PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

FINAL RESEARCH REPORT

Comparing Pain Management for Sickle Cell Disease Crises in Emergency Rooms and Infusion Centers

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TABLE OF CONTENTS

ABSTRACT

Background: Patients with sickle cell disease (SCD) suffer from frequent vaso-occlusive crises (VOCs). Typically, treatment for VOC occurs in the emergency department (ED), and patients are treated with parenteral pain medication and fluids. Infusion centers (ICs) are outpatient centers that can be alternatives to ED care for the management of VOCs and may provide patients with a better care experience.

Objective: In the Examining Sickle Cell Acute Pain in the Emergency vs Day Hospital (ESCAPED) study, we aimed to learn whether the ED or IC more rapidly provides analgesia to patients who present with an uncomplicated VOC.

Methods: The ESCAPED study is a prospective cohort study that recruited participants in 4 cities (Baltimore, MD; Cleveland, OH; Milwaukee, WI; and Baton Rouge, LA). Each city had many EDs but only 1 hospital with an IC SCD expertise. We screened adults (aged ≥18 years) with any SCD genotype living within 60 miles of a study site for enrollment between April 2015 and December 2016 during regular outpatient visits. We defined "uncomplicated crisis" as an acute episode of pain that had no other known cause and that required treatment with parenteral pain medications. Upon study entry, participants completed surveys to provide demographic data; we abstracted medical records for information on comorbidities. We prospectively collected data from the medical record after acute visits for VOC to record the location of care (ED vs IC), the time from arrival to first dose of pain medication (primary outcome), reassessment of pain after the first dose of parenteral pain medication, and visit disposition. Each participant was followed for 18 months, and data on their acute visits were collected during the follow-up period. We used time-varying propensity scores estimated by a random-effects model to balance covariates for patients at the 2 settings of care. We estimated treatment effects using a subclassification approach and computed standard errors by nonparametric bootstrapping at the individual level. In order to compare patients' experiences of care in the ED and IC settings, we created and validated a Patient Satisfaction with Pain Management in Adults Scale. Using this scale and structural equation modeling, we compared patient satisfaction with pain management in the ED and IC.

Results: We enrolled 483 patients in the cohort; 444 (92%) completed 18 months of follow-up (29 withdrew, 10 died). During the study period, participants had 4851 acute visits for uncomplicated VOC; of these, complete data were collected on 2910 visits (1445 visits to an ED and 1465 visits to an IC). Fewer than 6% of acute visits had missing primary or secondary outcome data. The mean number of visits per patient was 10.0 (SD, 15.5 visits); the median number was 4 visits (interquartile range [IQR], 1-12.5 visits); 114 patients had no acute visits during the study period. In the adjusted analyses, the mean time to first dose of parenteral pain medications was significantly shorter for patients seen in the IC (63 minutes) than in the ED (125 minutes). Thus, the mean difference between time to first dose was 62 minutes (95% CI, 54-69 minutes).

For the secondary outcomes in the adjusted analysis, the patients seen in an IC were significantly more likely to have had their pain reassessed within 30 minutes of their first dose of pain medication than patients treated in an ED (odds ratio [OR], 2.5; 95% CI, 2.1-3.0), and visits to the IC were significantly less likely to end in the patient being admitted than visits to the ED (OR, 0.17; 95% CI, 0.137-0.212). Finally, receiving care in the IC was associated with a statistically significant (0.40 SD) increase in satisfaction with pain management compared with receiving care in the ED.

Conclusions: With adjustment for differences between patients treated in these 2 settings, we demonstrated that those treated in an IC have significantly better treatment experiences than patients treated in an ED: a 50% reduction in time to first dose of pain medication, higher likelihood of being reassessed after their first dose of medication, an almost 6-fold decrease in hospital admission, and significantly higher patient satisfaction scores.

Limitations: We restricted this study to evaluating outcomes for patients with uncomplicated VOCs. Therefore, we cannot extrapolate our findings for patients who might present with other complications of SCD.

BACKGROUND

Overview of Sickle Cell Disease and Treatments of Vaso-Occlusive Crisis

Sickle cell disease (SCD) is a genetic disorder of the blood that leads to severe morbidity and early mortality. It is the most common disease detected by newborn screening efforts in the United States.[1] Between 80 000 and 100 000 individuals in the United States are affected by some form of SCD.[2] African American individuals are the most affected population in this country; 1 out of every 400 African American newborns is born with the disease. The disease reduces life expectancy by approximately 30 years compared with the life expectancy of the general population.[3] Furthermore, the disease limits quality of life as severely as does end-stage renal disease requiring hemodialysis.[4]

The best-known burden of SCD is the vaso-occlusive crisis (VOC). The exact etiology of a VOC is poorly understood; the pain is thought to manifest due to occlusion of small blood vessels, which leads to poor blood flow and diminished oxygen delivery to the tissues. These acute, excruciatingly painful events are the leading cause of hospital and emergency department (ED) use.[5] They can be associated with such lethal and disabling complications as acute chest syndrome and stroke. Acute and chronic pain, psychiatric comorbidity, and disease severity are factors that likely contribute to extraordinarily high levels of unemployment and decreased productivity in this patient population; an estimated 40% of adults with SCD are unemployed.[6]

The ED has been the usual location where patients with SCD seek care for the treatment of acute painful events. In this setting, patients are typically treated with parenteral pain medications and fluids. Although SCD is considered a rare disease in the United States, the burden of ED care and subsequent hospitalization is high, and it is borne mostly by adults. The number of ED visits by patients with SCD has increased yearly, with a 28% increase since 2006. Sixty-eight percent of these visits are coded as acute painful crises. In 2011, there were 317 557 ED visits for people with SCD, and 82% of these visits were by people aged ≥18 years. Of ED visits that resulted in hospital admissions, for every 100 people estimated to be living with the disease in the United States (in 2006), 68.4 admissions were for SCD, compared with 1.1

hospital admissions for 100 people living with asthma and 17.3 hospital admissions for congestive heart failure.[7] In addition, 30-day readmission rates for this patient population are the highest of any recorded diagnosis, at 31.9%.[8] These estimates suggest that SCD is a significant burden for patients, with a parallel excessive impact on the health care system.

Numerous studies show that patients and health care providers are dissatisfied with the quality of SCD pain management, which is currently centered in the ED.[9] ED care for SCD is marked by long delays, lack of efficacy, and conflict. Nationally, 40% of ED visits for SCD pain are concluded by hospital admissions.[7] SCD patients report that they do not have enough involvement in decisions about their own care and also that providers do not demonstrate respect, trust, and compassion.[9] Many studies have demonstrated that providers hold highly negative attitudes toward SCD patients and are strongly predisposed to suspect drug addiction in patients presenting for VOC care.[9]

A strong body of literature supports the assertion that a subspecialty infusion center (IC), staffed by expert clinicians and delivering individualized care, can improve care quality while reducing costs. These clinics are alternatives to ED care for the management of pain in people with SCD, and they provide parenteral pain medications and fluids as needed. Benjamin et al[10] found that establishing a dedicated SCD day hospital led to a 40% reduction in inpatient admissions relative to ED management. Since this seminal finding, several supporting papers have confirmed that rapid assessment of VOC, close monitoring, social service support, and individualized care improve outcomes compared with usual care in the ED.[11-14]

Yet IC clinics and the ED setting have never been directly compared. The absence of data has contributed to the lack of widespread adoption of the IC model of care, so few patients have access to such clinics, and acute care for painful episodes thus continues to occur primarily in the ED. The goal of our Examining Sickle Cell Acute Pain in the Emergency vs Day Hospital (ESCAPED) study is to compare care provided in ICs with that provided in EDs, examining which site of care provides more patient-centered and efficient care for adults with SCD and uncomplicated VOC.

Even though VOC is the most common complication of SCD, no randomized controlled trials have been conducted to inform the management of these events.[15] Using an expert panel and a modified Delphi method, Wang et al[16] developed a set of quality measures for the treatment of children with SCD. The authors identified 41 measures for assessing health systems' quality of care for children with SCD. Two of these measures were for the management of acute pain. The first measure was that children who present with an acute pain episode should receive a parenteral analgesic (nonsteroidal or opioid) within 60 minutes of registration or within 30 minutes of triage. The second measure was that a patient's pain level should be reassessed within 30 minutes of the first dose of analgesic.

No similar consensus-forming studies have been carried out among adults, but the National Heart, Lung, and Blood Institute (NHLBI) guidelines, based on a systematic review of the literature, include similar recommendations for acute pain management for all people with SCD. Neither of these quality outcomes is routinely achieved in the ED setting. Data on the average wait time to see a physician for a patient with SCD in the ED shows that it is more than an hour.[17] This wait is 25% longer than for patients in the general ED population. As the physician must see the patient before writing an order for pain medication, the average time to first dose of analgesia in this nationwide sample is clearly more than an hour.

How acute painful events are diagnosed and managed in the acute setting continues to vary widely because management of VOC has never been studied in a systematic fashion. No objective clinical or laboratory measures exist for the presence or severity of a crisis, and so the only way to confirm a crisis is to ask the patient (ie, patient self-report). The current pain scales used for self-report have not been validated in this patient population.[15] Owing to this uncertainty, it is not surprising that many patients receive suboptimal care in the acute setting, especially when that care is delivered by clinicians, as in the ED, who are unfamiliar with them and who are not trained to manage their disease and its complications.

The purpose of this study was to compare patient-centered outcomes for patients being treated for an uncomplicated VOC in ICs and EDs. Patients with SCD seldom receive care in settings with the necessary resources and expertise to manage their condition. This occurs in an

era when well-validated disease-modifying treatments are available, such as hydroxyurea, that can reduce morbidity, mortality, and hospitalizations. Nevertheless, these treatments are underutilized.[18,19]

In 2011, Health and Human Services (HHS) Secretary Kathleen Sebelius named the SCD population as a priority area of focus for HHS.[20] In response, HHS has instituted a new SCD Initiative that has the overall goal of improving health care and health outcomes for the SCD population. Before the HHS SCD Initiative, 2 independent Maryland state reports developed by a broad range of stakeholders addressed the needs of adults with SCD. These reports recommended the development, first, of a dedicated acute care facility to manage acute painful events outside the ED and, second, interventions to improve the acute management of pain in patients with SCD.[21,22]

Key Study Questions and Specific Aims

If treating patients in an IC setting decreases the time to first dose of parenteral pain medications, reduces hospitalizations, and improves patient experiences of care compared with care in an ED, this will lead to more stakeholder engagement in disseminating this model of health care delivery. This study will help patients and health systems answer the key PCORI questions for adults with SCD about where they should go to get the best care for the acute management of their pain:

- For patients, the results of this study will allow them to evaluate outcomes that are important to them so that they can make decisions about whether they should seek care in an ED or in an IC for acute management of their pain.
- For health care delivery systems, this study will help them to decide whether they should provide IC services to adults with SCD either in a dedicated IC or in a shared-space model.

The 3 specific aims of this project, and their related hypotheses, are as follows:

Specific aim 1: To compare pain management processes in ED and IC settings for patients with SCD presenting with uncomplicated VOC.

Hypothesis 1.1: Patients treated in the IC will receive their first dose of pain medication more quickly than those treated in the ED.

Hypothesis 1.2: A greater proportion of patients treated in the IC will be assessed for adequacy of pain relief within 30 minutes of their first dose of medication than patients treated in the ED.

Specific aim 2: To compare disposition (hospital admission vs release to home) in ED and IC settings for patients with SCD treated for uncomplicated VOC.

Hypothesis 2.1: Patients treated in the IC will have higher rates of being discharged to home than patients treated in the ED.

Specific aim 3: To compare the patient experience of care delivery in ED and IC settings.

Hypothesis 3.1: Patients treated in an IC will report more satisfaction with their pain management than those treated in an ED.

Hypothesis 3.2: Patients treated in an IC will express greater feelings of safety in their treatment environment than will patients treated in the ED.

PATIENT AND STAKEHOLDER ENGAGEMENT

The partners for this study included several patients, community-based organizations (CBOs), parents and children of people with SCD, and a representative from the insurance community. The CBOs in Maryland have helped organize community forums to discuss the needs of the SCD community and advocacy. The Proudford Foundation, one of the Maryland CBO partners for this study, has moderated many of these community events, and the organization has played a role in collecting patient stories so that providers and other stakeholders have a better understanding of the needs of the community. It is in these settings that patients have requested expanded access to IC services in their communities. These conversations led to this study to help establish ICs as a key, much-needed resource to meet the needs of people with SCD.

Community Partners

The following is a list of community partners for this project. Partner representatives from each site where the study was performed were recruited by the local team. These sites were Baltimore, Maryland; Cleveland, Ohio; Milwaukee, Wisconsin; and Baton Rouge, Louisiana.

Marc Proudford, MBA, MS, is the vice president of the William E. Proudford Foundation, Inc (WEP). WEP is a CBO located in Maryland, whose mission is to support SCD awareness, education, state-of-the-art treatment, and research. His father had SCD.

Derek Robertson, JD, is the president of the Maryland Sickle Cell Disease Association (MSCDA); the MSCDA is a CBO located in Maryland. Its mission is to provide education and awareness about SCD. Mr. and Mrs. Robertson run this organization and have 2 sons with SCD.

Charles Green Jr, is from Milwaukee. He has a background in operational research engineering and is an adult living with SCD.

Adrienne Kincaid is the founder of Kincaid's Kindred Spirits, Inc (KKS), established in 2004 in Cleveland. KKS is a nonprofit organization created to bring greater awareness to

individuals, family members, and community residents about SCD. The organization provides community outreach by holding annual fundraising and community awareness events, convening monthly support group meetings, and setting up health literature information tables in various locations throughout the city of Cleveland.

Lorri Burgess is the executive director of Baton Rouge Sickle Cell Anemia Foundation, which was established in 1974. The Foundation serves 11 parishes in Louisiana. Currently, >600 people with SCD live in their service area. The Foundation assists people living with SCD by providing a Medicaid application center, a weekend retreat for adult clients and caregivers, support groups, and an emergency assistance program for those with financial needs.

Marcus Wallace, MD, MBA, is an internist who holds an MBA with an emphasis on health care. He is the Senior Vice President of Medical Affairs for the Louisiana Health Care Connection Center, a Medicaid health plan. As a hospitalist and health care executive, he has a unique perspective on how to improve care for patients and make the health care system more efficient and affordable. Dr Wallace contributed to the PCORI study by providing input regarding managed care and the management of SCD.

Activities of the Community Partners

In preparation for this grant, the community partners listed above participated in conference calls about the grant and the study design. During these calls, the issue of feeling safer being treated in an IC vs an ED was discussed. Based on that discussion, we added this topic as one of the important questions for the study to evaluate.

In addition to assisting with study design, during the study period the community partners participated in quarterly meetings with the entire study team. The group discussed recruitment, study progress, and data. They were equal partners, each with a vote in decisions that needed to be made as the grant progressed. We also held separate, quarterly calls with the community-based partners to discuss issues at the sites, such as brainstorming on ways to encourage patients to remain in the study.

The community partners were provided with funds to travel to the annual in-person meetings held each year of the project. They also requested financial assistance for their websites to help disseminate information about the study, and this was provided to those sites who made those requests (Maryland, Ohio, and Louisiana).

Finally, one of our research team members, Carlton Haywood Jr, lives with SCD and was integral in the development and analysis of our patient experiences-of-care scales.

METHODS

Study Overview

Frequent VOCs are the leading cause of hospitalization and ED visits for patients with SCD. ICs are alternatives to ED care and may provide patients with a better care experience. We previously demonstrated in a single center that the use of ICs provides more rapid pain control and can decrease the risk of a hospital admission compared with ED care.

For the management of VOC, guidelines from the NHLBI recommend that patients receive analgesic therapy within 60 minutes of registration and that pain be reassessed every 15 to 30 minutes until pain is controlled. The purpose of the ESCAPED study (an observational, nonrandomized study) was to compare patient-centered outcomes between the IC and ED.

Interventions and Comparators or Controls

This was an observational study without any specific intervention; rather, we compared our outcomes (specified below) for patients' visits to the IC for uncomplicated VOC and for visits to the ED. For the purposes of this study, we defined an uncomplicated VOC as an acute episode of pain with no other known cause that required parenteral therapy for pain relief in a person with SCD.

Study Outcomes

The primary outcome was the time to first dose of parenteral analgesia after the patient had registered at the site of care with an uncomplicated VOC. Secondary outcomes included whether patients had their pain assessed 30 minutes after their first dose of pain medications and whether the acute visit resulted in discharge to home or hospital admission (disposition). Finally, we collected patient-reported outcomes as described below.

We collected data on patient satisfaction with care in the acute setting using an instrument developed during this study. In addition, we collected data on patients' perception of safety at their site of care.

In the ESCAPED study, we conducted all the study aims' methods and results in the same study setting, with the same study participants who underwent the same study procedures. These study design elements are described next. We provide more details about analyses and results separately for aims 1 and 2 and then those for aim 3.

Study Setting

We enrolled patients from 4 different centers; each center had 1 IC where patients with SCD were treated. Two of these centers have ICs in academic settings that are solely for the care of adults with SCD (ie, single-focused, academic settings in Baltimore and Milwaukee). Another site is an academic setting with infusion space shared with other hematology-oncology patients who need infusions (ie, shared focus/academic, Cleveland). The fourth site is a community-based hospital with an infusion space shared with other hematology-oncology patients (ie, shared focus/community, Baton Rouge). All 4 sites were located within hospitals, all of which had EDs. None of the ICs was open 24 hours, so patients presenting in pain when the IC was closed could go to the same hospital ED for care. We did not restrict patients to where they could seek out care; therefore, they could have been seen at any ED of their choosing. All the care in the IC was overseen by a hematologist with a specific interest in caring for adults with SCD. Advanced practice providers and nursing staff received specific education on SCD.

We chose these sites because they broadly represent patients throughout several US communities. Planning and creating new dedicated ICs for SCD populations, especially if they are moderate in size, would be time intensive. Incorporating even modest SCD populations into already existing hematology/oncology ICs could be done with less new infrastructure investment. For that reason, we included sites with dedicated ICs and those with shared space in this study to see if these structural differences in sites might change the outcomes seen between the IC and ED.

Study Participants

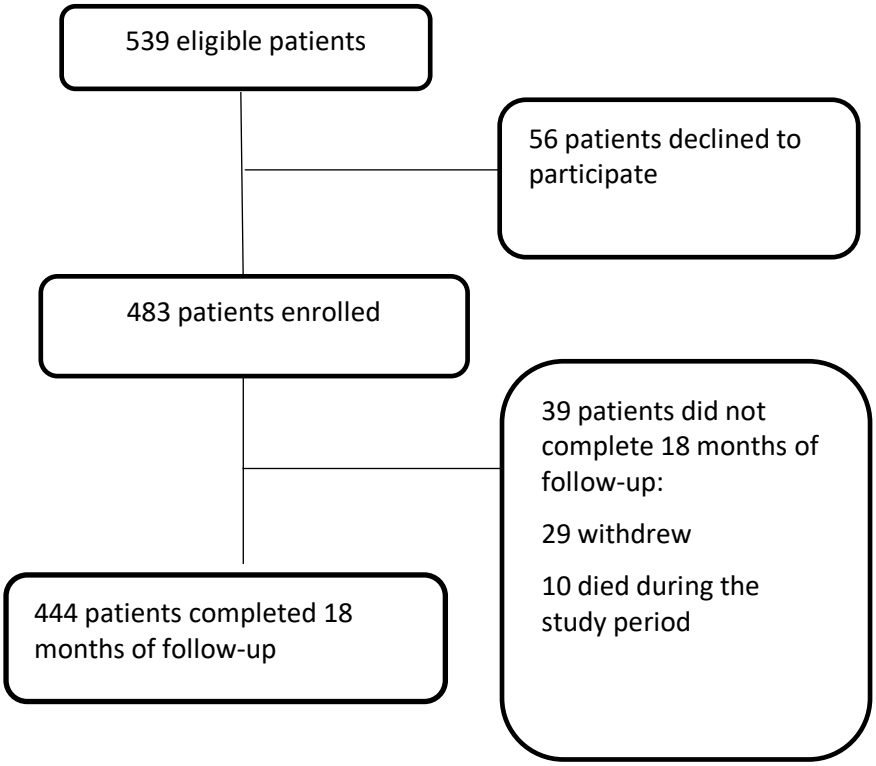
We screened adults (aged ≥18 years) with any SCD genotype living within 60 miles of a study site for enrollment between April 2015 and December 2016. We enrolled participants during their regular outpatient clinic visits. As the purpose of this study was to evaluate acute care use, we excluded individuals whose disease was well controlled on chronic transfusion therapy and who had had no acute visits in the 2 years before screening. We did this to avoid enrolling patients who were unlikely to have acute visits during the study period (<20 patients from all sites were excluded on this basis). We also excluded pregnant women because they were likely to receive care for acute pain in a hospital's labor and delivery wards and not in an IC or ED.

After a member of the study team explained the study and answered any questions about it, they asked prospective eligible patients whether they would like to participate in the study. After patients signed the written consent form, they filled out a form to collect demographic details, medical information, and self-reported presence or absence of chronic pain.

We reviewed medical records to confirm self-reported disease complications. By convention in SCD, we defined kidney disease as albuminuria >30 mg/g (or proteinuria) or an estimated glomerular filtration rate of <90 mL/min body surface area-corrected.

If the patients declined to participate in the study, the study staff would ask why the patient did not want to participate. Each participating site kept a list of patients who declined to enroll in the study and their stated reasons. In total (at all 4 sites), 56 patients declined to participate (Baltimore = 32, Cleveland = 4, Milwaukee = 10, and Baton Rouge = 10). Figure 1 shows the patient flow diagram.

Figure 1. Patient Flow Diagram



Study Procedures (Data Collection and Sources)

We asked each patient to remain in the cohort for 18 months. We collected both subjective and objective data at the time of visits for acute uncomplicated VOCs. For this study an uncomplicated VOC was defined as an acute episode of pain with no other known cause that required parenteral therapy for pain relief. Any visit that met criteria for a complicated VOC (eg, acute chest syndrome, priapism, stroke) was reviewed and confirmed by the site principal investigator; we did not collect data for those visits.

Because of concerns early in the study about the burden of collecting data for several high-use patients, the research team chose to collect full data on all acute visits once each month from each site of care. As a case in point: If a patient had 4 visits during a month, we collected all data for that person at his or her first visit to the IC or to the ED. If a patient went to 2 different EDs, we collected all data for each of those different ED visits. If, however, a patient had >1 visit to a single ED or IC in a month, we collected all the data from just the *first* of

those visits. If a patient had >1 visit to the ED or IC in a month, we tallied those visits, but they were considered ineligible visits and were not included in analysis of outcomes.

Table 1 provides an example of data collection for both eligible and ineligible visits. This change in protocol was discussed in an all-team meeting before making the change.

Table 1. Hypothetical Patient A and Explanation of Data Collection Based on Eligible and Ineligible Visits

Patient A site of visit	Month in study	Data collected
ED X	1	Yes
IC	1	Yes
ED X	1	No
ED Y	1	Yes
IC	1	No
ED X	2	Yes
ED Y	2	Yes
ED Z	2	Yes
IC	2	Yes
ED Y	2	No
Total visits = 10; total eligible visits = 7; total ineligible visits = 3		

Abbreviations: ED, emergency department; IC, infusion center.

Trained research coordinators collected the following data at each eligible visit to an ED or IC:

1. Time to first dose of parenteral analgesic, defined by the difference between the time recorded of the patient arrival to site of care and the time documented of the first parenteral dose of medication
2. Time to nurse reassessment after the first dose, defined as the time between the time of first dose of parenteral pain medication and the time of the next nurse assessment
3. Disposition—whether the patient was discharged or admitted at the end of the visit

We also collected data on whether any changes in medical history occurred or new complications arose.

After each eligible acute care visit, we administered a multipart questionnaire that included questions concerning patients' satisfaction with their experience with care at ICs or EDs; we also asked 2 questions concerning patient perception of safety while being treated in these settings. In addition to the questions about satisfaction and safety, we asked 2 descriptive questions about how patients traveled to the acute visit (who accompanied them) and 2 open-ended questions to ensure that any additional concerns about the visits were reported. All the questions were included as 1 questionnaire that patients were asked to complete within 72 hours of their acute visit (Appendix A).

After an eligible acute care visit, trained research coordinators administered the questionnaire within 72 hours. We judged that a period of 72 hours would allow us to capture experiences robustly and to minimize recall bias.[23] The questionnaire was administered in different modalities to accommodate patient preferences and to maximize response rates.[24] The questionnaire was interview-administered by telephone or self-administered to participants. When self-administered, participants completed the questionnaire either in-person before leaving the ED or IC using a paper-pencil form or by computer, for which we sent a link via email.

Patients were compensated $25 for completing baseline questionnaires and $25 every 6 months thereafter for a total of $100 if they remained in the study for the entire study period.[25] Patients who did not respond to the postvisit survey were either too sick, refused to participate, or were not contacted within the 72-hour window after their acute care visit.

We contacted all patients monthly (by telephone, email, or in-person) to obtain information on acute care visits. At each interaction, we reminded participants to contact the study staff if they had visited an ED outside the study sites in the previous month. We also reviewed statewide health information exchanges, where available, to ensure that we had captured all acute visits. If a visit occurred at an outside ED, research staff contacted those

facilities, sent a copy of the signed consent form to those sites, and obtained medical records of that ED visit. Data on the primary and secondary outcomes were then extracted from those medical records.

The IRBs at all participating sites approved this study.

Sample Size Calculations and Power

We based our sample size calculations on our second specific aim: to compare disposition (hospital admission vs release to home) in ED and IC settings for patients with SCD treated for uncomplicated VOC. This aim was expected to require the most participants. We hypothesized that we would observe an admission rate of 50%[26] from an ED visit and an admission rate of 27% from an IC visit. We took the following design considerations into account in estimating the sample sizes needed to detect this difference.

We had a 2-arm study (IC vs ED) with 4 clusters (sites) per arm. With a type I error of 0.05, a type II error of 0.15 (power, 0.85), and an estimated intracluster correlation coefficient of 0.02, we would require an average of 51 participants in each cluster (site) per arm. We required a total of 408 participants (204 per arm) to detect our hypothesized difference in hospital admission rate. We estimated that we would observe a lost-to-follow-up rate of 18%, so our total required sample size was 500 participants (408/[1 – 0.18]). Our lost-to-follow-up rate was 8%, so we were able to meet our end points with 483 patients enrolled.

Time Frame for the Study

We followed all patients for 18 months after enrollment. We chose 18 months to capture 1 or 2 visits per patient, with the expectation that each patient would have 1 or 2 acute care visits a year. We based this estimate on data from the Cooperative Study of Sickle Cell Disease.[5] The final patient completed 18 months of follow-up in December 2018.

RESULTS

Analytical and Statistical Approaches: Aims 1 and 2

Overview of Aims 1 and 2 and Hypotheses

Specific aim 1: To compare pain management processes in ED and IC settings for patients with SCD presenting with uncomplicated VOC.

Hypothesis 1.1: Patients treated in the IC will receive their first dose of pain medication more quickly than those treated in the ED.

Hypothesis 1.2: A greater proportion of patients treated in the IC will be assessed for adequacy of pain relief within 30 minutes of their first dose of medication than patients treated in the ED.

Specific aim 2: To compare disposition (hospital admission vs release to home) in ED and IC settings for patients with SCD treated for uncomplicated VOC.

Hypothesis 2.1: Patients treated in the IC will have higher rates of being discharged to home than patients treated in the ED.

This was an observational cohort study from which we drew inferences about outcomes of care attributable to the treatment setting. As we could not randomly assign patients to either IC or ED care, we needed to control for confounders in the relationship between the treatment setting or groups (IC, ED) and outcomes. These potential confounders were largely at the level of the individual. Differences attributable to the clinicians practicing in these settings were not considered to be confounders because they are integral parts of the “treatment” and are mediators of the site-outcome relationship.

Propensity Scoring

As we could not randomly assign patients to site of care, we used propensity score methodology. The use of the propensity score allowed us to eliminate bias from the naive

estimation on the treatment effects attributable to the measured confounders. We then applied this analysis to our collected data.

Given the anticipated differences in patients who seek care in these settings, we used propensity score techniques to balance patient characteristics in the 2 treatment arms (IC vs ED) both within a given site (ie, city) and across the 4 sites. We used relatively new methods developed for use of propensity scores in the context of repeated-measures data, where each participant has multiple visits and hence multiple treatments (either IC or ED). Our treatment assignment was at the individual patient level; we used appropriate propensity methods to generate valid causal inferences, under the assumption of absence of unmeasured confounders.

We used time-varying propensity score models. In particular, we fit logistic regression with a random intercept to model the probability of visiting an IC for a given individual *i* and visit *t*, given the history of covariates before the current visit, including baseline and time-varying covariates. The best linear unbiased prediction (BLUP) from the random-effect model provides the estimated propensity score for individual *i* and visit *t*. The BLUP estimates of the propensity scores are classified into quintiles (see Table 2).

Each individual can have multiple propensity scores, one for each visit to either the IC or the ED. Hence, for the purposes of propensity score modeling and evaluation of covariate balance, we have taken the unit of analysis to be individual *i* at visit *j* (*i*,*j*). Let $Z_{i,j}$ denote the treatment ($Z_{i,j}$ = 0 denotes ED and $Z_{i,j}$ = 1 denotes IC), and $X_{i,j}$ denote the vector of covariates. The time-varying propensity score model estimates are: $\hat{e}_{i,j} = P\left(Z_{i,j} = 1 \left| X_{i,j}\right.\right), i = 1, \dots, N; j = 1, \dots, J_i$. Within the quintiles of $\hat{e}$, we compared the covariate distributions of $X_{i,j}$ for those with $Z_{i,j} = 1$ and those with $Z_{i,j} = 0$. We did not feel the need to account for correlation (arising due to multiple visits of each participant) when evaluating covariate balance between treatment groups, because the goal was only to show that balance is greatly improved using propensity scores compared with the large imbalance in covariates between the groups $Z_{i,j} = 1$ and $Z_{i,j} = 0$.

For estimating treatment effects, however, we did account for the correlations by using a clustered bootstrap approach. We used traditional subclassification methods and bootstrap, where each unit for bootstrapping is each individual patient, to estimate unbiased standard errors. Because each individual can have multiple propensity scores, the standard error for the combined causal effect from the subclassification must take the correlation into account. This approach provides unbiased standard error estimates within strata and across strata.

Under the assumption of sequential ignorable treatment assignment, within each patient *i*, at each time *t*, the history $H_{i,t}$ has all variables used in the mechanism of assigning treatment $Z_{i,t}^{obs}$. Let $Y_{i,t}(z_t)$ denote the potential time to first dose for an individual *i* at visit *j* if that individual had visited the clinic denoted by z_t (where $z_t = 1$ denotes IC and $z_t = 0$ denotes ED). The ignorability assumption implies that across patients, $Y_{i,t}(z_t)$ $\coprod Z_{i,t}^{obs} \mid H_{i,t}, e_{i,t}(H_{i,t})$; in other words, at every time *t*, the treatment is as if randomized with probabilities depending on the observed history, where the time-varying propensity scores $e_{i,t}(H_{i,t})$ provide the remaining factors of unit (*i*) that are in $e_{i,t}(H_{i,t})$ but not in $H_{i,t}$. This, of course, assumes that there are no unmeasured confounders. These methods do not call for an assumption that the data need to be normal, so no log transformation was required, and no data were censored.

Covariates were a key element of the propensity modeling described below. The covariates used for our propensity score modeling are listed in Table 2 along with the subclasses based on similar propensity scores and their *z* statistic that demonstrate the substantial improvement in the balance of the covariates between the 2 treatment arms (IC vs ED) achieved by the propensity score modeling. There were 5 subclassification groups, quintiles of the propensity score. Table 2 demonstrates, through the *z* statistic (*P* values are in parentheses), that once balanced, the covariates for the most part were no longer significantly different within the subclasses, which is the goal of propensity modeling. For example, consider the covariate “graduated high school.” The difference between proportions of individuals graduating from high school was quite different in the 2 treatment arms, the *z* statistic for the

difference in proportions being 8.635 ($P < .001$). However, this difference was much smaller within each quintile of the propensity score, with a maximum difference of −0.739 ($P = .46$).

The means (SEs) and counts (percentages) for each intervention arm (within subclasses) are shown in Appendix B. The final SEs for the ORs were based on log(OR) and then transformed back.

Table 2. Covariates Included in Time-Varying Propensity Score Modeling Pre- and Postbalancing[a]

Variables	Before balancing	Group 1 (*P* value)	Group 2 (*P* value)	Group 3 (*P* value)	Group 4 (*P* value)	Group 5 (*P* value)
Probability of going to IC before current visit	27.62[b]	−0.071 (.944)	1.395 (.163)	−0.423 (.673)	−1.99 (.047[c])	−0.423 (.672)
Probability of being hospitalized before current visit	−9.87[b]	−0.374 (.708)	−1.582 (.114)	1.413 (.158)	0.373 (.709)	−0.177 (.859)
No. of ED visits in last 12 mo	−9.026[b]	−0.009 (.993)	1.901 (.057)	−1.618 (.106)	−0.913 (.361)	−1.273 (.203)
No. of IC visits in last 12 mo	15.705[b]	0.742 (.458)	−0.931 (.352)	0.575 (.565)	−0.397 (.691)	−0.653 (.514)
No. of admissions in last 12 mo	−0.747 (0.454)	0.729 (.466)	−0.577 (.564)	0.319 (.750)	−0.226 (.821)	0.193 (.847)
Comorbidity						
Avascular necrosis	1.955	1.155 (.248)	1.14 (.254)	−0.931 (.352)	0.431 (.667)	−0.230 (.818)
Stroke	−1.554 (0.120)	−0.170 (.865)	−1.116 (.264)	1.172 (.241)	−0.092 (.927)	0.053 (.958)
Retinopathy	4.628[b]	−0.564 (.572)	0.991 (.322)	−0.498 (.618)	0.009 (.993)	0.320 (.749)
Gallbladder disease	−0.732 (0.464)	−0.084 (.933)	−0.981 (.327)	1.027 (.304)	−0.416 (.678)	−0.529 (.597)
Leg ulcer	−2.238[d]	−0.012 (.99)	1.702 (.089)	−0.700 (.484)	−1.563 (.118)	0.008 (.994)
Pulmonary hypertension	0.882 (.378)	−0.010 (.992)	−1.303 (.193)	1.550 (.121)	−2.254 (.024[c])	0.837 (.402)
Kidney disease	3.471[b]	−0.012 (.99)	−0.484 (.628)	0.933 (.351)	0.182 (.855)	0.009 (.993)

Variables	Before balancing	Group 1 (*P* value)	Group 2 (*P* value)	Group 3 (*P* value)	Group 4 (*P* value)	Group 5 (*P* value)
Not receiving chronic transfusions	−4.042[b]	0.851 (.394)	0.595 (.551)	−1.294 (.196)	1.187 (.235)	−0.198 (.843)
Graduated high school	8.635[b]	0.562 (.574)	−0.739 (.460)	−0.046 (.963)	−0.235 (.814)	−0.009 (.993)
Marital status, married or significant other	6.585[b]	−0.013 (.99)	−1.003 (.316)	0.145 (.885)	0.662 (.508)	−0.230 (.818)
Low annual income, <$20 000	−1.162	1.038 (.299)	1.537 (.124)	−1.187 (.235)	−0.004 (.997)	−0.004 (.997)
No disability	−4.96[b]	1.379 (.168)	−0.271 (.787)	1.391 (.164)	−0.871 (.384)	−0.035 (.972)
Does not have primary care physician	−5.571[b]	1.583 (.113)	−0.477 (.633)	0.297 (.767)	−0.452 (.651)	0.305 (.761)
Does not have hematologist	−1.280	0.896 (.371)	−0.035 (.972)	−0.106 (.916)	NA	NA
Taking long-acting (vs short-acting) opioids	3.539[b]	−0.011 (.991)	−0.288 (.773)	0.583 (.560)	NA	NA
Taking long- and short-acting (vs short-acting) opioids	10.965[b]	−0.561 (.575)	−2.259 (.023[c])	1.857 (.063)	0.212 (.832)	−0.837 (.402)
Taking hydroxyurea (SCA only)	−0.508 (0.611)	0.365 (.715)	1.116 (.264)	0.137 (.891)	−1.759 (.079)	−0.735 (.462)
Age (centered at mean), y	11.46[b]	−2.171 (.029[c])	−2.576 (.01[c])	2.045 (.041[c])	0.388 (.698)	1.414 (.157)
Insured by Medicaid	−6.905[b]	−0.419 (.675)	0.679 (.497)	−0.513 (.607)	−0.210 (.834)	0.396 (.692)
Residence, living alone	1.356 (.175)	−0.728 (.467)	−0.071 (.943)	−0.125 (.900)	−0.731 (.465)	0.789 (.43)

Variables	Before balancing	Group 1 (*P* value)	Group 2 (*P* value)	Group 3 (*P* value)	Group 4 (*P* value)	Group 5 (*P* value)
SCA	0.153	−0.084 (.933)	0.452 (.651)	0.314 (.753)	−1.417 (.157)	−0.051 (.959)
Unemployed	−0.794	−0.174 (.862)	1.229 (.219)	−1.289 (.197)	0.059 (.953)	0.488 (.626)
Sex, male	−3.716[b]	−0.793 (.428)	−0.163 (.871)	0.199 (.842)	0.127 (.899)	0.463 (.643)
Male with priapism	−0.559 (0.576)	−0.011 (.991)	0.591 (.555)	0.328 (.743)	−0.820 (.412)	−0.120 (.905)
Site (Baltimore is reference)						
Cleveland	−5.322[b]	−0.010 (.992)	−0.402 (.688)	0.214 (.830)	0.112 (.911)	0.164 (.870)
Baton Rouge	−4.916[b]	−0.955 (.340)	0.574 (.566)	−0.796 (.426)	−0.598 (.550)	0.030 (.976)
Milwaukee	−10.828[b]	0.178 (.859)	0.171 (.864)	−0.295 (.768)	0.624 (.533)	−0.831 (.406)

Abbreviations: ED, emergency department; IC, infusion center; NA, not applicable; SCA, sickle cell anemia.

[a]The numbers in the cells represent the *z* statistic for the difference in the mean of each variable between the 2 treatment arms (IC vs ED). The numbers in parentheses are the *P* values corresponding to the *z* statistics.

[b]Significant at $P < .001$.

[c]Significant at value noted.

[d]Significant at $P = .025$.

Analyses for Aims 1 and 2

Primary outcome: aim 1. To test the primary outcome (time to first dose of pain medication), we used the observed time to first dose (a continuous outcome) in the 2 arms (IC and ED). We had a complicated data structure because patients had multiple visits, and the covariates used in the propensity score modeling could have varied over time.

A traditional propensity score model is not appropriate for these types of data as it can balance only the covariates at baseline level between the 2 arms. To overcome this issue, we developed a time-varying propensity score model. The time-varying propensity score is the conditional probability of an individual participant receiving the treatment (ie, going to an IC or ED) given the covariates (Table 2); we updated the covariates over time at each of the visits. This technique balanced the covariates between the 2 arms (IC vs ED) at each single acute visit of each patient. We used this time-varying propensity model for the primary outcome and the binary outcomes of whether pain was reassessed within 30 minutes of the first dose of parenteral analgesic and whether the visit ended in discharge to home or hospital admission.

We then used a subclassification on the propensity scores to estimate the potential outcome for each of the 2 arms and the average treatment effects (time to first dose of parenteral medications). We conducted bootstrapping to estimate the standard error of the average treatment effect. The use of the time-varying propensity model was not initially part of our analysis plan. We recognized, however, that given the large number of acute visits, we needed a new method to account for potential changes in patient characteristics over time. For that reason, we developed the time-varying propensity model that accounts for changes in patient characteristics.

Heterogeneity of treatment effect: patients with high use of ICs or EDs. We had planned to examine heterogeneity of treatment effect (HTE) before starting the study by evaluating whether high-use patients had different outcomes than the entire study population. We planned this analysis because of our concerns that high-use patients might be treated

differently in the acute care setting. Because far more acute care visits per patient occurred than anticipated over the study period, we performed a sensitivity analysis with several different cutoffs to define a patient with high acute care use.

Because the low- and high-use groups are independent, we constructed a Wald test of interaction as follows. Let β_{high} and β_{low} be the estimated treatment effects and let s_{high} and s_{low} be the SEs in the high- and low-use groups, respectively. We computed a *z* statistic for Wald test as: $z = (\beta_{high} - \beta_{low}) / (s^2_{high} + s^2_{low})^{1/2}$, which will be asymptotically normally distributed.

Changes to the original study protocol. We made a few changes to the original protocol. PCORI staff were updated about changes to the protocol during quarterly meetings.

First, we originally planned to collect data on all acute visits, but it quickly became apparent that collecting all the data would be a challenge for our research team. We discussed options with the entire team, including our methodologists, and decided to change the collection of repeated visit data over the course of a month. As described previously and detailed in Table 1, we defined monthly eligible and ineligible visits. As we had no reason to believe that people might be more ill or more likely to seek out care at one site or another based on the visit number per month, we did not feel this would bias our results.

Second, use of the time-varying propensity model rather than standard propensity models (discussed as part of aims 1 and 2) was a change to the proposed analytical plan. This change was adopted when it became clear that there were many acute care visits and that baseline comorbidities might change over time. We collected data on comorbidities at the time of each acute care visit. If the comorbidities did change at subsequent visits but we chose to use the original propensity score, visits might end up with an incorrect propensity score. The methodology team recognized this problem and developed a new time-varying propensity score to handle the changes in comorbidities that occurred over time.

Third, we had to refine our definition of “high use” for the planned sensitivity analysis to examine whether patients with frequent visits had different outcomes than those with fewer

visits. As there is no established number of acute care visits that defines high use in the literature, we ended up performing a sensitivity analysis using 3 different definitions of high use.

Fourth, for the patient experiences-of=care scale, we had planned to use a tool that Drs Haywood and Lanzkron were validating with a postgraduate student before funding. The student did not finish that project, and we recognized and shared with PCORI (discussed on January 14, 2016) the need to validate the scale as part of this study. We used the entire 23-question patient satisfaction survey (Appendix A) throughout the study period, but after formally validating the tool, we used only 15 of those questions in the analysis provided in this report.

Results for Aims 1 and 2

Patient characteristics. A total of 483 patients with SCD enrolled in the cohort; of these, 444 (92%) completed 18 months of follow-up (29 withdrew, 10 died). For these 39 patients who did not complete the study, the median follow-up was 8.2 months (IQR, 5.7-12.0 months). The 39 patients were lost to follow-up for the following reasons: withdrawal (10 patients), death (10 patients), or could no longer be located (19 patients).

Table 3 shows patient characteristics for all 483 enrolled patients. Of this group, 98% identified as African American and 99% were non-Hispanic.

The mean age of the sample was 34.4 years (SD, 11.5 years; range, 19-79 years), 61% were female, 81% had graduated high school, and 39% were employed. The majority of patients were receiving Medicaid (54%). Fifty percent had an annual income of <$20 000. About 69% of patients had sickle cell anemia (SCA: hemoglobin-SS or hemoglobin S–β^0 thalassemia), which is the most severe type of SCD; 63% of patients with SCA, the genotype for which hydroxyurea is recommended, were taking the medication at the start of the study. About two-thirds of patients had chronic pain. Fewer than 40% of patients had a comorbidity of kidney disease, leg ulcer, stroke, retinopathy, avascular necrosis, or priapism in male patients. The median pain level on arrival to the ED or IC was severe at 9 (IQR, 8-10; range, 0-10). The median

number of acute care visits in the year before enrollment was 5 per patient (IQR, 2-12 visits; range, 0-65 visits).

Table 3. Patient Characteristics for the Entire Sample (N = 483)

Characteristic	Value[a]
Sex: female	60.7
Genotype: SCA	69.2
Age, mean (SD), y	34.4 (11.5)
Graduated high school	80.7
Employed	39.3
Insured by Medicaid Y	53.8
Married or with significant other	21.5
Living alone	28.3
Low annual income, <$20 000	49.9
Disability	61.7
Kidney disease	14.3
Leg ulcer	4.8
Stroke	12.8
Retinopathy	19.0
Avascular necrosis	32.5
Receiving chronic transfusion	10.8
Chronic pain	66.9
Taking hydroxyurea (SCA only)	63.1

Abbreviation: SCA, sickle cell anemia.
[a]Values are percentages, unless otherwise indicated.

For the 483 enrollees, the study recorded 4851 acute visits for uncomplicated VOC; 2910 of these visits (60%) were eligible visits, and we collected complete data on them. The remaining visits were for situations in which patients had multiple visits to the same site over the course of a month; those visits were therefore considered ineligible and we did not collect

complete data for them. Of the 2910 visits, 1445 occurred in an ED and 1465 in an IC. The mean (SD) number of visits per patient was 10.0 (15.5); the median number was 4 visits (IQR, 1-12.5 visits).

Of the 483 patients enrolled, 114 patients (24%) had no acute visits during the study period. The analyses presented below for aims 1 and 2 are based on complete-case analysis of the 369 patients with acute visits. The times that patients spent in the IC or the ED were as follows: for the IC, mean (SD), 266 (93) minutes; median, 261 minutes; IQR, 191-328 minutes; and for the ED: mean (SD), 476 (429) minutes; median, 332 minutes; IQR, 235-521 minutes.

Study Outcomes: Aims 1 and 2

The primary outcome was time to first dose of pain medications. In the adjusted analyses, the mean time to first dose of parenteral pain medications was 63 minutes in an IC setting and 125 minutes in an ED setting. Thus, the mean difference between time to first dose was 62 minutes (95% CI, 54-69 minutes).

For the secondary outcomes in the adjusted analysis, the patients seen in an IC were significantly more likely to have had their pain reassessed within 30 minutes of their first dose of pain medication than patients treated in an ED. The odds in the IC were 0.54 (95% CI, 0.47-0.62), and the odds in the ED were 0.21 (95% CI, 0.18-0.25), with an odds ratio (OR) of 2.5 (95% CI, 2.1-3.0). Visits to the IC were significantly less likely to end in the patient being admitted than visits to the ED. The odds of admittance in the IC were 0.10 (95% CI, 0.08-0.13), and the odds in the ED were 0.53 (95% CI, 0.46-0.62), with an OR of 0.17 (95% CI, 0.137-0.212).

Handling missing data. We used data from all visits to estimate the time-varying propensity scores. We imputed missing data on patient medical characteristics based on the previous visits. We carried the last observation forward as the method of imputation. We felt comfortable using this method because we had very few participants with changes in medical history for those where full data were collected (3.3% of visits); that is, we considered this method of imputation a reasonable choice.

Among those with acute visits, <6% had missing primary or secondary outcome data, and we used complete-case analysis.

Addressing HTE

We planned on exploring the HTE, which in this case is an examination of whether we had subgroups of patients that benefited more from ED care and other subgroups that benefited more from IC care. We had just 1 prespecified subgroup about which we had a hypothesis: high-use patients. A priori, we had defined high users as patients with ≥3 visits for VOC in the past 12 months.[27] We hypothesized that the benefits they experienced from IC care would exceed the benefits experienced by other patients. (High-use patients are expected to benefit from the continuity of care offered by a stable IC staff with consistent use of guideline-informed care.)

After assessing the data, we recognized that we needed to redefine high users because the mean number of acute visits in the first 12 months was 7.5, significantly higher than the 3 visits we had estimated before starting the study. Because far more acute care visits per patient occurred than anticipated over the study period, we performed sensitivity analyses with several different cutoffs for classifying a patient as having high acute care use. We examined our outcomes (time to first parenteral medication, whether the patient was reassessed after the first dose of parenteral pain medication and disposition of the visit) as follows:

1. Patients who had 1 to 4 acute visits over the study time period compared with patients who had 5 to 8 acute visits and compared with patients who had ≥9 acute visits
2. Patients who had 1 to 8 acute visits over the study time period compared with patients who had ≥9 visits
3. Patients who had 1 to 11 acute visits over the study time period compared with patients who had ≥12

The results of these sensitivity analyses of high-use patients did not show any differences in the primary outcome (time to first dose in ED vs IC) based on the number of acute care visits patients had during the study period, regardless of the cutoff used for the

definition of a patient with high acute care use (primary outcome *z* score = 1.66, *P* = .1; details are provided in Appendix C). There was also no difference in the sensitivity analysis for the hospitalization outcome (*z* score = 0.17, *P* = .48). In the sensitivity analysis of high and low users, regardless of use, those seen in the IC had higher odds of being reassessed 30 minutes after the first dose of parenteral medications than those seen in the ED. However, the low users and the high users differed in the sensitivity analysis in that high users seen in the IC had a higher likelihood of being reassessed than low users seen in the IC (*z* score = 2.98, *P* = .003). The detailed sensitivity analysis is in Appendix C.

Analytical and Statistical Approaches and Results: Aim 3

Overview of Aim 3 and Hypotheses

Specific aim 3: To compare the patient experience of care delivery in ED and IC settings.

Hypothesis 3.1: Patients treated in an IC will report more satisfaction with their pain management than those treated in an ED.

Hypothesis 3.2: Patients treated in an IC will express greater feelings of safety in their treatment environment than will patients treated in the ED.

The purpose of aim 3 was to examine the patient experience of care in the acute setting. We did this in several ways. For the first hypothesis in this aim, we examined patients' satisfaction with their pain management; for the second hypothesis, we examined patients' perception of safety in the 2 types of treatment settings. Because no validated tool existed by which we could assess patient satisfaction with pain management, we developed and validated the Patient Satisfaction with Pain Management in Adults (PSPA) scale tool. For the issue of safety, we used a 2-item questionnaire that has been used in the ED setting.[28,29]

Below we detail how we developed and validated the PSPA and analyzed both this tool and the 2 safety questions. In addition to the questions about satisfaction and safety, we asked 2 descriptive questions about how patients traveled to the acute visit (who accompanied them)

and 2 open-ended questions to ensure that any additional concerns about the visits were reported. All these questions were given to patients as a single questionnaire that they responded to within 72 hours of an eligible acute visit. The complete tool provided to patients is in Appendix A.

Patient Satisfaction With Pain Management in Adults: Scale Development

We developed the satisfaction scale in several steps. First, the research team conducted a literature review of quantitative and qualitative studies in patients with SCD to identify aspects of pain management that are important to patients.[9,17,30,31] We identified several important aspects of pain management:

1. Aspects of pain delivery and pain control (eg, assessment of pain, timeliness of medication treatment, pain medication at home)
2. Interpersonal aspects of care (eg, ability of physicians and nurses to communicate with patients, be sympathetic, involve patients in decision-making)
3. Stigmatization of patients with SCD
4. General perception of quality of care

Second, research team members who are experts in SCD research searched for and evaluated validated satisfaction and satisfaction-related instruments that exist in general populations who are being treated for pain in various clinical settings.[32-37] None of the identified instruments was comprehensive with respect to the 4 aspects of pain management listed above or specific to the acute care setting.

Third, we selected some scale items that were thought to reflect aspects of pain management in adults with SCD from those existing instruments. Ultimately, the research team selected and reviewed a total of 23 scale items (Appendix A). All 23 items came from previously validated surveys (or were adapted from those surveys)[32-36] except for 2 items that were newly developed. The 2 new items were thought to be important to include based on group consensus, and they did not appear in earlier instruments. These new items included the statements, “The provider ensured that you had enough pain medication to manage your pain

at home" and "Bringing someone with me when I am in the ED/IC helps improve the quality of care I receive." We adapted only a few items in some minimal way, such as replacing the word "ED physicians" with "physicians," so that the scale would apply to patients receiving care at an IC as well. The entire questionnaire is provided in Appendix A.

Fourth, all 23 items were discussed during the annual PCORI study meeting for ESCAPED. We received feedback from research team members, including experts in hematology care and SCD research and our community partners during team meetings.

We incorporated this input into the next version of the instrument. Specifically, we eliminated 8 items that were thought to be redundant or included words that were confusing. Eliminating these items also supported the practicality and feasibility of future applications and reduced respondent burden given the extent of pain that patients with SCD experience.

The process undertaken helped establish face and content validity of the final scale, which we called the Patient Satisfaction With Pain Management in Adults With SCD (PSPS). It included 15 items, shown in Table 4. Patients reported the extent of agreement or disagreement during their recent acute care visit with the 15 items in this scale (as shown in Table 4). All 15 items were positively worded. We scored them on a 7-point Likert scale from *very strongly disagree* (1) to *very strongly agree* (7), which is similar to the response options from previously published satisfaction scales.[33,35] Higher scores on each item indicated higher satisfaction levels.

Table 4. PSPS Scale

1. The staff adequately assessed your pain.
2. You received treatment in a timely manner.
3. The doctor seemed to know just what to do for my problem.
4. Your pain was adequately controlled.
5. The provider ensured that the patient had enough medication to manage pain at home.
6. You were satisfied with the communication with the nurses.
7. Your nurse believed your reports about your pain.
8. You were satisfied with the communication with the doctors.
9. Your doctor believed your reports about your pain.
10. The doctor seemed warm and friendly to me.
11. I really felt understood by my doctor.
12. This is a doctor I would trust with my life.
13. The doctor has relieved my worries about my illness.
14. During your visit, you were allowed to participate in decisions about your pain treatment as much as you wanted to.
15. Overall, you are satisfied with the quality of care you received.

Abbreviation: PSPS, Patient Satisfaction With Pain Management in Adults With SCD.

Validating the PSPS. We validated the PSPS with a cross-sectional analysis of scale responses after patients' first acute visit during the study period. We included only those patients who had complete responses to the scale administered after their first acute care visit. Although no strict rule for sample size has been established for factor analysis, we considered both the total number of participants and the participant-to-scale item ratio because of their interaction with one another.[38] We considered at least 200 participants adequate for analysis along with a suggested participant-to-scale item ratio of 10:1 based on previous studies.[39]

The outcome was patients' mean score on the scale. We calculated this score by adding each of the patients' responses and then dividing them by the number of scale questions

answered. To characterize our sample for the validation step, we used a subset of the sociodemographics included for aims 1 and 2 (Table 5).

Table 5. Patient Characteristics Used for Validation of PSPS

Age, y
Sex
Graduated high school (yes or no)
Employed (yes or no)
On disability (yes or no)
Insured by Medicaid (yes or no)
Annual income <$20 000: (yes, no, or did not mention)
Married or with significant other (yes or no)
Lived alone (yes or no)
SCA genotype (yes or no)
Had chronic pain (yes or no)
Kidney disease (yes or no)
Leg ulcer (yes or no)
Stroke (yes or no)
Retinopathy (yes or no)
Avascular necrosis (yes or no)
Priapism in male patients (yes or no)
Receiving chronic transfusions (yes or no)
Taking hydroxyurea in SCA only (yes or no)
Pain level on arrival to the ED or IC using the pain intensity numeric rating scale (0-10)
Acute care use in the past year before study enrollment (No. of acute care visits to the ED and IC)
Use of opioids (long-acting only, short-acting only, both, none)
Has a primary care provider (yes or no)

Abbreviation: ED, emergency department; IC, infusion center; PSPS, Patient Satisfaction With Pain Management in Adults With SCD; SCA, sickle cell anemia.

Descriptive statistics for the PSPS. We described the overall sample using frequencies and percentages, mean and SD, or median and IQR when data were skewed. For each scale item, we calculated the mean and SD, median and IQR, skewness, kurtosis,[40] and corrected item-total correlation (Pearson correlation coefficient), for which a value of >0.20 was considered satisfactory.[41] The corrected item-total correlation (item-rest correlation) is the Pearson correlation coefficient between each survey item score and the total survey score omitting the survey item that was assessed. We examined the responses of each scale question for any floor or ceiling effects.

Exploratory factor analysis. To understand and interpret the concept of patient satisfaction with pain management based on the 15-item PSPS, we conducted an exploratory factor analysis (EFA).[42] We explored the relationships among the scale items using the Pearson correlation coefficient before proceeding to EFA, because EFA depends mainly on the correlations among the scale items to explain the factor structure underlying these items.

Factor analysis is a 3-step process: To select the number of factors, we used principal component analysis, scree plots, and parallel analysis.[39]

We extracted the initial factors using maximum likelihood estimation.[43,44] To increase confidence in our EFA results, we used a least-squares method (iterative principal factor) and compared that result with the maximum likelihood estimation method. We considered dropping items with low factor loadings (<0.40) or with high uniqueness (>0.50) unless we saw a strong conceptual reason for keeping those items. We considered a factor loading ≥0.40 to be significant.

Construct validity. After conducting EFA, we calculated the mean score of the PSPS. We investigated the construct validity of the initial PSPS by testing the correlation between each of 2 validated safety measures (described in detail below) and the scale's mean score for each patient.

For this validation, we made 2 assumptions: (1) that patients' perceptions of global safety in the acute care setting would be positively correlated with their mean score on the PSPS scale, and (2) that patients' numbers of perceived concerns would be inversely correlated with their mean score on the PSPS. We based our expectations on an extensive review of the literature linking patient satisfaction or outcomes related to satisfaction, such as patient experiences and safety measures, including reports by patients or objective measures.

The main independent variable for the validation study of the PSPS was patients' perception of medical safety measured by 2 items that we administered along with the PSPS in the same sample of this analysis. These 2 items came from a previously validated survey to assess patients' perception about safety and medical concerns in the ED; it had been developed to be used in conjunction with ED satisfaction surveys.[28]

The first item measured the overall level of medical safety by asking patients, "Please rate the overall level of medical safety you felt during your acute stay." Respondents recorded their answers on a 5-point Likert scale (poor, fair, good, very good, and excellent), with higher scores indicating greater feelings of safety. The second item measured 8 specific medical concerns by asking patients, "During your acute visit, were you ever concerned that any of the following would occur:". Responses for these 8 concerns were coded yes/no.

1. Falling and being injured
2. A mistake or error with medications
3. Problems with medical equipment
4. A mistake by nurses
5. A mistake by physicians
6. Being mistaken for another patient
7. Having the wrong test/procedure
8. That you would be misdiagnosed

We converted the reports of concerns to a summary variable, which was the total number of concerns per patient with a possible range from 0 to 8 (see Burroughs et al[28]).

Internal consistency reliability. We calculated Cronbach α (range, 0-1) to determine the internal consistency reliability of the PSPS. A priori, we considered a value of >.7, as a general rule of thumb for group-level testing, to be acceptable for measuring the degree of homogeneity of items within our scale.[45]

Statistical Analysis: Patient Satisfaction Using the PSPS

We reported the sociodemographic and clinical characteristics of the overall sample and stratified by either IC or ED to characterize our sample. For each scale item in PSPS, we calculated the mean and SD by IC vs ED. We used structural equation modeling (SEM) to evaluate our first hypothesis for aim 3 that patients seen in an IC would report more satisfaction with their pain management than those treated in an ED.[46]

SEM: patient satisfaction using the PSPS. After we conducted confirmatory factor analysis and assessed goodness of fit of the model, we specified 2 structural models to investigate the association between care provided in the IC or ED and patient satisfaction with pain management for the treatment of acute VOC. Model 1 assessed the simple (unadjusted) association between IC and ED and patient satisfaction with pain management. Model 2 assessed the association between IC and ED and patient satisfaction with pain management controlling for age, sex, chronic pain, pain level on arrival, acute care use, and mode of scale administration.

For SEM results, we reported the standardized and unstandardized coefficients, 95% CI, and *P* values. For standardized estimates in SEM, we fixed the variance of the factor to 1. A standardized coefficient is interpreted as an SD increase or decrease in the outcome in the IC compared with that in the ED.

Statistical analysis: additional questions. For descriptive purposes, we asked 2 additional access to care questions:

1. Did you come to the ED/IC by yourself today?
2. If you brought someone with you, was it because: (check all that apply)
    a. You could not get here without help because you were too sick?
    b. You could not get here by yourself because of transportation issues?
    c. Your companion acts as your advocate while you are receiving care?
    d. Your companion helps make sure you get the treatment you need?
    e. Your companion keeps you company while you are being treated?

We also adopted 2 open-ended questions from Bhakta's satisfaction survey: "What went well during your visit?" and "What did not go well during your visit?"[33] These 2 open-ended questions were included as common practice in survey methodology; they offered participants an opportunity to raise issues or concerns that were not included in the close-ended questions and to elaborate on their experiences during their acute care visit.[47]

We reported frequencies and percentages in the overall sample and by care provided in the ED and IC in the 2 questions related to access to care and for the responses to the safety questions. For open-ended questions, we compiled and organized the free-text responses under themes based on what patients consistently reported. Themes emerged from the data but were also based on aspects of pain management that were presented in the close-ended scale questions. We provided verbatim quotations from patients to illustrate each theme.

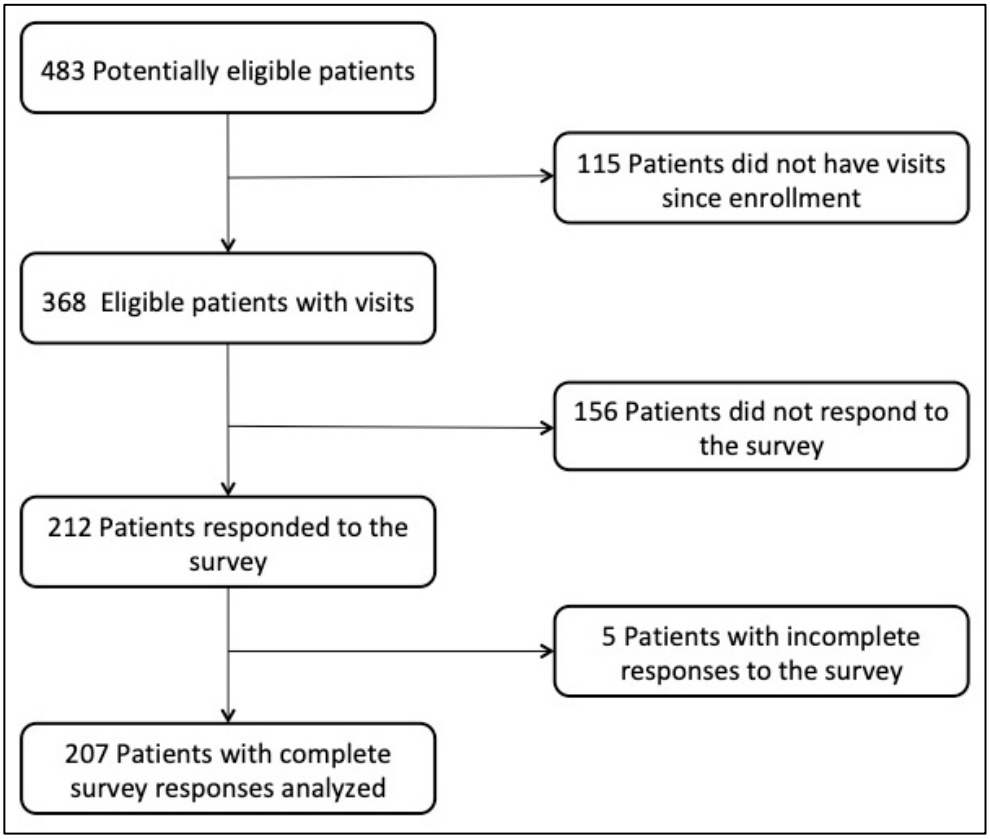
Although we considered the context of the IC and ED in our analysis, free-text responses lacked richness and depth. Thus, we did not use any rigorous qualitative methods in the analysis of these 2 open-ended questions. All analyses were performed using Stata/SE version 15.1 statistical software (StataCorp LP).[48] The significance level was $\alpha = .05$.

Results for Aim 3

Patient characteristics. Of the 368 enrolled patients with at least 1 IC or ED visit, 212 patients responded to all the survey questions in Appendix A (Figure 2). We excluded 5 patients

(2.4%) who had some missing responses to the survey items. The final sample was 207 patients (207/368 [56%]).

Figure 2. Patient Flow Diagram for Aim 3



Patient characteristics for the 207 respondents are presented in Table 6.

Table 6. Characteristics of Patients Completing the Full Survey

Patient characteristic (N = 207)	Value[a]
Age, mean (SD), y	33.8 (10.8) (range, 19-79)
Sex, female	130 (62.8)
Graduated high school	169 (81.6)
Employed	77 (37.2)
On disability	136 (65.7)
Insured by Medicaid	116 (56.0)
Low annual income (<$20 000)	
Yes No Did not mention	97 (46.9) 97 (46.9) 13 (6.2)
Married or with significant other	47 (22.7)
Lives alone	56 (27.1)
SCA	137 (66.2)
Chronic pain	157 (75.8)
Kidney disease	28 (13.5)
Leg ulcer	9 (4.3)
Stroke	34 (16.4)
Retinopathy	45 (21.7)
Avascular necrosis	69 (33.3)
Priapism (male patients only)	31 (40.3)
Receiving chronic transfusions	27 (13.0)
Taking hydroxyurea (SCA only)	83 (60.6)
Pain level on arrival, median (IQR)	9 (8-10) (range, 0-10)
No. of acute care visits in the past y, median (IQR)	5 (2-12) (range, 0-65)
Opioid use	

Patient characteristic (N = 207)	Value[a]
Long-acting only	7 (3.4)
Short-acting only	116 (56.0)
Both long- and short-acting	80 (38.7)
No opioids	4 (1.9)
Has primary care provider	153 (73.9)

Abbreviations: IQR, interquartile range; SCA, sickle cell anemia.
[a]Data are presented as No. (%), unless otherwise indicated.

Table 7 documents the descriptive statistics of the 15 final items used for the PSPS. In all, 207 patients completed the scale. As noted in the description of this scale above, it used Likert scoring that ranged from 0 (very strongly disagree) to 7 (very strongly agree); higher numbers reflect greater satisfaction.

Table 7. Results of the PSPS (N = 207)

Item	Mean (SD)	Median (IQR)	Skewness	Kurtosis	Corrected item-total correlation
1. The staff adequately assessed your pain.	5.6 (1.3)	6 (5-7)	−1.2	5.1	0.73
2. You received treatment in a timely manner.	5.3 (1.6)	5 (5-6)	−1.0	3.6	0.65
3. The doctor seemed to know just what to do for my problem.	5.4 (1.3)	5 (5-7)	−0.7	3.4	0.86
4. Your pain was adequately controlled.	5.1 (1.4)	5 (5-6)	−0.6	2.9	0.78
5. The provider ensured that the patient had enough medication to manage pain at home.	5.0 (1.5)	5 (4-6)	−0.6	2.8	0.74
6. You were satisfied with the communication with the nurses.	5.6 (1.4)	6 (5-7)	−1.2	4.8	0.73
7. Your nurse believed your reports about your pain.	5.6 (1.2)	6 (5-7)	−1.0	4.5	0.78
8. You were satisfied with the communication with the doctors.	5.5 (1.4)	6 (5-7)	−1.0	4.1	0.84
9. Your doctor believed your reports about your pain.	5.5 (1.4)	6 (5-7)	−1.1	4.5	0.81
10. The doctor seemed warm and friendly to me.	5.6 (1.3)	6 (5-7)	−1.1	4.6	0.81
11. I really felt understood by my doctor.	5.4 (1.5)	5 (5-7)	−1.1	4.2	0.86

Item	Mean (SD)	Median (IQR)	Skewness	Kurtosis	Corrected item-total correlation
12. This is a doctor I would trust with my life.	5.2 (1.6)	5 (4-7)	−0.9	3.5	0.86
13. The doctor has relieved my worries about my illness.	5.0 (1.5)	5 (4-6)	−0.6	2.9	0.82
14. During your visit, you were allowed to participate in decisions about your pain treatment as much as you wanted to.	5.3 (1.4)	5 (5-6)	−0.8	3.4	0.79
15. Overall, you are satisfied with the quality of care you received.	5.5 (1.4)	5 (5-6)	−0.9	3.6	0.86

Abbreviations: IQR, interquartile range; PSPS, Patient Satisfaction With Pain Management in Adults With SCD.

As shown in Table 7, we observed minimal negative skewness (range, −0.2 to −1.2) and minimal positive kurtosis (range, 2.4-5.1) in the PSPS. These values satisfy the multivariate normality assumption. The corrected item-total correlation was at least 0.65 and generally exceeded that value. We observed no floor or ceiling effects >30% based on the response distribution of each scale item.

Exploratory factor analysis. We conducted factor analysis on the PSPS. Correlations among the 15 items are reported in Table 8. Based on the correlations between the scale items, our data were appropriate for EFA. The results of our factor analysis identified a single factor that underlies 15 survey items.

Table 8. Correlation Coefficients Among the 15 Items on the PSPS

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	—														
2	0.59	—													
3	0.63	0.60	—												
4	0.59	0.62	0.68	—											
5	0.49	0.46	0.72	0.61	—										
6	0.69	0.60	0.59	0.60	0.45	—									
7	0.67	0.60	0.66	0.68	0.56	0.71	—								
8	0.60	0.47	0.77	0.61	0.64	0.62	0.65	—							
9	0.60	0.43	0.74	0.60	0.62	0.56	0.63	0.81	—						
10	0.59	0.46	0.73	0.62	0.68	0.57	0.58	0.71	0.75	—					
11	0.61	0.49	0.78	0.66	0.67	0.58	0.66	0.82	0.82	0.80	—				
12	0.60	0.57	0.77	0.66	0.68	0.61	0.64	0.75	0.76	0.75	0.82	—			
13	0.56	0.51	0.80	0.65	0.68	0.60	0.60	0.72	0.71	0.71	0.76	0.76	—		
14	0.56	0.52	0.67	0.71	0.66	0.60	0.67	0.67	0.65	0.67	0.67	0.71	0.66	—	
15	0.64	0.67	0.74	0.73	0.67	0.69	0.70	0.76	0.69	0.70	0.77	0.74	0.72	0.71	-

Abbreviation: PSPS, Patient Satisfaction With Pain Management in Adults With SCD.

Extracting initial factors and interpreting factor loadings. Based on the kurtosis and skewness of the 15 items, our data satisfy the multivariate normality assumption. Therefore, we used a maximum likelihood estimation approach for our EFA for this scale.

Table 9 presents the factor loadings and uniqueness values. All factor loadings ranged between 0.64 and 0.90, and all uniqueness values were <0.50 except for 1 item. The exception was, "You received treatment in a timely manner," which had a uniqueness of 0.59. We decided to keep this item because timeliness of care is a salient component of patient satisfaction with pain management among patients with SCD who are experiencing a VOC.

Table 9. Factor Loading Patterns for 15-Item PSPS Using Maximum Likelihood Estimation Analysis

Item	Factor loadings	Uniqueness
1. The staff adequately assessed your pain.	0.72	0.48
2. You received treatment in a timely manner.	0.64	0.59
3. The doctor seemed to know just what to do for my problem.	0.88	0.23
4. Your pain was adequately controlled.	0.78	0.39
5. The provider ensured that the patient had enough medication to manage pain at home.	0.76	0.42
6. You were satisfied with the communication with the nurses.	0.72	0.48
7. Your nurse believed your reports about your pain.	0.77	0.41
8. You were satisfied with the communication with the doctors.	0.87	0.25
9. Your doctor believed your reports about your pain.	0.85	0.28
10. The doctor seemed warm and friendly to me.	0.83	0.30
11. I really felt understood by my doctor.	0.90	0.19
12. This is a doctor I would trust with my life.	0.88	0.23
13. The doctor has relieved my worries about my illness.	0.85	0.28
14. During your visit, you were allowed to participate in decisions about your pain treatment as much as you wanted to.	0.80	0.36
15. Overall, you are satisfied with the quality of care you received.	0.87	0.25

Abbreviation: PSPS, Patient Satisfaction With Pain Management in Adults With SCD.

Construct validity and internal consistency reliability. The internal consistency reliability of the satisfaction score with pain management factor was high (Cronbach α = .97). For evaluating validity, we saw that the mean score was positively correlated with the safety measure of global safety in the acute care setting (Spearman ρ = 0.63; *P* < .001) and inversely correlated with the number of safety concerns patients felt during their stay (*r* = −0.47; *P* < .001).

Results for the PSPS, Patient Safety Questions, Access to Care Questions, and Open-Ended Questions

For the 207 respondents, 115 (56%) self-administered the complete survey and 92 (42%) had an interviewer-administered survey. On average, patients were 33.8 years of age (range, 19-79 years); 63% were female. About two-thirds of these respondents had SCA genotype and about two-thirds reported chronic pain. The median pain level on arrival at either an IC or an ED was 9 on a 0 to 10 scale; the median number of acute care visits in the past year was 5 per patient.

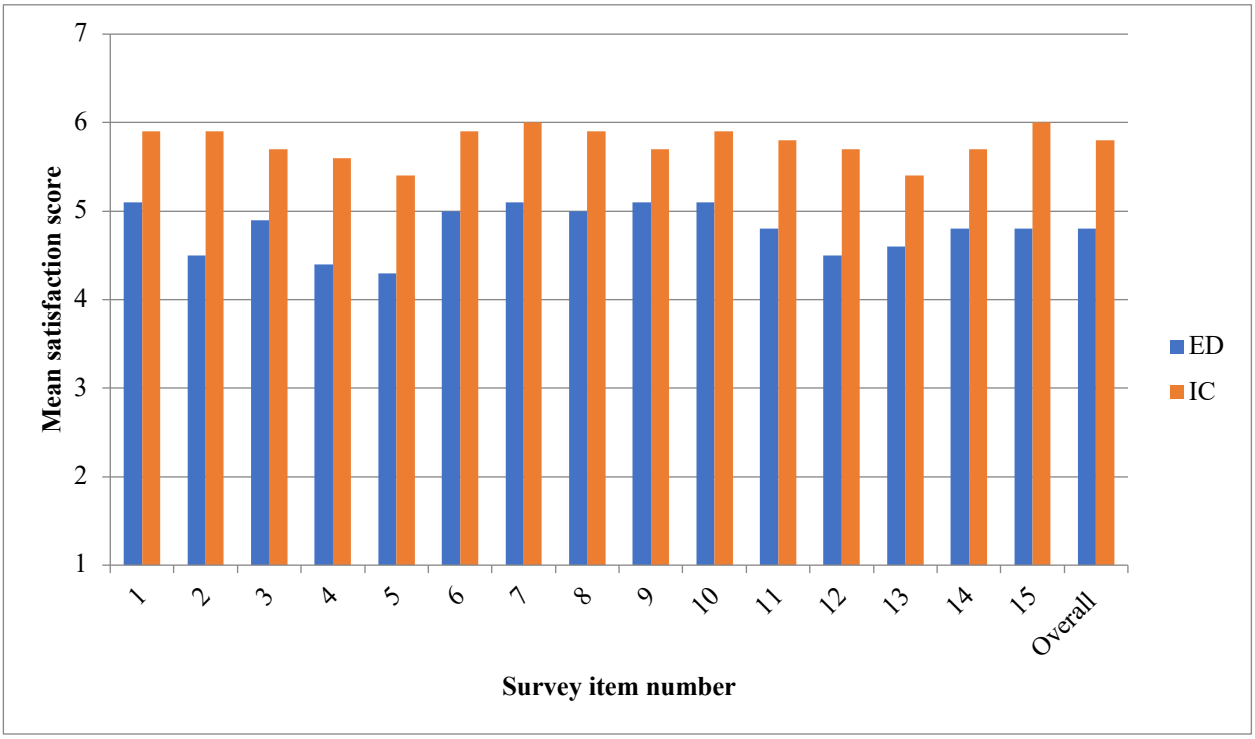
Results for patients by setting of care. Of these 207 patients, about 59% received care at an IC (n = 122) and 41% at an ED (n = 85). For the IC patients, 64% (78/122) completed the survey via self-administration; by contrast, in the ED, 56% patients (48/85) completed the survey via interviewer administration. This difference was statistically significant (*P* = .004).

We found statistically significant differences (*P* < .05) between patients receiving care in the IC and the ED with respect to age, pain level on arrival, married or with a significant other, and living alone. Compared with patients receiving care in an ED, patients who received care at the IC were significantly older than those in the ED (35.8 vs 31.0 years), had a lower pain level on arrival (8 vs 9) on a 10-point scale, were more likely to be married or with a significant other (30% vs 12%), and were less likely to live alone (21% vs 35%).

For patients who received care at an IC, the overall mean (SD) satisfaction score was 5.8 (1.0), whereas for patients who received care at an ED, the overall mean (SD) satisfaction score was 4.8 (1.1). Table 7 shows the mean satisfaction scores by scale item in the ED and IC groups.

Figure 3 shows a graphical representation of responses to each of the 15 items, and overall, from IC patients (orange) and ED patients (blue).

Figure 3. Mean Satisfaction Scores in the ED and IC by PSPS Scale Item[a]



Abbreviations: ED, emergency department; IC, infusion center; Patient Satisfaction With Pain Management in Adults With SCD.

[a]We calculated the overall score by adding the responses to all 15 questions and then dividing the sum by 15. The questions can be found in Table 7.

Results from SEM. After evaluating the fit and factor loadings of the measurement model, we specified 2 structural models. In the unadjusted model, we found a positive association between care provided in the IC and patient satisfaction with pain management compared with care provided in the ED, and this association was statistically significant (standardized β = .40; 95% CI, .29-.51; unstandardized β = .74; 95% CI, .49-.99; $P < .001$). This model suggests that receiving care in the IC is associated with a 0.40 SD increase in satisfaction compared with receiving care in the ED. For regression analysis, SEM results are standardized β coefficients with SD units. Because our outcome of patient satisfaction with pain management is an unobserved latent factor with no defined unit of measurement, we have standardized our

outcome by fixing the variance of the factor to 1 in order to draw meaningful associations and relationships with other variables.

The adjusted model also produced a positive, statistically significant association between care provided in the IC and patient satisfaction with pain management compared with care provided in the ED, controlling for age, sex, chronic pain, pain level on arrival, acute care use in the past year, and mode of scale administration (standardized β = 0.35, 95% CI, 0.23-0.47; unstandardized β = 0.64, 95% CI, 0.39-0.89; $P < .001$). This model suggests that receiving care in the IC is associated with a 0.35 SD increase in satisfaction compared with receiving care in the ED after controlling for certain sociodemographic and clinical characteristics.

Results comparing respondents and nonrespondents. In a comparison of the characteristics between respondents and nonrespondents in our sample, we found statistically significant differences ($P < .05$) for 2 characteristics or variables: the setting of care and acute care use in the past year (shown in Table 10).

Table 10. Comparison Between Respondents and Nonrespondents (N = 368)

Variable	All eligible participants (N = 368)	Respondents (n = 207)	Nonrespondents (n = 161)	*P* value
Setting of care, No. (%)				
ED IC	188 (51) 179 (49)	85 (41) 122 (59)	102 (64) 58 (36)	<.001
Age, mean (SD), y (range, 19-79)	33.9 (10.7)	33.8 (10.8)	34.0 (10.7)	.908
Sex, No. (%)				
Female Male	224 (61) 143 (39)	130 (63) 77 (37)	94 (59) 66 (41)	.430
Graduated high school, No. (%)				
Yes No	294 (80) 61 (17)	169 (82) 32 (15)	125 (78) 29 (18)	.471
Employed, No. (%)				
Yes No	133 (36) 230 (63)	77 (37) 129 (62)	56 (35) 101 (63)	.738
On disability, No. (%)				
Yes No	246 (67) 118 (32)	136 (66) 70 (34)	110 (69) 48 (30)	.467
Insured by Medicaid, No. (%)				
Yes	204 (56)	116 (56)	88 (55)	.365
No	150 (41)	86 (42)	64 (40)	
Low annual income (<$20 000), No. (%)				
Yes No Did not mention	179 (49) 168 (46) 20 (5)	97 (47) 97 (47) 13 (6)	82 (51) 71 (44) 7 (4)	.506
Married or with significant other, No. (%)				
Yes No	78 (21) 287 (78)	47 (23) 159 (77)	31 (19) 128 (80)	.443

Variable	All eligible participants (N = 368)	Respondents (n = 207)	Nonrespondents (n = 161)	*P* value
Living alone, No. (%)				
Yes No	103 (28) 264 (72)	56 (27) 151 (73)	47 (29) 113 (71)	.623
SCA, No. (%)				
Yes No	253 (69) 104 (28)	137 (66) 67 (32)	116 (73) 37 (23)	.075
Chronic pain, No. (%)				
Yes No	264 (72) 103 (28)	157 (76) 50 (24)	107 (67) 53 (33)	.058
Pain level on arrival, median (IQR) (range, 0-10)	9 (8-10)	9 (8-10)	9 (8-10)	.361
No. of acute care visits in the past y, median (IQR) (range, 0-9)	4 (2-11)	5 (2-12)	4 (1-9)	.014

Abbreviations: ED, emergency department; IC, infusion center; IQR, interquartile range; SCA, sickle cell anemia.

As we had full information about whether nonrespondents were treated in an IC vs ED, we generated probability weights using the variable "setting of care." We chose this variable because it is the main independent variable in our analysis; thus, it may highly skew results if not accounted for.

As shown in Table 11, we found no differences between unweighted and weighted standardized coefficients, 95% CI, or *P* values in the 2 models using SEM.

Table 11. Unweighted and Weighted Results of 2 Models Using SEM

Setting	Unweighted		Weighted	
	Standardized coefficient	95% CI	Standardized coefficient	95% CI
Model 1. Unadjusted				
IC vs ED	0.40[a]	0.29-0.51	0.40[a]	0.29-0.52
Model 2. Adjusted[b]				
IC vs ED	0.35[a]	0.23-0.47	0.35[a]	0.24-0.47

Abbreviations: ED, emergency department; IC, infusion clinic; SEM, structural equation modeling.
[a]*P* <.001.
[b]Adjusted for age, sex, chronic pain, pain level at arrival, acute care use in the past year, and mode of scale administration.

Results for patient safety questions. We asked patients about the level of medical safety during their stay in the ED or IC by using the following 2 questions: first, "Please rate the overall level of medical safety (defined as freedom from any medical error or mistake) you felt during your acute stay." Respondents recorded their answers on a 5-point Likert scale (poor, fair, good, very good, and excellent), with higher scores indicating greater feelings of safety. The second item measured 8 specific medical concerns by asking patients, "During your acute visit, were you ever concerned that any of the following would occur"; these were coded as yes/no:

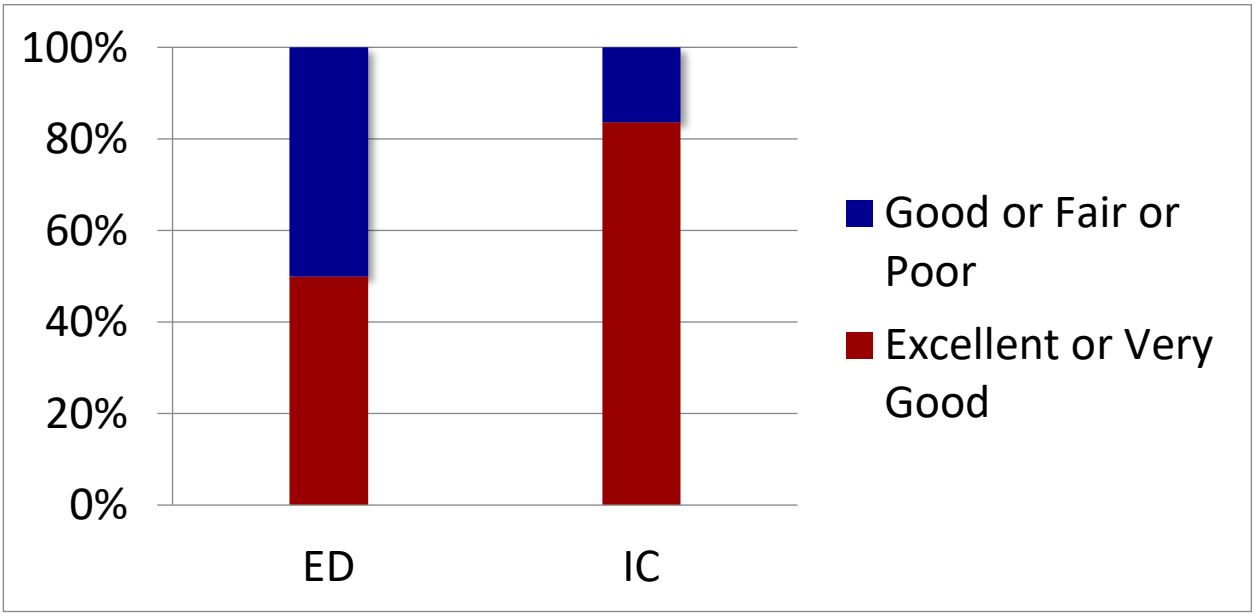
1. Falling and being injured
2. A mistake or error with medications
3. Problems with medical equipment
4. A mistake by nurses
5. A mistake by physicians
6. Being mistaken for another patient
7. Having the wrong test/procedure

8. That you would be misdiagnosed

We converted the reports of concerns to a summary variable, which was the total number of concerns per patient with a possible range from 0 to 8.[28]

Patients' responses to the questions about safety are shown in Figures 4 to 6. Similar to the findings for patient satisfaction, a larger percentage of patients treated in the IC than in the ED reported the overall level of medical safety in a positive way (ie, excellent or very good; Figure 4). Among the patients with visits to the ED, 50% reported that they felt that the overall level of safety was excellent or very good; that percentage was 80% for those seen in the IC.

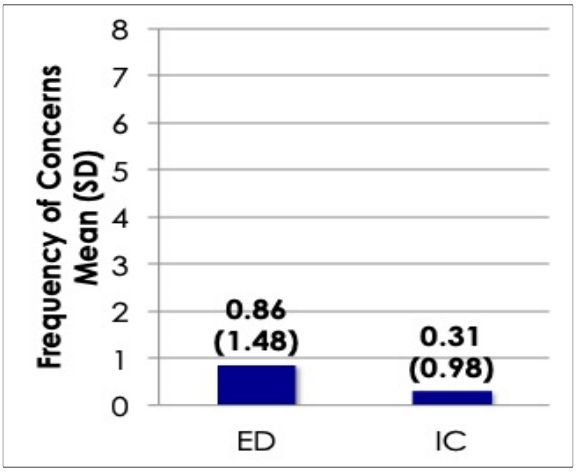
Figure 4. Overall Level of Medical Safety Felt During Acute Stay



Abbreviations: ED, emergency department; IC, infusion center.
Note: the comparison is significant at $P < .01$.

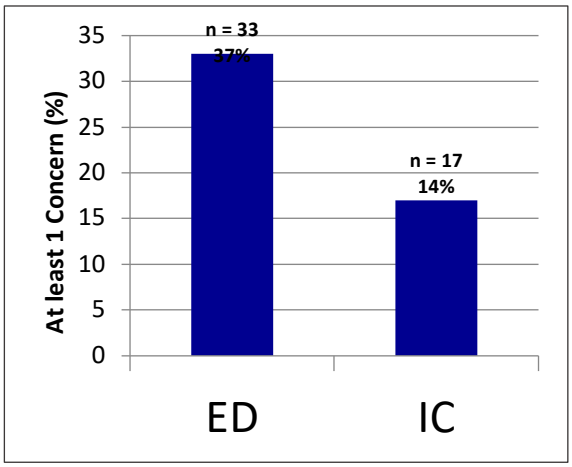
In addition, patients treated in the ED had a significantly higher number of concerns and were more likely to report at least 1 concern with medical safety than those treated in the IC (Figures 5 and 6).

Figure 5. Frequency of Patient Concerns



Abbreviations: ED, emergency department; IC, infusion center.
Note: the comparison is significant at $P < .01$.

Figure 6. Patients With at Least 1 Concern



Abbreviations: ED, emergency department; IC, infusion center.
Note: the comparison is significant at $P < .01$.

Results for additional questions asked after acute care visits. Of the 207 patients in our sample, 124 patients (60%) came for care unaccompanied; 83 patients (40%) came for care with someone. The acute care settings did not differ significantly on this variable.

Patients who came to the ED or IC with someone had different reasons for having a companion. The majority of patients (52%) could not get to the ED or IC without help, which was attributed to their illness; 43% of patients reported that their companion kept them company while they were being treated; 34% said they could not get to the ED or IC because of transportation issues; 33% of patients reported that their companion helped make sure that they got the treatment they needed; and 22% of patients felt that their companion acted as their advocate while they were receiving care. We found no major differences between the IC and ED groups of patients.

Results for other open-ended questions. As part of the overall survey, we explored what went well and what did not through 2 open-ended questions. Overall, 176 of the 207 patients responded to the question, "What went well during your visit" and 150 of the 207 patients responded to the question, "What did not go well during your visit?" As shown in Table 12, we compiled answers to these 2 questions to form 4 similar themes: (1) pain treatment and delivery, (2) staff communication and trust, (3) general or unspecified, and (4) issues not mentioned in the PSPS. We also present illustrative quotations in Table 12.

Table 12. Themes and Quotations Regarding Responses to 2 Open-Ended Questions

Theme	Quotation
What went well?	
Pain treatment and delivery	• The amount of medication and frequency [with which] it was delivered • I was seen and treated for my pain in a timely manner • They got my IV on first stick
Staff communication and trust	• The nurses really took the time to talk and understand my problems and issues • Communication with the ED physician
General or unspecified	• Everything went well • Good experience
Issues not mentioned in the scale	• Linen change • They had me in a room right next to the entrance and then moved me to a better room
What did not go well?	
Pain treatment and delivery	• The amount of time I had to wait to be treated • Had to remind them to administer home meds • Number of sticks for an IV
Staff communication and trust	• Doctor did not listen to my symptoms and opinions on what works best • Staff did not believe reports about my pain and needing meds until I threw up
General or unspecified	• Everything went well • Nothing to say
Issues not mentioned in the scale	• Waiting area was too cold • Problems with insurance

Abbreviations: ED, emergency department; IV, intravenous.

Specifically, these 4 categories included various issues. Pain treatment and delivery included medication administration, timeliness of care, frequency and dose of medications delivered, and pain medication at home. Staff communication and trust included how physicians, nurses, and physician assistants communicated with patients and how patients

perceived their relationships with their providers. General or unspecified reactions reflected comments that were unspecific as to a certain aspect of care. Finally, issues not mentioned in the survey entailed environmental concerns or insurance issues.

These themes applied to patients receiving care at either the IC or ED. We found no major differences in comments between these groups except for insurance issues, which were specific to the IC.

Assessing Data Source Adequacy

We had few difficulties in capturing data for covariates. The data collected from acute visits were part of the usual medical record and the time stamps were recorded automatically for much of the data. Visits outside of the main treatment facilities were the only ones for which some data were difficult to collect. These data accounted for <4% of all the acute data collected and, therefore, any expected impact on outcomes would be expected to be quite small.

Handling missing data: PSPS results. We calculated the response rate using the number of patients who had complete responses to the PSPS scale divided by the number of eligible patients (patients who had first time visits). We used complete-case analysis because <10% of participants had some missing scale item responses.[49]

To assess the impact of nonresponse on the results of our study, we compared sociodemographic and clinical characteristics, and the setting of care (ED vs IC) between respondents and nonrespondents using descriptive statistics as appropriate to our data. Nonrespondents were participants who had had an acute care visit but did not respond to the survey or had some missing item responses. To adjust for nonresponse, we calculated nonresponse weights using available information about the nonrespondents in the sample. We then assigned a weight for each respondent in the study by dividing the population percentage (participants who had an acute care visit) by the sample percentage (respondents to the overall scale).[50] We re-ran the 2 structural models using the weighted data and compared estimates with our results from the unweighted data. Results appear in Table 11.

DISCUSSION

The ESCAPED study is the first to compare outcomes of EDs and ICs in the management of uncomplicated VOC in adults with SCD. Our study demonstrated that patients treated in an IC received parenteral pain medications significantly faster than patients treated in an ED. Patients seen in the IC were also more likely to have their pain reassessed 30 minutes after their initial parenteral dose of medication. In addition, the guideline-based care provided in the IC setting significantly decreased the odds of hospital admission compared with the care received in an ED. These results suggest that ICs are more likely to provide guideline-based care than EDs and that such care can improve overall outcomes for adults with SCD.

In this study we developed an instrument that evaluated patient satisfaction with pain management in the acute setting. The PSPS is the first SCD-specific scale to examine patients' experiences while they are being treated for uncomplicated VOC. Our study provides preliminary evidence of the reliability and validity of the scale. In our study, this scale demonstrated that receiving care at an IC was associated with higher levels of satisfaction with pain management than receiving care at an ED. This association remained positive and statistically significant even after controlling for age, sex, chronic pain, pain level on arrival, acute care use in the past year, and mode of scale administration. In addition, using 2 validated questions to assess safety in these 2 treatment settings, we found that patients seen in the ED had more concerns about their safety than those seen in the IC.

Several possible explanations exist for the difference in outcomes we saw in the ESCAPED study for patients treated in an IC vs those treated in an ED. Structural problems such as overcrowding and ED providers' limited knowledge about individual patients can contribute to the limitations of care provided in this setting.[51,52] Adequacy of pain management in the ED setting has also been a well-recognized problem despite guidelines to assist with management.[51] In contrast, ICs are staffed by clinicians and staff with experience caring for people with SCD; these nurses, physicians, and advanced practice providers have significant knowledge about individual patients and specific training in the management of acute uncomplicated VOC.

We conducted the ESCAPED study at 4 sites, in 4 different cities in the Eastern, Midwestern, and Southern parts of the United States, where the majority of people with SCD live in this country. These sites used varying models for their individual ICs, such as shared-space infusion models and both academic and community-based hospitals. The benefits of the IC model were consistent across the sites.

This finding suggests that a dedicated center that only sees patients with SCD might not be necessary to provide guideline-based care and that shared space with dedicated personnel might be just as effective as single-focus ICs in improving patient outcomes. Using multiple sites across the United States and imposing very few exclusion criteria for patient enrollment supports the conclusion that our results are generalizable to people with SCD across the country. We restricted this study, however, to evaluating outcomes for patients with uncomplicated VOCs. Therefore, we cannot extrapolate our findings for patients who might present with other complications of SCD.

Subpopulation Considerations

Before starting the ESCAPED study, we hypothesized that patients with high acute care use might be treated differently than those without high levels. We suspected that the "high users" might have had delays in care and have had to wait longer for their first dose of parenteral medication. We performed a sensitivity analysis looking at several different definitions of high acute care use and were unable to identify any differences in the time to first dose of medication. This finding is reassuring and suggests that decisions about moving patients from triage to their first dose of opioid is not influenced by the frequency of visits for acute care. Future analysis of our data will examine whether other characteristics, such as pain level on arrival, influenced the time to first dose of medication.

Currently, the paucity of ICs for adults with SCD in the United States and the lack of access to high-quality care is a well-recognized problem.[53] Although SCD is more common than hemophilia or cystic fibrosis in this country, many more comprehensive centers for hemophilia and cystic fibrosis exist. Even in states where ICs are available for SCD patients, the majority of patients do not live close enough to the facilities to access them when they are having pain.[18]

The American Society of Hematology and other organizations have identified access to care as one of the issues and challenges in providing high-quality care to patients with SCD.[54] Therefore, this study is timely in providing evidence that promotes the use of ICs over EDs to improve quality of care for this population. Our use of multiple sites, with different models of ICs, suggests that the idea of ICs (of different types) can be broadly applied across multiple settings to improve access to this care model.

Patient and Stakeholder Engagement

The need for the ESCAPED study was driven by a clear mandate from people living with SCD that ED care was suboptimal. Stakeholders were active participants in the study and contributed to its design. After receiving their input, we added questions about safety to the postvisit patient questionnaire. Stakeholders were involved in our annual meeting and monthly all-team calls about the study. Stakeholders were also involved in disseminating information about this study via social media. Dr Haywood, who is living with SCD, was a member of the research team; he assisted with sample size calculations and was instrumental in the design and analysis of the PSPS scale.

Study Strengths

Our study has several design strengths. First, to increase the representativeness of our sample, we recruited patients from 4 diverse geographic regions and clinical settings in the United States. This approach allowed us to make some broad generalizations of our results to adults living with SCD throughout the country.

Second, the ESCAPED study is the first prospective cohort study examining acute care use since the Cooperative Study of SCD (CSSCD), which enrolled participants in the 1970s and 80s,[5] the first in the modern era since the approval of hydroxyurea to treat SCD. We are the first to demonstrate the significant increase in acute care use that has occurred since the publication describing the CSSCD population.[55] We had far more acute care visits than anticipated in this study based on the CSSCD experience, and this large number of acute care visits provided a robust amount of data.

Finally, given our large number of visits, we were able to develop and validate a patient satisfaction with pain management scale (ie, the PSPS). We have provided evidence of face and content validity, as well as construct validity using factor analysis, and we tested the correlation between patient satisfaction and the safety measure that was administered to the same population. Furthermore, we demonstrated that the PSPS has good internal consistency and reliability using Cronbach α. This instrument will be available for both future study and as a tool for quality improvement in acute care settings once the manuscript on the development of the scale is published in the coming months.

Study Limitations

Our study also had some limitations. Ideally, to compare outcomes between 2 sites of care, investigators should conduct a randomized controlled trial. However, randomly assigning people with SCD and VOC to sites of care is not possible. The need for this study, comparing the IC with the ED setting, was driven in large part by the community of people living with SCD. The need for improved care in the ED was widely recognized before our study; the likelihood that patients would agree to be randomly assigned to ED-only care was considered very low. We believe, however, that the use of propensity score modeling overcame this possible bias of the treatment effects attributable to confounders.

An additional limitation is the patient self-report of additional ED visits that occurred outside the study site ED. We did use health information exchanges available at the Baltimore site as an additional way of identifying these rare visits, but this technology was not available at the other sites. We also relied on self-report of chronic pain because at the time of the study no rigorous definition of chronic pain was available for people with SCD. The decision to limit collection of data to the initial visit to each site each month might have led to underreporting of some outcomes from the high-user population. Our sensitivity analysis, however, did not find significant differences in our outcomes for the high-user population.

We used a rigorous approach to select scale items to be included in the newly developed patient satisfaction scale. However, we may still have omitted scale items that are important to the concept of patient satisfaction with pain management.

Future Studies

Several additional studies can be conducted with the existing ESCAPED data. Those studies include examining the consistency of care in each setting for individual patients. Because some patients had many visits, we can examine whether the care they received at each visit (ie, time to first dose) was similar and evaluate whether care is more consistent in an ED or an IC setting. We can also examine whether patient satisfaction changes over time, as we currently have looked only at a cross-section of scale results after each patient's first acute care visit. Future studies can look at whether patient satisfaction or perception of safety changed over time during the study period.

Additional studies beyond the ESCAPED study should include further evaluation of the validity of the PSPS scale. As validity is a continuous process, we see an opportunity to improve the precision of measuring patient satisfaction in this population. This might include testing the PSPS scale's responsiveness to change (sensitivity to change) when applying a quality improvement intervention in the ED or IC and testing the scale in other populations outside the United States.

Finally, future research should address how to implement the IC model across populations with varying numbers of people living with SCD. Studies are needed that examine best practices in existing and new ICs.

CONCLUSIONS

The ESCAPED study focused on the acute management of uncomplicated VOC in adults with SCD by comparing treatment in an IC with that in an ED. After adjusting for differences among patients, we demonstrated that patients treated in an IC had significantly better treatment experiences than those treated in an ED: a 50% reduction in time to first dose of pain medication and an almost 6-fold decrease in hospital admission. In addition, using a questionnaire for patient satisfaction with care, we found that receiving care at an IC was associated with higher levels of satisfaction with pain management than receiving care at an ED. ICs provided patients with more rapid delivery of pain medication and improved patient-reported outcomes. Increasing access to ICs is essential to improving the quality of care for uncomplicated VOC in adults with SCD.

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APPENDICES

Appendix A: All Survey Items

Patient Satisfaction Initial Survey

1. The staff adequately assessed your pain
2. You received treatment in a timely manner
3. The staff adequately responded to your pain
4. You were satisfied with the communication with the nurses
5. Your nurse believed your reports about your pain
6. You were satisfied with the communication with the physicians
7. Your doctor believed your reports about your pain
8. The doctor told me all I wanted to know about my illness
9. The doctor seemed interested in me as a person
10. The doctor seemed warm and friendly to me
11. The doctor seemed to take my problems seriously
12. I really felt understood by my doctor
13. This is a doctor I would trust with my life
14. The doctor seemed to know what (s) he was doing
15. The doctor has relieved my worries about my illness
16. The doctor seemed to know just what to do for my problem
17. You are satisfied with the treatment you received for your pain
18. Overall, you are satisfied with the quality of care you received
19. During your visit you were allowed to participate in decisions about your pain treatment a much as you wanted to
20. Your pain was adequately controlled
21. You received enough medication/treatment to deal with your pain
22. The provider ensured that you had enough pain medication to manage your pain at home
23. Bringing someone with me when I am in the ED/IC helps improve the quality of care I receive

Extra Questions

24. Did you come to the ED/Infusion clinic by yourself today?
25. If you brought someone with you was it because: (check all that apply)
    a. You could not get here without help because you were too sick
    b. You could not get here by yourself because of transportation issues
    c. Your companion acts as your advocate while you are receiving care
    d. Your companion helps make sure you get the treatment you need
    e. Your companion keeps you company while you are being treated

Other _____

Safety survey:
Please rate the overall level of medical safety (defined as ‘‘freedom from any medical error or mistake’’) you felt during your acute stay. With 1 being excellent and 5 being poor (coded as excellent = 100, very good = 75,

good = 50, fair = 25, poor = 0).
12345

Was there a specific time during your acute stay where you were concerned that the following medical error or problem would happen to you (coded as Yes = 1 ; No = 0):
1) Falling and being injured _____
2) A mistake or error with medications _____
3) Problems with medical equipment
4) A mistake by nurses
5) A mistake by physicians
6) Being mistaken for another patient
7) Wrong test/procedure
8) Would be misdiagnosed

Appendix B: Summary Statistics on Covariates Included in Time-Varying Propensity Score Modeling Pre- and Postbalancing

	Before Balancing		Sub-group I		Sub-group II		Sub-group III		Sub-group IV		Sub-group V	
	ED	IC	ED	IC	ED	IC	ED	IC	ED	IC	ED	IC
Probability going to IC before current visit, mean(se)	0.35(0.32)	0.65(0.31)	0.064(0.11)	0.066(0.10)	0.27(0.20)	0.27(0.19)	0.53(0.27)	0.52(0.26)	0.81(0.19)	0.76(0.24)	0.86(0.16)	0.87(0.14)
Probability being admitted before current visit, mean(se)	0.17(0.25)	0.20(0.18)	0.34(0.31)	0.38(0.27)	0.21(0.24)	0.19(0.22)	0.14(0.17)	0.16(0.20)	0.11(0.16)	0.12(0.15)	0.09(0.15)	0.1(0.14)
# of ED visits in the past 12 months prior to enrollment, mean(se)	8.8(11.5)	6.2(6.8)	10.9(19.3)	9(9.8)	10.0(9.2)	11.0(10.0)	6.5(7.0)	6.3(6.3)	5.3(5.3)	4.2(5.1)	5.6(5.1)	5.1(5.1)
# of IC visits in the past 12 months prior to enrollment, mean(se)	7.8(10.5)	13.2(11.0)	3.6(8.6)	2.8(4.6)	8.2(11.3)	7.9(10.5)	8.0(8.9)	8.4(8.6)	14.1(9.5)	13.3(10.2)	21.4(10.6)	20.4(10.9)
# Of admissions in the past 12 months prior to enrollment, mean(se)	3.5(3.3)	3.3(3.4)	3.5(3.8)	3.5(3.0)	4.1(3.0)	3.9(3.1)	2.7(3.1)	3.3(3.5)	3.8(3.5)	3.2(3.4)	3.4(3.8)	3.2(3.8)
Avascular necrosis(%)	36	41.7	22.3	31.2	37.6	39.5	38.9	37.8	39.1	36.7	59.6	63.3
Stroke(%)	18.9	17.2	21.3	25	18.5	18.1	22.3	23	16.4	18.5	14	13
Retinopathy(%)	20.4	33.8	7.3	9.4	12.8	19.4	35.4	25.2	42.2	50	61.4	55.2
Gall bladder disease(%)	61.7	59.8	60.2	56.3	64.3	66.6	62.4	67	57.8	50.6	55.3	55.5
Leg ulcer(%)	9.4	6.5	1.8	0	12.5	15.1	8	6.9	1.6	1.8	11.4	8.2
Pulmonary hypertension(%)	13	15.1	4.7	0	12.0	12.0	17	18.3	22.7	22.7	16.7	13.6
Kidney disease(%)	14	23.9	4.9	3.1	18.5	15.4	11.5	14.5	21.9	26.3	49	39.5

Not on chronic transfusions(%)	86.5	82.4	90.7	93.8	89.8	87.3	83.7	85.1	83.6	81.3	73.7	72.8
Graduated high school (%)	75.5	86.1	54.4	56.3	82.3	79.9	83.7	85.3	79.7	79.5	89.5	90.9
Marital status, married or significant other(%)	14.5	21.7	8.5	3.1	18.5	13.7	12.3	12.5	21.9	26.1	23.7	28.6
Low annual income, < $20,000 (%)	56.3	53.4	57	62.5	53.1	60.9	54.4	49.2	62.5	60	36	38.6
	Before Balancing		Sub-group I		Sub-group II		Sub-group III		Sub-group IV		Sub-group V	
	ED	IC	ED	IC	ED	IC	ED	IC	ED	IC	ED	IC
No disability(%)	25.6	19.8	30.4	46.9	10.1	10.4	23.8	21.4	17.2	15.6	23.7	22.5
Do not have primary care physician(%)	38.9	32.4	52.3	40.6	44.3	45.8	17.5	20.2	39.1	38.1	44.7	39
Do not have hematologist(%)	38.9	32.4	52.3	40.6	44.3	45.8	17.5	20.2	39.1	38.1	44.7	39.0
On short-acting opioids(%)	50.2	33.4	62.3	62.5	52.7	56.9	46.4	43.4	30.5	36.3	13.2	11.1
On long-acting opioids(%)	4.7	5.1	2.8	3.1	8.2	7.7	3	3.6	3.1	4	0	0
On long- & short-acting opioids(%)	44.1	60.4	34.1	34.4	38.3	35.1	48.9	50.4	64.8	58.8	86.8	88.9
On hydroxyurea (sickle cell anemia only)(%)	46.5	44.4	38.9	50	56.3	57.2	45.3	49	49.2	40.5	31.6	24.9
Age, mean(se)	31.1(8.8)	34.2(9.1)	30.9(9.1)	26.4(5.2)	30(8.7)	29.8(8.1)	31.1(8.2)	31.6(8.7)	33.6(8.5)	35(9.1)	38.2(8.9)	38.2(8.6)
Insured by Medicaid(%)	68.2	57.3	74.4	71.9	70.5	71.6	64.9	65.7	72.7	70.2	36.8	36.8
Residence, live alone(%)	27.1	29.9	24.3	12.5	25.6	32.4	32.1	29.8	18.8	16	45.6	41.8
Sickle cell anemia(%)	71.5	70.3	56.4	65.6	73.9	76.6	73.9	76.6	69.5	61.2	58.8	57.1
Unemployed(%)	75.3	73.9	80.3	78.1	77.6	80.3	68.6	66.1	60.2	67.7	76.3	76.4

Male(%)	41.5	35.7	53.5	62.5	43	39.1	31.1	35	35.9	33.4	34.2	39.8
Male with priapism(%)	21.3	21.3	16.2	9.4	24.1	21.7	16.6	19.7	25.8	22.3	17.5	13
Site Hopkins(%)	28	40.7	3.7	9.4	32.3	33.1	45.4	40.2	37.5	39.9	57	57.8
Site_cleveland(%)	19.4	18.5	20.1	3.1	25.5	24.7	10	11.3	25	26.5	22.8	19.2
Site baton rouge(%)	25.5	24.1	15.4	12.5	25.2	21.7	34.3	38.9	31.3	25.6	13.2	14.7
Site Milwaukee(%)	27.1	16.7	60.9	75	17	20.4	10.3	9.6	6.3	8	7	8.2

Appendix C: Sensitivity Analysis

Primary Outcome
Time to First Dose (low number of visits: 1 to 11 visits during 18 months)

Site	Mean (min) time to first dose	SE	95% CI
ED	135.4	5.69	(124.2, 146.6)
IC	59.5	2.77	(54.1, 64.9)
Average Treatment Effect	75.9	6.52	(63.1, 88.7)

Primary Outcome
Time to First Dose (high utilizers, 12 or more visits in 18 months)

Site	Mean (min) time to first dose	SE	95% CI
ED	121.4	4.1	(113.4, 19.4)
IC	61.8	1.49	(58.9, 64.7)
Average Treatment Effect	62.0	4.75	(52.7, 71.3)

Secondary Outcome
Pain- Reassessment within 30 Minutes of 1st Dose of Parenteral Pain Medication

(low number of visits: 1 to 11 visits during 18 months)

Site	Values (Odds, OR)	95% CI
IC	0.38	(0.265, 0.556)
ED	0.28	(0.222, 0.353)
OR (IC vs ED)	1.37	(0.896, 2.102)

Secondary Outcome
Pain- Reassessment within 30 Minutes of 1st Dose of Parenteral Pain Medication

(high utilizers, 12 or more visits in 18 months)

Site	Values (Odds, OR)	95% CI
IC	0.57	(0.50, 0.66)
ED	0.2	(0.16, 0.25)
OR (IC vs ED)	2.86	(2.27, 3.60)

Secondary Outcome:
Disposition from Acute Care Visit
Odds for Admission to the Hospital v. Discharge Home (ED vs IC)

(Low number of visits: 1 to 11 visits during 18 months)

Site	Values (Odds, OR)	95% CI
IC	0.179	(0.124, 0.259)
ED	1.0	(0.835, 1.196)
OR (IC vs ED)	5.58	(3.81, 8.18)

Secondary Outcome:
Disposition from Acute Care Visit
Odds for Admission to the Hospital v. Discharge Home (ED vs IC)

(high utilizers, 12 or more visits in 18 months)

Site	Values (Odds, OR)	95% CI
IC	0.077	(0.059, 0.1)
ED	0.412	(0.338, 0.5)
OR (IC vs ED)	5.35	(4.0, 7.14)

Table. Sensitivity Analysis on High versus Low Utilizers

	Utilizers	Estimate (SE)	Odds Ratio (95% CI)	Comparison between the Estimates of Low and High Utilizers z-score (p-value)
Mean Time Difference to First Dose, IC vs ED (min)	Low	- 75.9 (6.52)	NA	1.66 (0.1)
	High	- 62 (4.75)	NA	
Log (Odds Ratio) of being reassessed in 30 min, IC vs ED	Low	0.315 (0.218)	1.37 (0.9, 2.1)	2.98 (0.003)
	High	1.051 (0.118)	2.86 (2.27, 3.6)	
Log (Odds Ratio) of being hospitalized, IC vs ED	Low	-1.719(0.197)	0.179 (0.122, 0.264)	0.17 (0.87)
	High	-1.677(0.147)	0.187 (0.14, 0.249)	

For the primary outcome (TFD), there is no significant difference between high versus low utilization group, z-score = 1.66, pvalue=0.1.

For the secondary outcome --- Reassess pain within 30 min, there is significant difference between high and low utilization group, z-score = 2.98, pvalue = 0.003.

For the secondary outcome --- being hospitalized, there is no significant difference between high and low utilization group, z-score = 0.17, pvalue = 0.87.

Disclaimer:
The [views, statements, opinions] presented in this report are solely the responsibility of the author(s) and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute® (PCORI®), its Board of Governors or Methodology Committee.

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