Sickle Cell Disease Workgroup:

Topic Brief

March 7, 2016

High-Level Research Questions

- What is the comparative effectiveness of different models of care for children with sickle cell disease transitioning from pediatric to adult care?
- What is the comparative effectiveness of interventions to improve the treatment and management of acute pain crises in patients with sickle cell disease?

Assignment for Workgroup Participants

- Based on your perspective (patient, clinician, payer, etc.), what are two key patient-centered, comparative effectiveness research questions relevant to reducing disparities and improving sickle cell disease outcomes that warrant further research to address current gaps in knowledge?
  - Please refer to the following when developing your questions:
    - PCORI's Tier 3 Criteria
    - How to Write a Research Question
- Submitted questions will be used to guide the discussion at the workgroup meeting.

"This document was prepared for informational purposes only and should not be construed as medical advice or used for clinical decision making."

Topic: "Management of Sickle Cell Disease"

PCORI Scientific Program Area: Addressing Disparities

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1. Overview

Sickle cell disease (SCD) is a chronic genetic disorder affecting the body's red blood cells (RBCs).[1] It is estimated that between 70,000 and 100,000 Americans, predominantly African Americans, have SCD.[2] This disorder affects the hemoglobin in RBCs that is responsible for transporting oxygen from the lungs to the rest of the body.[3] In SCD, the body produces abnormal RBCs that become rigid once they have given up their oxygen and take on a crescent-shaped ("sickle") form.[3] The sickled cells clump together, causing blood vessels to become obstructed and consequently reduce blood flow to many parts of the body.[3] This process induces a series of disease-related complications, such as acute chest syndrome and stroke. However, the hallmark complication for patients with SCD is recurrent acute pain episodes, or "pain crises".[2] These episodes are periodic, typically recurrent, and occur throughout life.[4] It is important to note that there are a number of SCD genotypes, each associated with varying clinical severity, which affects the extent to which pain manifests itself.[5]

The management of acute pain is central to the care of SCD; however, it is inadequately addressed across all types of healthcare settings.[2, 8] Individuals with SCD are frequently seen by a primary care physician (PCP) or at community clinics for routine care; however, when suffering from a pain crisis, many patients seek treatment in emergency departments (ED).[9] Varying levels of experience in managing pain associated with SCD among both primary care and emergency department physicians lead to inconsistent care and treatment.[10]

Many of the evidence-based guidelines that exist to aid healthcare professionals in the management of individuals with SCD are based on weak evidence and/or consensus-based opinion, leaving physicians and patients with little information to make informed healthcare decisions regarding treatment.[2] Additionally, the number of comprehensive centers to treat patients with SCD is sparse. For example, there are approximately 10 comprehensive adult SCD centers in the United States, compared to 100 centers each for the treatment of hemophilia and cystic fibrosis, which are both less prevalent than SCD.[9]

The primary approach for treating SCD pain focuses on alleviating symptoms with pharmacological agents (i.e., non-opioid and opioid analgesics with or without adjuvants) and replacement of fluids to slow or stop the sickling process.[2, 4] However, there is little evidence

regarding the type of opioid that should be used.[8, 11] Suboptimal trial designs have contributed to the lack of a strong evidence base.[11] To date, SCD trials suffer from insufficient sample sizes, lack of standardized measures for pain intensity and pain relief, and non-random allocation of patients to study arms.[8, 11] Additionally, while opioid use in the treatment of SCD is frequent, assessing when to prescribe has long been controversial.[7] Physicians do not have reliable guidelines to assess the presence of a pain crisis.[5] The perceived stigma associated with prescribing opioids for SCD also remains a barrier. Fifty-three percent of ED physicians and 23 percent of hematologists state that more than 20 percent of their adult patients with SCD are addicted to opioids.[6] However, actual rates of narcotic dependency and abuse are low among patients with SCD.[5]

There is ongoing interest in preventing pain crises in SCD patients through the modification of the underlying pathophysiology.[8] Preventive measures include hydroxyurea treatment and chronic blood transfusions.[8] These two disease modifying therapies are widely available but remain underutilized.[2] Currently, hydroxyurea is the only US FDA–approved disease modifying medication for the treatment of SCD.[12] While hydroxyurea does modify the underlying disease process and reduces the severity and frequency of pain crises, it does not eliminate them.[10]

Hydroxyurea treatment and some improvements in general supportive care have increased the average lifespan of children with SCD to live past adolescence.[13] However, SCD-related mortality rates are highest among young adults transitioning from pediatric to adult care and there are no established evidence-based guidelines for facilitating this transition.[14]

2. **Patient-Centeredness**

Studies show that patients and clinicians are dissatisfied with the quality of SCD pain management.[9] Recent literature documents that SCD patients report: not having enough involvement in decisions about their own care, poor pain management, lack of access to outpatient care services, poor communication between healthcare professionals, and inadequate follow-up.[9, 10]

3. **Impact (Burden) of the Condition**

Approximately 73.1 out of 1,000 newborn African Americans in the United States are born with SCD.[15] Despite some improvements in care, the average lifespan ranges between 36 and 53 years for men, and 39 and 56 years for women.[3]

Nearly all individuals with SCD will suffer from an acute pain crisis in their lifetime, accounting for approximately 90 percent of their hospital admissions.[2, 8] In the "Pain in Sickle Cell Epidemiology Study (PiSCES)," adults who completed the daily diary entries reported pain on 54.5 percent of the 31,017 days surveyed.[15]

By the time a patient with SCD reaches age 45, he/she will have accrued over $900,000 in undiscounted medical expenses.[16] Eighty percent of the medical costs accrued by patients with

SCD are associated with hospitalization, suggesting that interventions to reduce complications, such as pain crises, could be cost-saving.[16] In addition to the economic repercussions, those suffering from SCD pain also face emotional, behavioral, and psychological difficulties.[8]

4. Evidence Gaps

General Guidelines for Pain: The National Heart, Lung, and Blood Institute (NHLBI) released an expert panel report in 2014 on "Evidence-Based Management of Sickle Cell Disease."[2] The report highlights that appropriate management of acute pain crises is central to the care of individuals with SCD.

- The evidence-based recommendations made by the panel in regard to pharmacologic treatment are as follows:
  - **Strong Recommendations with High-Quality Evidence:**
    - Rapidly initiate treatment with parenteral (injected) opioids for severe pain.
  - **Moderate Recommendations with Low-Quality Evidence:**
    - Continue treatment with NSAIDs in patients with mild to moderate pain who report relief with NSAIDs.
    - Initiate around-the-clock opioid administration by patient-controlled analgesia (PCA) or frequently scheduled doses versus "as requested" administration.
    - Do not administer a blood transfusion unless there are other indications for transfusion.
- Many recommendations (consensus-panel expertise) included **practices that have *not yet been validated by evidence*,** but are currently in use. Some of these recommendations include:
  - Rapidly initiate analgesic therapy within 30 minutes of triage or within 60 minutes of registration.
  - Use an individual prescribing and monitoring protocol or an SCD-specific protocol wherever possible to promote rapid, effective, and safe analgesic management and resolution of the pain crisis.
  - Administer oral NSAIDs as an adjuvant analgesic in the absence of contraindications.
  - Use adjunctive non-pharmacologic approaches to treat pain such as local heat application and distraction.

Analgesic Treatment for Pain: A 2014 Cochrane systematic review assessed the effectiveness of pharmacological analgesic interventions for pain management, including the treatment of acute and chronic pain in children and adults.[8]

- Nine RCTs of analgesic use in SCD patients suffering from acute pain crises were identified; however, the sample sizes in these trials were small.

    - No studies addressed the efficacy of acetaminophen or weak opioids.
    - There was some evidence that suggested that NSAIDs given by injection can reduce pain.
    - One study demonstrated that morphine given orally was as effective as morphine given by injection.
- Lack of data, small patient numbers, variations in study design and outcome measures limit the review.
- Overall, there was **insufficient evidence** to determine the effectiveness of pharmacological analgesic interventions for pain management in SCD.
- The review called for the following when designing future studies:
    - More multi-center trials to ensure sufficient recruitment for adequately powered studies.
    - A standardized protocol of pain management as the basis for control arms.
    - Standardized measures of pain intensity and pain relief to facilitate the comparison between studies.
    - Appropriate outcome measures that are relevant to patients and families.

Psychological Treatment for Pain: A 2015 Cochrane systematic review examined the evidence for psychological interventions to improve the ability of people with SCD to cope with their condition and related pain.[17]

- Seven RCTs were eligible for inclusion in the review. Only five studies, with a total of 260 participants, provided suitable data to be entered into the review.
    - One study suggested that cognitive behavioral therapy (CBT) helped with pain management but not the sensory aspect of pain intensity.
- **There was insufficient evidence** to draw strong conclusions about the efficacy of psychological interventions for patients with SCD. The review called for the following:
    - Further research using a structured approach to assess psychological therapies, taking into account clinical and demographic variables.
    - Well-designed and adequately powered studies that incorporate treatment manuals to promote consistency and allow for replication.
    - Future studies that identify the most important components of psychological interventions for the SCD community.

Fluid Replacement for Pain: A 2015 Cochrane systematic review sought to examine randomized controlled trials (RCTs) that demonstrated the best approaches for replacing fluids; however, no such trials were found.

- Due to **insufficient evidence**, the authors concluded that a large, multi-center trial is needed to fill evidence gaps regarding fluid replacement for individuals with SCD.

Hydroxyurea: A systematic review published in 2008, commissioned by the National Institutes of Health Office of Medical Applications of Research, assessed the efficacy, effectiveness, and toxicity of hydroxyurea when used to treat adults with SCD.[12]

- A single RCT tested the efficacy of hydroxyurea in adults with SCD.
  - The high-quality, multicenter trial enrolled 299 adults.
  - The primary endpoint was the reduction in the frequency of painful crises.
  - The median number of painful crises was 44 percent lower than the placebo group.
  - The time to first painful crisis was three months compared to 1.5 months in the placebo group.
  - Costs for hospitalization for pain were significantly lower in the hydroxyurea group.
- There is **strong evidence** that the use of hydroxyurea has a positive effect on the frequency and severity of pain crises.

Barriers to Appropriate Care: A 2009 systematic review examined interventions to approve appropriate use of therapies for SCD treatment, focusing on appropriate pain management during pain crises.[18]

Barriers

- Thirteen studies identified patient- and provider-related barriers for appropriate pain management during pain crises.
- The most common barriers identified by both patients and providers were negative provider attitudes (n=13) and lack of provider knowledge (n=5). Negative provider attitudes included:
  - Not believing that patients were genuinely in pain,
  - Being suspicious of drug abuse or addiction,
  - Stigmatization of patients with SCD,
  - Insensitivity or lack of sympathy, and
  - Unspecified negative perceptions or attitudes.
- There is **strong evidence** that negative provider attitudes and poor provider knowledge are barriers to use of appropriate pain medications during pain crises for patients with SCD.

Transition to Adult Care: A 2012 systematic review conducted by the Sickle Cell Disease Association of America examined barriers to and approaches for successful transition of patients with SCD from adolescent to adult care.[19]

- 14 studies were reviewed:
  - Four studies explored factors directly attributable to adolescence during the time of transition, such as transition readiness.
  - Three studies observed the patient's status shortly after transition.

- Three studies identified systemic or patient-related factors that can interrupt the transition process (i.e., provider knowledge and patient education).
- Four studies proposed model programs to inform better management approaches.

- The review recommended the following based on **limited evidence**:
  - Patient-centric transition plans to be implemented in pediatric facilities that allow for:
    - Enough flexibility to accommodate individual patient needs,
    - Patients to explore their opportunities for independence and to develop skills in managing SCD,
    - Parents and caregivers to be actively involved, and
    - The inclusion of pediatric and adult physicians, nurse practitioners, social workers, education coordinators, and clinical psychologists.

5. Ongoing Research

As of September 2015, there are currently 41 ongoing studies listed on ClinicalTrials.gov using the search terms "sickle cell disease" and "pain." There is also one ongoing study listed on ClinicalTrials.gov using the search terms "sickle cell disease" and "transition to adult care." Studies with unknown status were excluded in the initial search. Twenty-three studies were excluded due to lack of relevance, duplicate listings, or because they were being conducted outside the United States. While international studies were excluded from this topic brief, leveraging findings from countries where SCD is more prevalent (e.g., Nigeria), may provide valuable information that could be applied in the US setting.

- Almost all studies currently taking place are Phase 0-4 RCTs (n=15), or observational (n=1). See "Table 1: Ongoing Trials in ClinicalTrials.Gov."
  - There are no current head-to-head comparative effectiveness research (CER) trials comparing pain treatments for persons with SCD.
  - The majority of RCTs are focusing on new drugs for the treatment of pain in SCD.
  - One Phase 4 study is assessing two ways to treat pain crises (standardized, weight-based dosing with opioids vs. patient-specific dosing) to determine if a large RCT is feasible.

PCORI is currently funding a number of research awards with focuses on SCD:

***Three** Broad Funding Announcement Awards*

- Comparative Effectiveness of a Decision Aid for Therapeutic Options in Sickle Cell Disease
- Patient Centered Comprehensive Medication Adherence Management System to Improve Effectiveness of Disease Modifying Therapy with Hydroxyurea in Patients with Sickle Cell Disease

- Comparing Patient Centered Outcomes in the Management of Pain between Emergency Departments and Dedicated Acute Care Facilities for Adults with Sickle Cell Disease

***One** Engagement Award*

- Tennessee Sickle Cell Disease Network

***One** Pipeline to Proposal Award*

- We'll Take the Village: Engaging the Community to Develop Better Health

***Three** Clinical Data Research Networks (CDRNs) within PCORnet*

- Three CDRNs in PCORnet are developing a rare disease cohort specific to SCD
  - REACHnet
  - Mid-South Clinical Data Research Network
  - Chicago Area Patient Centered Outcomes Research Network (CAPriCORN)

Additionally, in 2015, NHLBI released a funding announcement entitled "Using Implementation Science to Optimize Care of Adolescents and Adults with Sickle Cell Disease." Awards are set to be made to seven geographically diverse sites in 2016.

6. **Likelihood of Implementation of Research Results in Practice**
   Current practices for treatment of SCD are being used with limited evidence. This gap in the evidence base needs to be addressed as clinicians and patients are seeking guidance about treatment options to inform decision making regarding the treatment of SCD to improve outcomes.

7. **Durability of Information**
   Well-designed studies are needed and can have lasting benefit.

8. **Potential Research Questions**
   - What is the comparative effectiveness of different models of care for children with SCD transitioning from pediatric to adult care?
   - What is the comparative effectiveness of different approaches to facilitate better management and improve patient-centered and clinical outcomes during transition from pediatric to adult care taking into consideration patient and family, clinician, health system, and community factors?
   - What is the comparative effectiveness of interventions to improve the treatment and management of acute pain crises in patients with SCD?

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Table 1: Ongoing Trials in ClinicalTrials.Gov

Study	Intervention	Type	Completion Date	Location	Sample Size	Funder
Pain Management in Children and Young Adults With Sickle Cell Disease	Gabapentin vs. Placebo	Phase 2	October 2017	St. Jude Children's Research Hospital	190	Scan | Design Foundation
Comparing Acute Pain Management Protocols for Patients With Sickle Cell Disease	Compare two ways to treat pain crises (standardized, weight-based dosing vs. patient-specific dosing) in the ED for adults with sickle cell disease, and to determine if a large randomized controlled trial is feasible and required.	Phase 4 (Pilot Study)	September 2016	Duke University	77	NHLBI
Methadone in Pediatric and Adult Sickle Cell Patients (MSCD)	Methadone vs. Standard of Care	Efficacy study	September 2015	Washington University School of Medicine	54	Not listed
MBSR for Pain Catastrophizing in SCD*	Mindfulness-based Stress Reduction	Exploratory; Feasibility study	August 2016	Duke University	60	NIH; NINR
Vaporized Cannabis for Chronic Pain Associated With Sickle Cell Disease (Cannabis-SCD)*	Cannabis vs. Placebo	Phase 1/ Phase 2	March 2016	University of California, San Francisco	35	NHLBI

Study of SANGUINATE™ In the Treatment of Sickle Cell Disease Patients With Vaso-Occlusive Crisis	SANGUINATE vs. Placebo	Phase 2	April 2016	Prolong Pharmaceuticals	24	Prolong Pharmaceuticals
Efficacy and Safety of Rivipansel (GMI-1070) in the Treatment of Vaso-Occlusive Crisis in Hospitalized Subjects with Sickle Cell Disease	Rivipansel vs. Placebo	Phase 3	July 2018	Pfizer	350	Pfizer
Music Therapy in Sickle Cell Pain Mixed Methods Study	Music Therapy vs. Music Listening vs. Control (standard of care)	Exploratory/ Feasibility Study	June 2016	University Hospital Case Medical Center	120	Kulas Foundation
Safety of Rivipansel (GMI-1070) in the Treatment of One or More Vaso-occlusive Crises in Hospitalized Subjects with Sickle Cell Disease	Single group assignment to Rivipansel	Phase 3	February 2020	Pfizer	250	Pfizer
Ketamine Infusion for Acute Sickle Cell crisiS in the Emergency Department (KISS)	Ketamine vs. Placebo (Saline)	Safety/ Efficacy Study	January 2017	Billy Sin	106	Not listed
Use of a Mobile-Based App for SCD Patients (SMART)	Collect information about differences in the use of two traditional pain assessment modes (verbal scale and paper) versus the use of a pain assessment tool on a mobile device in the form of a smartphone, tablet, or iPad with an Android or iOS operating system.	Observational	June 2015	Duke University	100	Not Listed
Intravenous Gammaglobulin	Immune Globulin Intravenous vs. Placebo	Phase 1/	December	Albert Einstein	60	Not Listed

for Sickle Cell Pain Crises	(Saline)	Phase 2	2014	College of Medicine of Yeshiva University		
Effect of Simvastatin Treatment on Vaso-occlusive Pain in Sickle Cell Disease	Single group assignment to Simvastatin	Phase 2	June 2015	Children's Hospital & Research Center Oakland	25	Not Listed
Inhaled Mometasone to Reduce Painful Episodes in Patients with Sickle Cell Disease (IMPROVE)	Mometasone Furoate vs. Placebo	Phase 2	February 2017	Jeffrey Glassberg, Mount Sinai School of Medicine	45	Not Listed
Apixaban in Patients With Sickle Cell Disease	Apixaban vs. Placebo	Phase 3	December 2015	Nirmish Shah, Duke University Medical Center	60	Bristol-Myers Squibb
Nitrous Oxide Analgesia Vaso-occlusive Crisis	Single group assignment to Nitrous Oxide	Phase 2	June 2015	Columbia University	12	Not Listed
Patient-Provider Tools to Improve the Transition to Adult Care in Sickle Cell Disease (iTransition)	Compares a chronic disease self-management program to a patient portal intervention (MyChart for SCD Intervention).	Interventional	July 2015	Children's Hospital Medical Center, Cincinnati	85	Children's Hospital Medical Center, Cincinnati
Evaluation of Purified Poloxamer 188 in Vaso-Occlusive Crisis of Sickle Cell Disease (EPIC) (EPIC)	MST-188 vs. Placebo (Saline)	Phase 3	February 2016	Not Listed	388	Mast Therapeutics, Inc.