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What is the future of patient reported outcomes in sickle cell disease?

Sharon A. Singh[1], **Nitya Bakshi**[2,3], **Prashant Mahajan**[4], **Claudia R. Morris**[3,5]

[1]Department of Pediatrics, Division of Pediatric Hematology/Oncology, University of Michigan Medical School, Ann Arbor, MI, USA

[2]Department of Pediatrics, Division of Pediatric Hematology/Oncology, Emory University School of Medicine, Atlanta, GA, USA

[3]Children's Healthcare of Atlanta, Atlanta, GA, USA

[4]Department of Emergency Medicine and Pediatrics, University of Michigan Medical School, Ann Arbor, MI, USA

[5]Department of Pediatrics, Division of Pediatric Emergency Medicine, Emory University School of Medicine, Atlanta, GA, USA

Abstract

Introduction—Sickle cell disease (SCD) is a complex, chronic disease caused by abnormal polymerization of hemoglobin, which leads to severe pain episodes, fatigue, and end-organ damage. Patient reported outcomes (PROs) have emerged as a critical tool for measuring SCD disease severity and response to treatment.

Areas covered—Authors review the key issues involved when deciding to use a PRO in a clinical trial. We describe the most highly recommended generic and disease-specific PRO tools in SCD and discuss the challenges of incorporating them in clinical practice.

Expert opinion—PRO measures are essential to incorporate into SCD clinical trials either as primary or secondary outcomes. The use of PRO measures in SCD facilitates a patient-centered approach, which is likely to lead to improved outcomes. Significant challenges remain in adapting PRO tools to routine clinical use and in developing countries.

Keywords

patient reported outcome; PRO; sickle cell disease; hemoglobinopathy; quality of life; HRQOL; PROMIS; ASCQ-Me; Peds-QL; SF-36

Corresponding author: Claudia R. Morris, Professor of Pediatrics and Emergency Medicine, The Wilbur Fisk Glenn Jr. Distinguished Faculty Chair for Clinical & Translational Research, Emory University School of Medicine, 1760 Haygood Drive NE, W458, Atlanta, GA 30322, USA, Tel.: +1 404 727 5500, claudia.r.morris@emory.edu.
Children's Healthcare of Atlanta, Atlanta, GA, USA

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1. Introduction

Sickle cell disease (SCD) a common inherited hemoglobin disorder, which affects more than 300,000 newborns per year around the world leading to an enormous global health and economic burden [1,2]. SCD, is caused by abnormal polymerization of sickle hemoglobin in red blood cells and leads to multiple severe outcomes caused by chronic hemolysis and vaso-occlusion resulting in severe morbidity, psychosocial distress, and early mortality [3]. The hallmarks of SCD are extremely variable even among individuals with the same genotype but generally include pain, fatigue (from severe anemia), vaso-occlusive complications, end organ damage and cognitive impairment.

Despite the discovery of the underlying molecular mechanism of SCD almost 70 years ago, treatment options have lagged, primarily because this disease mostly affects populations residing in geographical regions with limited economic resources [4]. The lack of clinically useful biomarkers to predict disease severity has been limiting and is an additional barrier to progress in clinical research [5]. As many key SCD manifestations are symptom-based and subjective, the use patient reported outcomes (PROs) have emerged as a critical measure to incorporate into both clinical trials as well as clinical practice in order to improve health care for patients affected by this disease [6–8].

The term PRO or PROM (patient reported outcome measure) refers to an assessment of the patient's health status, obtained directly from the patient without subsequent interpretation either by clinical/research staff or caregiver [9]. Recent research has produced numerous, robust PRO tools that are valid, reliable, and generalizable to populations, thus, resulting in their increased use as outcome measures in clinical trials. The use of PROs increased from 14% to 27% between 2004–2013 in the ClinicalTrials.gov registry with a more recent analysis in the Australian New Zealand registry (2005–2017) showing a rate of 45% [10,11]. For this article, we searched the PubMed database for relevant general PRO articles and PRO SCD articles from 2000-present using the keywords listed. We first present an overview of the benefits and challenges of using PROs in clinical research and practice. Next, we review the use of this measure in SCD using several tools validated for use in this disease and underscore the importance of incorporating PROs into sickle cell trials either as a primary or secondary outcome measure and to enhance the clinical care of patients with SCD [6–8]. We support our opinion by a comprehensive review of relevant literature.

2. PRO overview

The use of PROs in clinical trials has been exponentially increasing, driven by changing demographic and societal trends [10,12–14]. Medical advancements lead to a longer life expectancy and increased prevalence of chronic disease, which coupled with an increased access to health information and patient empowerment have escalated interest in PROs and shifted focus away from relying on claims data for patient related outcomes [15]. PRO data are often needed to demonstrate added value and competitive advantages of newer therapies compared to existing treatments for SCD [16]. Integration of PROs in clinical trials have been facilitated by various efforts including the FDA (Food and Drug Administration) 2009 Guidance for Industry, congressional mandates (FDA Safety and Innovation Act; 21st

Century Cures Act), the NIH-sponsored PROMIS initiative (Patient-Reported Outcomes Measurement Information System), EMA (European Medicines Agency), establishment of PCORI (Patient-Centered Outcomes Research Institute), the CONSORT (Consolidated Standards of Reporting Trials) investigators and PRO Consortium, among others [17–21].

PRO data can be obtained using electronic tools (online, phone app, tablet), paper surveys, and in person or telephone interviews. PROs may measure a single item such as pain or provide a comprehensive assessment of overall patient physical functioning and/or psychological/social well-being utilizing grouped questions to generate an overall domain score such as HRQOL (health-related quality of life). The decision to use a PRO measurement in a clinical trial must be carefully considered with a knowledge of their benefits and limitations (Table 1). There are many available PRO tools that measure outcomes in the general population as well as specific tools for use in certain disease populations, which are available in several databases [22]. One of these databases, the PROQOLID (Patient-Reported Outcome and Quality of Life Instruments database), was created by the Mapi Research Trust in Lyon, France in 2002 and current users have access to over 2500 instruments [23,24]. Two commonly used tools in SCD, PROMIS® and ASCQ-Me® can also be accessed from the HealthMeasures website [25]. Selection of the appropriate PRO measure(s) may be challenging as there are many options, although disease-specific options are more limited and often require further development, refinement, and subsequent validation. The CONSORT PRO Extension has established a checklist of 5 items that should be considered when using PROs in randomized controlled trials: PROs should be identified in the abstract along with a description of PRO hypothesis, reliability and validity of PRO measure, statistical approach for missing data and how PRO can be generalized to other populations and clinical practice [17]. Additional guidance in protocol development is provided by the SPIRIT-PRO Extension [26].

2.1. PRO advantages and challenges

There are many diseases or clinical scenarios where improvement or resolution of patient symptoms are the only way to measure treatment outcomes in clinical trials (E.g. insomnia, headache) and hence the use of a PRO is essential [12]. We can envision certain treatments may also be of great value to patients (i.e. improvement of pain or quality of life in end-stage diseases) without improvement of biological markers or overall survival. Treatment options that are similar but offer different PRO benefits may direct both patients and clinicians in their decision-making. These various situations highlight the utility of validated PRO tools in clinical research either as a primary or secondary endpoint although more work may be needed to justify the cost-benefit ratio (Table 2) [27]. A focus on PROs fosters a patient-centered approach where researchers and clinicians understand and incorporate patient symptoms and perspectives. Such approaches enhance communication, promote shared decision-making, treatment adherence, and improve quality of care [28]. In summary, many agencies, including the FDA, have recognized the importance of PROs and support its increasing use in clinical research and drug development.

General PRO tools have an advantage that they have been already developed but lack specificity. Disease-specific PROs while being more specific and applicable to that condition

require development and validation and may not be applicable if one were to compare PRO between different diseases. Selection of an appropriate PRO tool for clinical trials may therefore be challenging. In contrast, general PRO tools may be irrelevant and/or insensitive to certain disease aspects although they would allow comparison to other groups. When and how often to measure a PRO needs to be determined to accurately capture the maximum treatment effect. In order to incorporate PROs into clinical trials, this data must be captured via additional surveys as most EHRs (electronic health records) do not directly capture PRO data although this seems to be changing with the next version of Epic being designed to collect this information [29]. Clinical research staff require special training in collection and analysis of PROs to ensure reliability [30,31].

PRO data may be influenced by patient bias and statistical analysis needs to account for missing data and the testing of multiple outcomes (i.e. multiplicity), which are common issues encountered that may reduce study power and increase type 2 error [11,21]. Missing data is especially problematic and improper statistical analysis may reduce precision and introduce bias, which affects study validity [32,33]. In one analysis of 132 randomized clinical trials, 72% had missing data, yet only 24% reported how they handled missing data [34]. There are several strategies to prevent and handle missing data, which includes rigorous study design and collecting supporting data to determine the reason for missing PRO data from a proxy (caregiver or clinician) (reviewed by Mercieca-Bebber et al) [35]. There has been a recent effort to standardize PRO terminology and data analysis in cancer, which would be useful to adapt to SCD (Table 2) [36]. PRO data in children or from populations unable to directly provide information may sometimes utilize a caregiver proxy report, which has variable correlation with self-reports and is not interchangeable [37–40]. Some groups have suggested that the differences between proxy and self-reports may be small to moderate while others have found a bigger discrepancy in groups with more severe disease and worse caregiver stress [41,42].

3. PRO tools in sickle cell disease

Although there are >2500 PRO tools available, only 5 adult instruments and 3 pediatric instruments have been developed specifically for SCD with no instruments specifically designed for caregivers of SCD patients (see Sarri et al for comprehensive review) (Table 2) [43]. The following sections briefly review the most highly recommended tools in SCD although others are utilized and/or currently being developed.

3.1. Pain measurement

The hallmark of SCD is recurrent acute pain episodes that often require hospitalization and use of parenteral analgesics. Many patients also develop a chronic pain state that is refractory to many treatment strategies, which leads to a reduction in HRQOL and functioning [44]. Pain is a subjective measure, however endpoints such as length of hospitalization or composite endpoints like time to crisis resolution (discontinuation of parenteral opiates, a decrease in pain score, ability to ambulate, decision to discharge) have been used to measure treatment response [45]. These endpoints may be influenced by confounding variables such as concomitant comorbidities and social factors that prolong the

hospital admission and variable clinical practices for prescribing and weaning parenteral analgesics. Pain intensity is a commonly measured patient reported outcome, often measured by a 11-point numerical rating scale (NRS) and 100 mm visual analog scales (VAS) [6,46–49]. In pediatric patients with SCD, a decrease of 0.9 on the NRS or 0.97 cm on the VAS were identified as clinically meaningful change in pain among patients receiving treatment for acute pain, while a change of 13.5 mm was identified as a clinically significant change among adults with SCD receiving treatment for vasocclusive pain [47,48]. While pain intensity is a core outcome for chronic pain clinical trials, additional domains have been recommended by IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) including physical functioning, emotional functioning and participant ratings of overall improvement [50]. More recently validated domain PRO measures in SCD measure additional domains important to patients with chronic pain including pain interference, sleep etc. Use of the learning health system platforms like CHOIR (Collaborative Health Outcomes Information Registry) can assist clinicians and researchers to integrate these multiple PRO measures to test various pain aspects over time and is an area that requires future research in SCD (Table 2) [51,52]. There have also been several efforts to utilize measurement of pain using a daily electronic pain diary although there have not been similar efforts to our knowledge to study daily non-pain PRO measures (Table 2) [53–55]

3.2. PROMIS®

Patient-Reported Outcomes Measurement Information System (PROMIS®) is a NIH (National Institutes of Health)-funded network established in 2004 in order to create reliable and valid PRO measurements in chronic disease to determine HRQOL in research and clinical settings [19,56]. PROMIS® measures allow for assessment of patient reported outcomes in chronic health condition across diseases in adults and children [57,58]. The core outcomes measured are physical health (fatigue, pain intensity/interference, physical function/mobility, sleep disturbance), mental health (anxiety, depression) and social health. These tools were developed by robust consensus methods and include self-report tools for adults, children (8–17 years) and parent-proxy reports (age 5–17 years) [59,60]. Short forms and computer adaptive tests (CAT, a form of computer-based test that adapts to the examinee's ability level designed using item response theory), are also available [61]. One study found an improvement in completion rates in pediatric patients with SCD when short paper forms were used instead on computerized testing suggesting a lack of computer and/or internet access in the SCD population [62]. PROMIS® measures have been validated in adult and pediatric SCD patients and shown to be responsive over time in SCD and other chronic diseases [62–67]. PROMIS scores also strongly correlate with SCD severity. When scores in SCD are compared with the general population the most profound effect were seen in Physical Functioning, Pain Impact and Pain Behavior [64]. Patients with severe SCD symptoms have T-scores >64 in pain interference and > 57 in pain behavior modules [68].The minimally important difference or MID (smallest change in score that is clinically significant) in pediatric PROMIS measures is about 2 points on the T-score scale [69,70]. Differences similar or above this level were seen in PROMIS measures of pain interference, fatigue, depressive symptoms, anxiety, and physical functioning during hospitalization for severe sickle cell pain [62].

3.3. ASCQ-Me®

As healthcare improves for children with SCD, more patients are living into adulthood and there is an increasing demand for PRO measures in adults living with this disease [71]. The Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me®) was specifically designed to measure PROs in adults with SCD and to be complementary to other generic tools including PROMIS® measures. This tool was created after extensive literature review and from information gathered in focus groups and interviews of both adults with SCD and their healthcare workers [72,73]. ASCQ-Me® measures physical health (pain impact/episodes, sleep impact, stiffness impact), mental health (emotional impact), social health (functioning/impact) and SCD disease severity (medical history) with short forms and CATs available. Initial work showed this tool is valid and reliable in SCD patients in the US and UK although further testing is required in other populations and to determine other aspects such as responsiveness over time [64,74]. ASCQ-Me® had greater sensitivity to detect disease severity when compared with PROMIS measures [64]. To our knowledge, the minimally clinically important difference has not been described for ASCQ-Me® measures, though Esham et al assumed a 3–5 point difference (SD of 0.3–0.5), similar to the minimally significant difference of PROMIS measures[75]. More studies are needed in adult patients with SCD with additional emphasis on the vulnerable pediatric-adult transition period (Table 2).

3.4. PedsQL™

The PedsQL™ 4.0 Measurement Model is a modular approach to measuring health-related quality of life in both healthy children and adolescents and in those with acute and chronic health conditions. The survey integrates generic core scales and disease-specific modules. There are several PedsQL™ scales that may be useful in SCD.

The PedsQL™ 4.0 Generic Cores Scale is a PRO measure developed and extensively tested in >35,000 healthy children and children with chronic disease and translation into many different languages is available [76,77]. This tool was designed to capture the perspective of the child with a self-report from ages 5–18 years and a proxy report for ages 2–18 years. The minimally clinically important difference is 4.4 change in total score for the child report and 4.5 for the proxy report [78] PedsQL™ consists of 23 items that measure physical, emotional, school and social functioning for the last 4 weeks and is valid, reliable and feasible in patients with SCD and shows improvement with hydroxyurea treatment [79,80]. Both the child-report and parent proxy can distinguish between those with and without SCD but only the parent proxy can differentiate mild and severe disease [79]. The PedsQL™ Multidimensional Fatigue Scale is another tool composed of 18 items that measures general fatigue, sleep/rest fatigue and cognitive fatigue and has been validated in SCD and other chronic illnesses [81–84].

The PedsQL™ Sickle Cell Disease Module was specifically designed for patients with SCD and is composed of 43 items that cover several domains: pain and hurt, pain impact, pain management and control, worry, emotions, treatment and communication [85]. This disease-specific measure was showed to be feasible, reliable and valid when tested in pediatric patients with SCD and their parents using self-report and parent proxy (age 5–18 years) and

parent proxy (2–4 years) [86]. Scores of 60 and below indicated poor HRQOL and 81 and above indicated good HRQOL [87]. Most items in this scale were responsive to a change in HRQOL from acute pain crisis hospitalization but these findings may not apply all patients with SCD so further analysis in other settings is required [88]. In this study, the minimal perceived improvement in HRQL pain domain score was 7–10.

3.5. SF-36v2™

The SF-36v2™ (Medical Outcomes Study Short Form 36) is a non-disease specific HR-QOL tool that is widely used and has been utilized in many large cohort SCD studies [89–91]. This tool measures eight health domains (general health, bodily pain, physical functioning, physical role limitation, vitality/energy, social functioning, mental health and emotional role limitation) in adults [92]. SF-36v2™ has been translated in many different languages and used in patients with SCD around the globe [93–95]. Efforts have been made to convert SF-36v2™ to PROMIS scores, which would be useful to compare data across studies using these different measures [96].

4. PROs in sickle cell clinical care

Although PRO measures are increasingly being used in SCD clinical trials, similar investment in application of PROs in clinical practice is lacking, largely due to the complexity and feasibility issues in collecting reliable data [97]. Clinicians may not be able to determine the type and frequency of data collection and too frequent collection adds to patient burden or may be irrelevant to that patient. Determining how to translate the data collected to a clinical outcome or intervention may not be easily interpreted. In addition, clinical practices must be able to incorporate PRO measures in their clinical practices so as not to compromise efficiency and burden staff with data that does not affect outcome. Although it would be preferable for patients/families to complete PRO measures prior to clinic visits, this may be challenging for some SCD families with limited resources, access to technology or for patient with cognitive deficits. Several recent SCD studies have focused on relating PRO measures to clinical practice and for quality improvement studies although translating this to routine clinical use would require significant investment by health care systems [29,68,87].

5. CONCLUSION

The use of PROs in clinical research and patient care has been increasing over the past several decades fueled by a societal recognition of their value to patients, caregivers, clinicians, researchers, pharmaceutical companies, and regulatory/federal agencies. PRO data provide a patient-centric disease perspective that can lead to improved quality of care and treatment adherence by shared decision-making. Although there is great value in utilizing PRO data, there are many challenges that users must be aware of in order to prevent using poorly designed tools or measures that have not been validated in a specific disease populations leading to inaccurate findings and conclusions. Analysis of PRO data may be difficult due to missing or multiplicity of data. Many SCD disease manifestations are symptom-based so PROs are an extremely important adjunctive measure to utilize in clinical practice and research studies. There are several excellent general and disease-specific PRO

measures that are commonly used in SCD including PROMIS®, ASCQ-Me®, PedsQL™ and SF-36v2™ as described in this article. A huge challenge remains to incorporate PROs into routine clinical practice to improve quality of health care and reduce the large economic cost of SCD (Table 2) [98].

6. Expert opinion

Sickle cell disease is a multisystem, complex disease affecting every facet of life and leads to a significant decrease in HRQOL, which is similar to or worse than other chronic diseases [99]. In 2014, The FDA-sponsored Patient-focused Drug Development Initiative conducted a public meeting to obtain the perspective from patients and their caregivers about their disease and treatment options. In the "Voice of the Patient" report, many participants identified chronic pain, fatigue and cognitive symptoms as having the largest impact on their lives [100]. In order to accurately capture disease severity and the impact of treatments on the items that matter the most to patients, the use of PROs are essential both in clinical trials and clinical practice although great challenges remain to implement PROs routinely in health care settings [101]. Using PRO tools enables us to systematically measure this silent suffering that patients endure daily and can measure treatment effectiveness. Collecting PRO data in the clinical setting enhances communication between patients and providers, which is a key component to building and preserving trust in a community that has historically experienced great injustice at the hands of the health care system and continues to experience discrimination and stigma, which directly impacts HRQOL [102–106]. In order to offer our perspective on the future of PROs in SCD we must first examine the unique history of this disease population, which may differ among various geographical areas around the world but in the United States involves deep reflections on race and inequality including access to health care and research funding [107,108].

Although there has been a lag in drug development in SCD with hydroxyurea as the only drug option for decades, there are now currently numerous drugs in the developmental pipeline that are likely to be in clinical trials in the near future [4,109]. These drugs all target different aspects of the complex underlying disease mechanism including anti-sickling, HbF inducing, anti-inflammatory, anti-oxidant, and anti-adhesive pathways, among others. The sickle cell community has seen the early results of these efforts with recent FDA approvals of L-glutamine, voxelotor and crizanlizumab within the last 3 years [110–112]. There has also been an increased interest in curative treatments like bone marrow transplant and gene therapy. *What role should PROs play in development of these new drug/curative treatments?* We propose that PROs should be incorporated into all clinical trials to test new drugs/ treatment strategies either as a primary or secondary endpoint as this information is of major importance to SCD patients (Table 2). We envision a future where PRO outcomes may be used to facilitate shared decision making about treatment strategies are presented with numerous treatment options and need to be active participants in directing the health care approach to their disease. For many, this may involve combination drug strategies while others with more severe disease manifestations may elect a curative approach. For some patients it is likely that PRO measures may be a way to track the disease course over time and chose new treatments that have been proven to improve their specific symptoms or combination of symptoms. Having accurate PRO data readily available for each new

treatment option will facilitate this process. Without actively engaging patients in these treatment decisions, understanding their subclinical disease burden and medical beliefs, adherence to old and new treatment options is likely to continue to be suboptimal [113,114].

Although there are great benefits to the increased use of PROs in clinical research and clinical practice, there are additional challenges to the incorporation of patient reported outcomes in low-resource settings. As a SCD community, we cannot forget that the largest burden of this disease lies in developing countries like sub-Saharan Africa, where there is limited access to health care [115–117]. Survival in SCD patient in these areas lags far behind the norms in the US and the immediate priority in many of these countries is to set up newborn screening in order to limit early mortality from infections and severe disability due to stroke. However, use of PRO tools in developing countries may require translation and additional validation due to cultural and language differences. An investment in developing robust PRO tools for specific geographical areas would provide a venue to collect valuable information about local differences in disease phenotype due to genetic factors, the influence of other common local comorbidities (malnutrition, infectious disease), cultural differences etc., which may be important to understand in order to offer best treatments to these patients. Alternatively, PRO measures in developing countries (e.g. to measure cognitive function) would likely be more practical and economical in some studies than imaging or specialized biomarkers from blood to follow the impact of treatment on various disease processes such as silent infarcts in the brain (Table 2).

We propose here that PROs are an invaluable part of the future of clinical care and research in SCD. There however remains significant work in the field to develop and validate existing and new PRO measures in SCD especially in developing countries and to determine how to overcome the challenges of using PROs in clinical settings. PRO measures are of tremendous value to patients with SCD-they are the “voice of the patient”. Devoting time and effort to their development holds great promise to improve and modernize health care and quality of life for those suffering from this disease across the globe.

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Declaration of interest

C Morris is the inventor or co-inventor of several UCSF-Benioff Children’s Hospital Oakland patents/patent-pending applications that include nutritional supplements, and biomarkers of cardiovascular disease related to arginine bioavailability, is an inventor of an Emory University School of Medicine patent application for a nutritional supplement, is a consultant for Pfizer and has received research support from MAST Therapeutics, the United States Food and Drug Administration, the Health Resources and Service Administration, and the National Institutes of Health. This project was supported in part by NIH/NCCIH K24AT009893 to Dr. Morris. P Mahajan’s effort is partially supported by grants awarded by the Agency for Healthcare Research and Quality (1R18HS026622, 1R01HS024953) and Eunice Kennedy Shriver National Institute of Child Health and Human 1R01HD08523. SA. Singh, MD has been a consultant for Emmaus Medical, Inc. Correct for Singh The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Article highlights

- Sickle cell disease (SCD) is a common inherited hemoglobinopathy, and is a complex, chronic disease caused by abnormal polymerization of hemoglobin in red blood cells
- SCD disease manifestations are variable, but most patients have recurrent pain episodes, hemolysis, fatigue from severe anemia, end-organ damage, and early mortality
- PROs (patient reported outcomes) are a “a report of the status of the patients health condition that comes directly from the patient without interpretation of the patient’s response by clinician or anyone else”
- Many SCD disease symptoms are subjective so PROs can complement clinician reported outcomes by measuring the patient experience
- PRO measures in pediatrics may be self-reported or by parent-proxy report, although the two types of data are not interchangeable and may not correlate in some situations
- PRO measures are increasingly being used in clinical trials and there are several excellent generic and disease-specific tools validated for use in sickle cell disease as primary or secondary outcomes
- Significant challenges remain in adapting PROs to clinical practice and for use in developing countries

Table 1:

Key issues to consider in the use of PROs in clinical trials

Benefits	**Challenges**
Essential to use in diseases where patient's report of symptoms is only measure of treatment efficacy	General PRO measurements may be irrelevant or insensitive to certain disease aspects
Can be used as a secondary measure to support primary endpoint/biological markers	Disease-specific PROs are limited; new tools require proper design and validation; may be unable to generalize to other disease populations and/or other geographic regions (language/cultural differences)
Fosters patient-centered health care (improved communication, shared treatment decision making and adherence)	Current EHRs do not effectively record PRO data
Regulatory agencies support use of PRO data	Data analysis may be more difficult (subjective, biased, missing data, multiplicity)
Improved health care quality	When and how often to administer PRO?
	May be limited in pediatrics (need to utilize caregiver proxy report)

Table 2:

Existing gaps in PROs research in SCD

Future research directions
1. PRO cost-benefit analysis
2. Determine best strategies for analysis and interpretation (missing data; determining MID)
3. Studies in adult patients and in pediatric-adult transition
4. Integrating PRO measures to study chronic pain
5. Adapt and utilize PRO in clinical settings
6. PRO validation and use in developing countries
7. Include in clinical trials for all new drugs/curative treatments
8. PROs to measure SCD caregiver burden
9. Daily non-pain PRO measures