	✓
Fatigue	--	--	✓	--	✓
Insomnia	✓	--	--	--	--
Joint stiffness	✓	--	--	--	--
Pain	✓	✓	--	--	✓
Impact domain					
ADLs	✓	✓	✓	--	--
Emotional	✓	✓	--	✓	--
Cognitive	--	--	✓	✓	✓
Financial	--	--	--	--	--
Leisure	--	✓	--	✓	--
Physical	✓	✓	✓	✓	✓
Social	✓	✓	--	--	--
Sleep	✓	✓	--	✓	✓
Work/School	--	✓	✓	✓	--

*Other symptoms reported in the conceptual model but not covered in any questionnaires: burning, decreased appetite, fever, headache, joint swelling, memory issues, nausea, swelling, vision issues, vomiting
-- Not covered in questionnaire; ✓ Covered in questionnaire

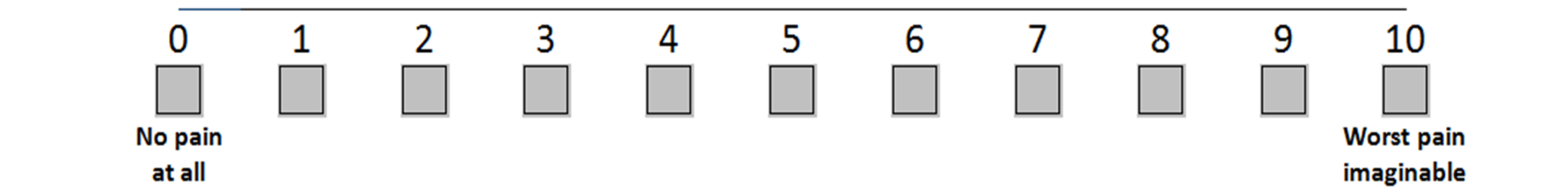
Results cont'd

Review of measurement properties and context of use

- The reviewed questionnaires did not meet the need for the current context of use, as they only assess a subset of concepts and do not assess the concepts in ways that can effectively measure the daily variability of symptom severity
 - For example, all but one utilize recall periods ranging from seven days to one month and use 5-point verbal rating scales that may be less sensitive to change.
- Considerations relating to concept selection, item generation, and measurement properties were reviewed in relation to a PRO measurement strategy in SCD (Table 2), and an example item is presented based on these considerations (Figure 3).

Table 2. Considerations for developing a SCD PRO measurement strategy: Best measurement practices	
Consideration	An approach for SCD
Instrument instructions	Clear instructions about the purpose of the questionnaire/questions (e.g., SCD symptoms or impacts), recall period to consider (e.g., over the past 24 hours or 7 days) using language that is familiar to SCD patients.
Selection of measurement concepts	Important and bothersome concepts should be considered for inclusion to ensure comprehensiveness of the SCD PRO measurement strategy. For example, pain, fatigue and other impacts proximal to SCD could be considered for inclusion. Scoring implications should be taken into account (i.e., single concept v. multi-concept or multi-domain scoring).
Recall period	The variability of SCD signs/symptoms/impacts that can be experienced chronically as well as intermittently suggests that a daily assessment with a 24-hour recall period may be ideal.
Item structure	Individuals with SCD reported daily symptom variability; items can be constructed using patient language to potentially measure the most severe or frequent experience over the recall period.
Response options	A numeric rating scale may be selected to measure varying severity levels of symptom experience while a categorical scale may be used to assess symptom frequency.

Figure 3. Example SCD PRO questionnaire item and response option scale
During the past 24 hours, how bad was your pain at its worst?



Conclusions

- Individuals with SCD experience numerous symptoms and impacts with varying frequency and severity.
- Existing SCD questionnaires may not be as appropriate for use in the assessment of daily variability in the severity of SCD symptoms.
 - Questionnaires with greater SCD impact coverage may be considered for assessing SCD impacts, particularly if administered in conjunction with other symptom-based questionnaires
 - Studies focused on single concepts may use the single-concept questionnaires.
- A newly developed symptom instrument may better assess treatment benefit from the patient perspective by measuring the most relevant and important symptoms associated with SCD at their worst on a daily basis.
 - Considerations for developing a PRO measurement strategy include, the comprehensiveness, understandability, mode of administration, respondent burden, measurement properties, translatability, and length of the instrument of choice.
- Conducting conceptual qualitative research, assessing the conceptual coverage and measurement properties of existing tools, and evaluating adherence to best measurement practices for a new or existing tool are key steps to inform the development of an effective PRO measurement strategy to support efficacy endpoints and product labeling goals in regulated clinical trials.

Disclosures

At the time of the study, OO and DR were employees of Ironwood; OO is currently an employee of Cyclerion. OO and DR may own stock/stock options in Ironwood, the study sponsor, and Cyclerion; MT served as a consultant to Ironwood; LL, LM, BK, SO, EC, and AR are employees of Adelphi Values contracted by Ironwood to conduct the research activities. Cyclerion is an independent spin-off of Ironwood focused on serious and orphan diseases including sickle cell disease.