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# Sickle Cell Clinical Research and Intervention Program (SCCRIP): A lifespan cohort study for sickle cell disease progression from the pediatric stage into adulthood

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## Abstract

**Background:** Previous natural history studies have advanced the understanding of sickle cell disease (SCD), but generally have not included sufficient lifespan data or investigation of the role of genetics in clinical outcomes, and have often occurred before the widespread use of disease-modifying therapies, such as hydroxyurea and chronic erythrocyte transfusions. To further advance knowledge of SCD, St. Jude Children's Research Hospital established the Sickle Cell Clinical Research and Intervention Program (SCCRIP), to conduct research in a clinically evaluated cohort of individuals with SCD across their lifetime.

Abbreviations: CDC, Centers for Disease Control and Prevention; EMR, electronic medical record; Hb, hemoglobin; NIH, National Institutes of Health; PRO, patient-reported outcome; SCCRIP, Sickle Cell Clinical Research and Intervention Program; SCD, sickle cell disease; St. Jude, St. Jude Children's Research Hospital

  

**Procedures:** Initiated in 2014, the SCCRIP study prospectively recruits patients diagnosed with SCD and includes retrospective and longitudinal collection of clinical, neurocognitive, geospatial, psychosocial, and health outcomes data. Biological samples are banked for future genomics and proteomics studies. The organizational structure of SCCRIP is based upon organ/system-specific working groups and is opened to the research community for partnerships.

**Results:** As of August 2017, 1,044 (92.3% of eligible) patients with SCD have enrolled in the study (860 children and 184 adults), with 11,915 person-years of observation. Population demographics included mean age at last visit of 11.3 years (range 0.7–30.1), 49.8% females, 57.7% treated with hydroxyurea, 8.5% treated with monthly transfusions, and 62.9% hemoglobin (Hb) SS or HbSB$^0$-thalassemia, 25.7% HbSC, 8.4% HbsB$^+$-Thalassemia, 1.7% HbS/HPFH, and 1.2% other.

**Conclusions:** The SCCRIP cohort will provide a rich resource for the conduct of high impact multidisciplinary research in SCD.

**KEYWORDS**
disease-modifying therapy, natural history, sickle cell anemia

## 1 | INTRODUCTION

An estimated 100,000 individuals in the United States live with sickle cell disease (SCD),[1] and worldwide an estimated 300,000 babies are born with the disease each year.[2,3] The clinical consequences are severe and include recurrent episodes of acute severe pain, chronic pain, cerebrovascular events, progressive organ damage, and early death.

In the United States and other high-income countries, survival to adulthood of children with SCD has increased over the past five decades from 50% to greater than 95%.[1,4–7] This survival increase is primarily due to mandatory newborn screening, infection prevention with penicillin prophylaxis and pneumococcal vaccination, improved supportive care, and increased use of disease-modifying therapies, such as hydroxyurea and chronic erythrocyte transfusions.[8–13] However, accumulation of end-organ damage to the heart, lungs, brain, kidneys, and bones continues to occur.[14] This organ damage manifests in young adults with higher rates of acute health utilization, emergency room reliance, and hospitalization.[15,16] Disease-related mortality rises in young adults and the median age of death among adults with hemoglobin (Hb) SS and HbS$\beta^0$-thalassemia is mid to late 40s.[1,17,18]

Understanding the natural history of SCD across the lifespan in the contemporary medical environment is crucial, because the substantial improvement in pediatric survival contrasts with lesser gains in health outcomes among adults. A particular challenge is the assessment of clinical outcomes during the vulnerable period of transition from the pediatric to the adult care setting. During this transitional period, deficits in preparation, planning, care coordination, and available skilled adult care providers lead to low rates of engagement in adult care and interrupt care continuity.[19,20] Without an appropriate infrastructure to collect longitudinal health outcomes data as children age into adulthood, information will be limited, insufficient to answer questions examining disease progression, and unlikely to stimulate progress in the field.

### 1.1 | Knowledge gained from early SCD cohorts

Three early cohort studies have informed much of our understanding of the epidemiology and natural history of SCD, although each began prior to the advent and widespread use of current disease-modifying therapies; these are the Jamaican Cohort Study (1973–1981),[21,22] the Cooperative Study of Sickle Cell Disease (1979–1999),[23,24] and the Dallas cohort study (1983 to present)[25] (Table 1). These studies provided the foundation for understanding variations in the disease severity phenotype, acute complications of SCD, survival rates, mortality risks, laboratory values, and the basis for sepsis and stroke prevention.[6,26–41] Over the past decade, clinical trials have demonstrated the benefit of hydroxyurea [42,43] and erythrocyte transfusions for stroke prevention, building on the knowledge from earlier cohort studies. More recently, smaller retrospective and prospective cohort studies have shown that hydroxyurea may reduce mortality and prevent organ damage.[44–48] Thus, SCD cohort studies that factor in long-term health effects of disease-modifying therapies, such as hydroxyurea and chronic erythrocyte transfusions begun in childhood, should be the gold standard for observational and interventional research studies in the modern era.

From our current perspective, important limitations of these earlier cohorts were the lack of sufficient longitudinal data to cover the full lifespan (i.e., studies were focused on either children or adults), the limited genotype–phenotype studies, and the insufficient exposure to disease-modifying therapies. The long-term follow-up of the phase III BABY HUG study (NCT00890396) has been monitoring the long-term effects of hydroxyurea therapy, but this cohort study is relatively small and data collection has ended. More recent cohorts that have included patients exposed to disease-modifying therapies have lacked sufficient internal comparative groups, such as patients not exposed to therapies, limiting their external validity.

### 1.2 | Scientific importance of SCCRIP

Longitudinal evaluation of outcomes throughout the lifespan will enhance our understanding of disease progression, identify early

**TABLE 1** Landmark cohort studies in sickle cell disease

| Cohort study | Date | Sample size | # sites | Objectives | Continuity from the pediatric stage into adulthood | Disease-modifying therapy exposure | Systematic organ function assessment | Knowledge gained | Eligibility | Biological samples banked |
|---|---|---|---|---|---|---|---|---|---|---|
| Jamaican Cohort Study[21,22] | 1973–1981 | 580 | 1 | To define a natural history of SCD and identify modulation factors | None | None | No | Frequency and clinical presentation of acute complications | Newborns born between 1973 and 1981, born in Jamaica, and screened positive for SCD | No |
| Cooperative Study of Sickle Cell Disease (CSSCD)[23,24] | 1979–1999 | 4,085 | 23 | To determine a natural history of SCD and identify factors contributing to morbidity and mortality in SCD | Limited | None | No | Frequency and clinical presentation of acute complications, severity risk factors, mortality causes, hematologic indices | Newborn to 25 years of age; Black male or females with SCD | DNA |
| Dallas Newborn Cohort[25] | 1983 to present | 940 | 1 | To determine contemporary survival data for children with SCD that reflect modern SCD therapy | Limited | Limited | No | Mortality causes, risk prediction of disease severity | Newborns with SCD as identified by newborn screening program in Texas | No |
| SCCRIP | 2014 to present | 1,044 currently | 5 | To create a lifetime longitudinal cohort and bank biospecimens | Yes | Yes | Yes | Pending analyses | A diagnosis of SCD | DNA, plasma, urine |

predictors of later outcomes, elucidate the roles of genetic, proteomics, and environmental factors on health outcomes, and define the long-term impact of therapies. To address these goals and circumvent the limitations of prior studies, we initiated the Sickle Cell Clinical Research and Intervention Program (SCCRIP, NCT 02098863). Here we describe the design of SCCRIP, including its systematic approach to data abstraction according to developmental stage, particularly the transition from pediatric to adult care, and how the phenotype data are being classified in a fashion that can be compared across multiple institutions.

## 2 | METHODS

### 2.1 | Study aims and design

Initiated in April 2014, SCCRIP is a cohort study with prospective follow-up, ongoing data accrual, and retrospective collection of extensive clinical history. The overarching goal of SCCRIP is to understand the clinical, biological, and psychosocial progression of SCD and factors contributing to early mortality across the lifespan, with the ultimate goal of facilitating effective therapies. The objectives are two-fold: (1) to establish a longitudinal clinical cohort of patients with SCD; and (2) to establish a biorepository of DNA, urine, and plasma.

### 2.2 | SCCRIP participating sites

SCCRIP enrolls patients from five institutions (Figure 1). These sites were chosen based on the size of their SCD population, their relationship with St. Jude Children's Research Hospital (St. Jude), and ability to perform uninterrupted data collection from birth through adulthood. St. Jude, the clinical and data coordinating site, treats 850 children with SCD from birth to age 18 years. Through Tennessee and Mississippi State Health Department contracts, St. Jude has been the referral treatment center for new SCD cases from west Tennessee and north Mississippi, diagnosed through the newborn screening programs in those states, for the past 20 years. Following referral to St. Jude, 100% of infants with newly diagnosed SCD are seen in the SCD clinic and initiate penicillin prophylaxis within 2 months.[49] Care provided by St. Jude is free (including medications), and support with transportation and meals is provided during regular and study visits.[50] Approximately 80% of St. Jude patients transfer care to the Comprehensive Sickle Cell Program in the partnering Methodist University Hospital, ensuring care continuity and uninterrupted research data ascertainment.[51] The Methodist University Hospital is located 2.5 miles from the St. Jude campus, and currently cares for 300 adults, of whom approximately 90% are former St. Jude patients. After transition of care, adults are followed similarly to children, with health-maintenance visits at least twice per year when chronic end-organ damage is performed as standard of care. The remaining three sites belong to the St. Jude Affiliate Program and share the purpose of extending protocol-structured treatment and research through clinical, research, and academic partnerships. Support with meal expenses and transportation costs related to study visits are provided by St. Jude. Collectively, these five institutions care for approximately 1,600 individuals with SCD and contribute geographic, social, and environmental diversity to the SCCRIP clinical cohort.

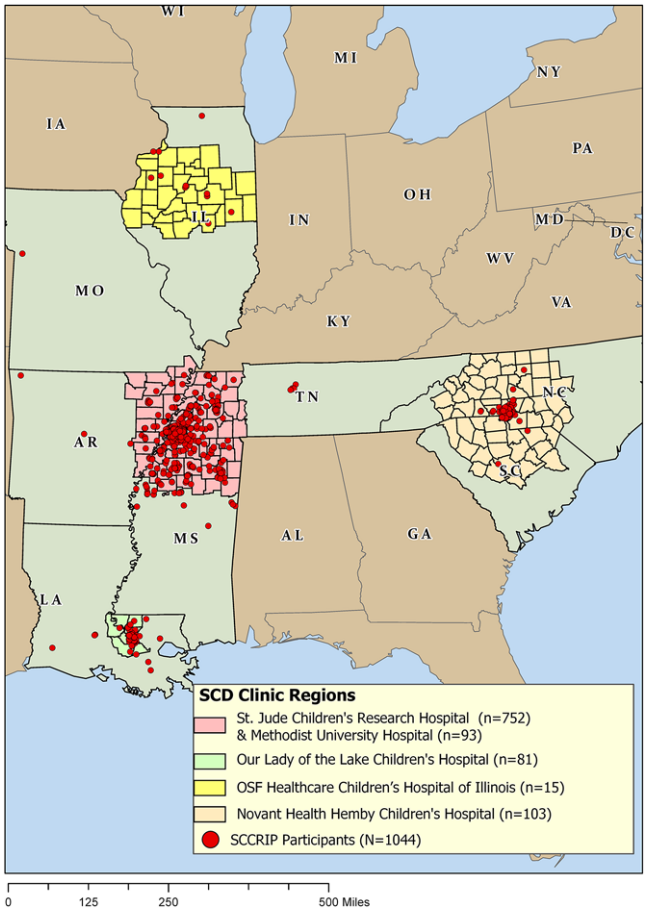


**FIGURE 1** SCCRIP participants' geographical distribution. The 1,044 SCCRIP participants are distributed among the following five sites in four states: two in Memphis, TN (St. Jude Children's Research Hospital and Methodist University Hospital), one in Peoria, IL (OSF Healthcare Children's Hospital of Illinois), one in Charlotte, NC (Novant Health Hemby Children's Hospital), and one in Baton Rouge, LA (Our Lady of the Lake Children's Hospital)

### 2.3 | SCCRIP organizational structure

The SCCRIP multidisciplinary research team blends expertise in pediatric and adult hematology, nephrology, pulmonology, cardiology, radiology, pain, psychology, bone metabolism, transfusion medicine, epidemiology, genetic epidemiology, biostatistics, social sciences, computational biology, bioinformatics, geocoding, and data management. Research-related activities within SCCRIP are divided into nine Working Groups, which focus on questions related to a specific organ system, disease complication, or therapy, and provide primary oversight for the development and conduct of research initiatives. Investigators seeking to answer specific research questions are required to collaborate with the appropriate Working Group(s) and complete a concept proposal (Supplementary Material S1) that is reviewed and

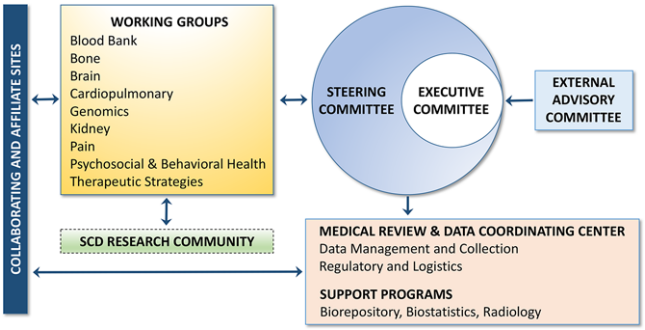


**FIGURE 2** SCCRIP organizational structure. SCCRIP's scientific initiatives are driven by the Working Groups, which are composed of St. Jude and external investigators. The Steering Committee vets all concept proposals from the Working Groups and follows recommendations from the Executive Committee regarding major study deliberations. Plans are in place to expand SCCRIP collaboration to the SCD community by allowing access to the SCCRIP resource to external collaborators beyond current collaborators

approved by the Steering Committee, comprised of SCCRIP investigators. The SCCRIP Steering Committee evaluates the quality of the science, design, and analytical plan for each new research proposal. The Executive Committee is responsible for major deliberations and conflict resolution within SCCRIP. A number of committees provide oversight of activities related to the publication of results from SCCRIP, and access and utilization of the SCCRIP resource. An external advisory committee, consisting of pediatric oncologists, pediatric hematologists, epidemiologists, and biostatisticians, provides input into the current and future activities. In the future, it is our plan to open SCCRIP data access to the broader SCD research community. In this model, non-SCCRIP investigators will have access to SCCRIP data and samples, once approved by the Steering Committee. Figure 2 outlines the organizational structure for SCCRIP.

## 2.4 | Subject sampling and follow-up strategy

Participants are prospectively recruited if they have a diagnosis of SCD of any type and receive treatment at one of the five participating sites. Participants are not selected based on disease severity or treatment exposure. Prospective data collection starts at study enrollment, but existing clinical and laboratory data, when available, are retrospectively collected from the point of first encounter with the health care system. This strategy for data collection allows for reconstruction of the participant's entire medical and treatment history regardless of the age at enrollment. There is no final enrollment goal for the study. Rather, we plan to approach and enroll the entire SCD population managed by all participating sites. Once enrolled, participants are categorized according to one of the following six developmental age cohorts: newborn (0 to 5.9 months), infant-toddler (6 months to 5.9 years), school age child (6–11.9 years), adolescent (12–17.9 years), young adult (18–24.9 years), and older adult (25 and older). This cohort categorization allows for the classification of clinical and laboratory-based variables according to age, facilitating both longitudinal and age-stratified analyses.

## 2.5 | Data variables

All clinical and laboratory assessments performed as standard of care for SCD are defined by national standards or institutional clinical practice.[52] SCCRIP data are collected at standard intervals and classified into the following three tiers (Table 2): universal (e.g. Hb fractionation, urine microalbumin), risk-based (e.g. transcranial Doppler ultrasound in children aged 2–16 years with HbSS and $HbS^{0}$-thalassemia), and symptom-based (e.g. magnetic resonance imaging to investigate osteonecrosis due to prolonged joint pain, impaired range of motion, and debility). Healthcare utilization (e.g. admission, acute care visits) and educational attainment data are also collected for the entire cohort. Additionally, participants are offered optional research activities every 6 years, including banking of biospecimens (urine, plasma, and DNA), measurement of high sensitivity C-reactive protein, and assessment of health-related quality of life using the PedsQL™ instrument (generic, SCD, and multidimensional fatigue modules, and the corresponding adult versions once participants reach adult age) (Table 2).[53–55] After transition from pediatric to adult clinical care, SCCRIP adult participants return to St. Jude every 6 years for comprehensive data collection to assess disease status.

## 2.6 | Consenting process and institutional review board oversight

Subjects are approached during nonacute health maintenance visits and informed consent is obtained directly from participants who are 18 years of age and older or their legal guardian, if subjects are minors. Verbal assent is obtained from minors who are between the ages of 7 and 13 years, and signed assent from those between 14 and 17 years of age. When participants reach the age of majority (18 years), they are reconsented into the study.

A tiered consent provides subjects with opt-in/opt-out choices for participating in the research activities beyond the collection of past and future standard of care data (Table 2, optional evaluations). Extensive discussion regarding future genetic testing takes place during informed consent, including the information that these studies are performed in a laboratory not approved by Clinical Laboratory Improvement Amendments and will not be returned to the participants. Opt-in/opt-out choices for recontacting participants due to incidental findings are provided. Examples of potential future research with subjects' biospecimens and the potential risks to loss of privacy are discussed in the context of genomics research. Public sharing of genetic data will occur according to the National Institutes of Health (NIH) Genomic Data Sharing Policy (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-124.html) for NIH-funded projects. Access requests from non-SCCRIP investigators for combined genetic and phenotypic data for hypothesis-driven research may be approved after completion of a concept proposal (Supplementary Material S1). The SCCRIP Steering Committee will evaluate external concepts on the scientific significance, innovation, and approach of their proposed project as well as the investigative team, research environment, and funding availability.

**TABLE 2** SCCRIP tiered schedule of evaluations

| | Cohort | Newborn | Infant-toddler | | | School age | | | Teenager | | | Young adult | | | Mature adult | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tier | Evaluation age ± 1 (years) | 0–0.59 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | At least every 2 years from age 26 | Every 6 years from age 30 |
| 1 | Vital signs, anthropometric measures, physical exam | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| | CBC and reticulocyte count | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| | Hemoglobin fractionation | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| | U/A, urine prot/creat ratio, microalbumin | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| | CMP, LDH, cystatin C, 25OH vitamin D | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| | Retinopathy screen | | | | | | x | x | x | x | x | x | x | x | x | |
| | Disease-specific literacy[a] | x | x | | | | | x | x | x | x | x | x | x | x | |
| | Transition readiness | | | | | | | | | | x | | | | | |
| | Parvovirus B19 index titer | | | | x | | | x | | | x | | | x | | x |
| | Pulmonary function test | | | | x | | | x | | | x | | | x | | x |
| | CT DEXA scan | | | | x | | | x | | | x | | | x | | x |
| | Brigance Developmental test | | x | x | | | | | | | | | | | | |
| | Neuropsychological screening | | | x | | x | | x | | x | | | | x | | x |
| 2 | Transcranial Doppler ultrasound | | x | x | x | x | x | x | x | x | | | | | | |
| | Serum ferritin, Epo, RBC Ab | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| | Liver R2[a]MRI | | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| | $T^{99}$ liver/spleen scan | | | | x | | | x | | | x | | | | | |
| | Glomerular filtration rate | | | | x | | | x | | | x | | | x | | x |
| 3 | Brain MRI/MRA and joint MRI | | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| | EKG/Echocardiogram | | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| | Polysomnography | | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| | Parathyroid hormone level | | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| Optional tests | | | | | | | | | | | | | | | | |
| DNA, serum, and urine, hs-CRP | | x | | | x | | | x | | | x | | | x | | x |
| HRQOL | | x | x | | x | | | x | | | x | | | x | | x |

CBC, complete blood count; prot/creat, protein to creatinine ratio; CMP, complete metabolic profile; CT DEXA, dual-energy X-ray absorptiometry; LDH, lactate dehydrogenase; Epo, erythropoietin; RBC Ab, red blood cell antibody screen; hs-CRP, high-sensitivity C-reactive protein; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; EKG, electrocardiogram; U/A, urine analysis; HRQOL, health-related quality of life measured with Peds QL™ generic, fatigue, and SCD modules.

Tier 1, universal data collection; Tier 2, risk-based data collection, done on those at risk of a complication (e.g. transcranial doppler velocities for HbSS/HbS$\beta^0$-thalasssemia ages 2–16 years, liver R2*MRI for those on chronic transfusions); Tier 3, symptom-based (e.g. MRI of the hip to investigate osteonecrosis in a patient with persistently severe hip pain).

[a]Disease-specific literacy collected from parent up to age 2 years and from patient after age 2 years.

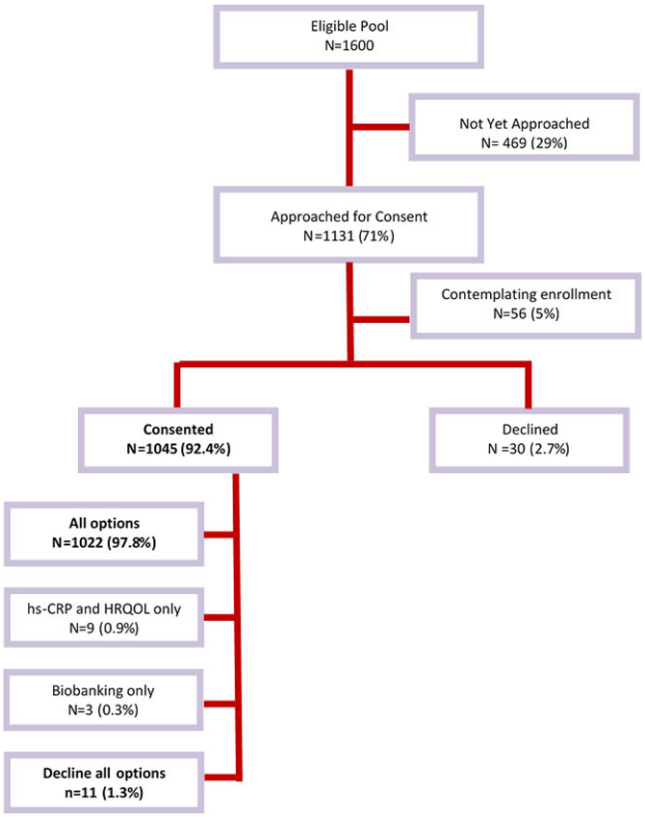


**FIGURE 3** Consort diagram for SCCRIP. The overall acceptance participation rate is 92.3% and acceptance of optional research activities (biobanking of DNA, urine, and plasma) is 97.9%

## 3 | DATA MANAGEMENT

SCCRIP study staff document all interactions with eligible and enrolled participants through an electronic tracking database. The program generates reports that summarize enrollment and study-related information and notifies study staff of upcoming study events for each subject, such as time to complete age of majority consents and time to enter study-specific orders. Data sources for SCCRIP include patient-reported outcome (PRO) surveys and data electronically or manually abstracted from medical charts. PRO data are gathered electronically using a mobile device (tablet), and stored in an electronic data management system, to later be extracted and deposited into the SCCRIP database. Clinical data are extracted in a table format from each site's electronic medical record (EMR, Cerner® or Epic® software systems) through a series of queries or custom reports, which local information technology staff develop and execute regularly. Data from external sites are securely transmitted and uploaded to St. Jude regularly using Health Insurance Portability and Accountability Act–compliant protocols. Participants' addresses are geocoded annually using ArcGIS (Esri, Redlands, CA) to determine the socio-economic characteristics of participants' neighborhoods and proximity to both resources (e.g. food access, parks, schools) and environmental hazards (e.g. interstates, airports). Once collected, SCCRIP phenotype data undergo an additional iterative step to match the clinical events according to the consensus measures for phenotypes and exposures (PhenX) toolkit. (https://www.phenxtoolkit.org).[56] Approximately 80% of SCCRIP and PhenX data are concordant (Supplementary Table S1).

To facilitate data analyses, an annual data freeze is performed. For each data domain, computer programs (1) download and perform quality control checks; (2) merge data from disparate sources; (3) import relevant data fields from other external sources; and (4) save a single analytical dataset containing all required data elements. SCCRIP data management operations require a substantial amount of human resources. Currently, the study has two data managers who perform data extraction, data structuring, and data cleaning and seven research coordinators who perform patient consenting, PRO collection, and manual data abstraction, and help coordinate data transfer from all sites.

### 3.1 | Data analysis plan and lost-to-follow-up tracing

The assigned study statistician will conduct the analytical plan and return aggregate results and graphical display of data to the investigators for manuscript or grant preparation. A system to trace lost-to-follow-up from death is in place through annual searches of the National Death Index, a program maintained by the National Center for Health Statistics from the Centers for Disease Control and Prevention (CDC). These annual searches will allow for mortality ascertainment (date and cause of death) for lost-to-follow-up cases.

## 4 | RESULTS

### 4.1 | Participant enrollment

As of August 27, 2017, 1,044 subjects (860 children and 184 adults) with SCD have enrolled across the five participating sites, yielding in 11,915 person-years of observation. The overall participation acceptance rate is 92.3% (Figure 3). Of the 1,131 subjects approached to date, only 30 (2.7%) declined participation. An additional 57 subjects refused enrollment when initially approached, but asked to be re-approached at a future date. Of those who agreed to participate, 1,022 (97.9%) consented to optional tests including quality of life questionnaires and biospecimen banking (Figure 3). Among the 22 subjects who refused the optional studies, the most common reason for refusal was "do not want to spend extra time due to research activities".

The characteristics of enrolled participants are shown in Table 3. Most participants (860, 82.4%) are younger than the age of 18 years. Collectively, 66.4% of participants are exposed to disease-modifying therapy; hydroxyurea 57.7%, chronic erythrocyte transfusions 8.5%, and bone marrow transplant 0.2%. The mean ages when hydroxyurea and chronic transfusions were initiated were 7.3 (±5.41) and 5.3 (±3.68) years, respectively. The mean age at the time of the bone marrow transplantation procedure was 11.9 (±5.59) years. For the subjects exposed to disease-modifying therapies, the observation period (in person-years) is slightly greater before study enrollment than that post enrollment, that is, 4,035 versus 3,438 person-years, respectively.

**TABLE 3** SCCRIP participants' characteristics

| | Age cohort | | | | | | |
|---|---|---|---|---|---|---|---|
| | Newborn, 0–0.59 years | Infant-toddler, 0.6–5.9 years | School age, 6.0–11.9 years | Adolescent, 12.0–17.9 years | Young adult, 18.0–24.9 years | Mature adult, >25.0 years | Total[a] |
| Number enrolled (%) | 0 | 259 (24.8) | 366 (35.1) | 235 (22.5) | 173 (16.6) | 11 (1.1) | 1,044 |
| Mean age in years (±1 SD) | 0 | 4 (1.6) | 10 (1.6) | 15.9 (1.7) | 21.2 (1.7) | 27 (1.6) | 11.3 (6.4) |
| Gender (% female) | 0 | 51.9 | 48.5 | 48.7 | 50.9 | 54.5 | 49.8 |
| Race (%) | | | | | | | |
| Black/African American (%) | 0 | 257 (99.2) | 361 (98.6) | 235 (100) | 172 (99.4) | 11 (100) | 1,036 (99.2) |
| White | 0 | 1 (0.4) | 3 (0.8) | 0 | 1 (0.6) | 0 | 5 (0.5) |
| Other | 0 | 1 (0.4) | 2 (0.6) | 0 | 0 | 0 | 3 (0.3) |
| Health insurance (%) | | | | | | | |
| Government[b] | 0 | 201 (77.6) | 264 (72.1) | 173 (73.6) | 111 (64.2) | 6 (54.5) | 755 (72.3) |
| Commercial | 0 | 56 (21.6) | 93 (25.4) | 55 (23.4) | 42 (24.3) | 1 (9.1) | 247 (23.7) |
| Uninsured | 0 | 2 (0.8) | 9 (2.5) | 7 (3.0) | 20 (11.6) | 4 (36.4) | 42 (4.0) |
| Disease-modifying therapy (%) | | | | | | | |
| Hydroxyurea | 0 | 114 (44.0) | 192 (52.4) | 134 (57.0) | 153 (88.4) | 9 (81.8) | 602 (57.7) |
| Monthly erythrocyte transfusions | 0 | 5 (1.9) | 32 (8.7) | 31 (13.2) | 21 (12.1) | 0 | 89 (8.5) |
| Hematopoietic stem cell transplant | 0 | 0 | 1 (0.3) | 1 (0.4) | 0 | 0 | 2 (0.2) |
| Mean distance from site (miles) | | | | | | | |
| ≤30 | 0 | 185 (71.4) | 215 (58.7) | 165 (70.2) | 123 (71.1) | 8 (72.7) | 696 (66.6) |
| 31–50 | 0 | 21 (8.1) | 39 (10.6) | 18 (7.6) | 10 (7.4) | 1 (9.1) | 89 (8.5) |
| 51–100 | 0 | 41 (15.8) | 84 (22.9) | 47 (20.0) | 35 (20.2) | 2 (18.1) | 209 (20.0) |
| >100 | 0 | 12 (4.6) | 28 (7.6) | 5 (2.1) | 5 (2.8) | 0 | 50 (4.7) |
| Sickle genotypes (total number) | | | | | | | |
| HbSS or HbS$\beta^0$-thalassemia | 0 | 167 | 213 | 158 | 113 | 6 | 657 |
| HbSC | 0 | 63 | 108 | 48 | 45 | 4 | 268 |
| Hbs$\beta^+$-thalassemia | 0 | 20 | 33 | 22 | 12 | 1 | 88 |
| HbS/HPFH | 0 | 5 | 7 | 3 | 3 | 0 | 18 |
| HbSD | 0 | 1 | 3 | 0 | 0 | 0 | 4 |
| HbS/Black $(^A\gamma\delta\beta)^0$-thalassemia | 0 | 1 | 0 | 1 | 0 | 0 | 2 |
| HbSOArab | 0 | 1 | 0 | 1 | 0 | 0 | 2 |
| HbS/N Baltimore | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| HbSE | 0 | 0 | 2 | 0 | 0 | 0 | 2 |
| HbS/Hope | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| HbC Harlem disease | 0 | 0 | 0 | 1 | 0 | 0 | 1 |

HPFH denotes hereditary persistence of fetal hemoglobin.

[a]Total count includes participants who expired while on study.

[b]Government insurance includes Medicaid and Medicare.

This order will reverse as the cohort ages. The distribution of sickle genotype and gender is similar among age cohorts, although treatment exposure and the proportion of uninsured subjects increase with age (Table 3). Approximately 40% of participants live within a census tract defined as high vulnerability using the CDC's Social Vulnerability Index.[57] There were no significant differences in sex, age distribution, sickle genotype, or treatment exposure between subjects who agreed (N = 1,044) and those who declined (N = 30) to participate in SCCRIP.

### 4.2 | Subject retention

Since enrollment initiation in 2014, four subjects have died and four have asked to be removed from the study. No participants have been lost to follow-up. Of the 10 participants who have reached the age of majority (18 years) and transferred from pediatric to adult care, nine reconsented to remain in the cohort, while one requested to leave the cohort. All but one of these nine consenting young adults elected to continue participating in the optional biobanking activity.

## 5 | DISCUSSION

The progression of end-organ damage and early mortality among individuals with SCD is not fully understood. Cohort studies are essential to evaluate the disease course and long-term effects of therapies. The SCCRIP modern cohort is designed to address these long-term objectives while addressing limitations of prior studies by (1) providing lifespan data that include the critical period when children become adults and end-organ damage becomes evident, (2) banking DNA, plasma, and urine for future genomic and proteomic studies, (3) harmonizing data variables with established classification of SCD phenotypes, and (4) providing an organizational structure that focuses its multidisciplinary/multi-institutional team of experts on elucidating SCD progression by organ system and disease complication.

The design of a prospective cohort like SCCRIP provides rigorous comprehensive, standardized interval classification of multiple patient exposures and outcomes over time. Contemporary cohort studies that can follow patients for the duration of their lifetime are rare and mostly found in European countries where healthcare is centralized and universal. SCCRIP parallels European cohorts by tracking participants' clinical acute and chronic outcomes and response to therapies in a similar fashion, but extends them by collecting PROs and systematic pulmonary, bone, developmental, and neurocognitive data, and through biobanking.[12,58]

SCCRIP is a large prospective lifetime cohort study of SCD with over 1,000 subjects enrolled that addresses many of the limitations of prior studies by providing a rigorous methodology for systematic data collection during the pediatric-adolescent years and into adulthood, and provides a platform for biomarker studies, including those of serum protein and metabolite levels and genetics. Furthermore, SCCRIP examines the influence of social determinants of health on clinical outcomes.[59]

Overall acceptance rates have been high for the study. In addition, acceptance of the optional banking of DNA for future genetic studies has been remarkably high (97.9%). Research study acceptance and enrollment have been traditionally low for SCD,[60–65] and some reports have indicated that African Americans are less likely than other racial and ethnic groups to support genetic studies that require a broad consent for the use of biospecimens in genetics research.[66,67] We attribute our high rate of enrollment to the possible benefit of genetic studies perceived by our patient population. Additionally, trust in the providers and low data collection burden (most data collection is passive) may play a role in this high acceptance rate. SCCRIP participants have raised no significant concerns regarding the use of their biospecimens for future genetic studies, and most cite possibly contributing to the development of curative therapies as a motivation for study participation.

Currently, important knowledge gaps impede progress in developing strategies for the surveillance and prevention of complications of SCD, and evaluation of effectiveness of new treatments. Examples include, but are not limited to (1) the long-term effects of hydroxyurea, hematopoietic stem cell transplantation, and transfusion therapy and the role of new interventions (e.g. anti-inflammatory agents,[68,69] Hb affinity modulators,[70–72] anti-oxidants,[73] and gene therapy[74]) in cumulative organ damage; (2) cognitive impairment, both its underlying mechanisms and the impact on social function; (3) the impact of the environment on the disease course, including poverty, which is prevalent in the SCD population; (4) pain control, particularly in patients who progress to chronic pain; (5) risk factors for bone mineral loss and osteonecrosis, including vitamin D deficiency, which is prevalent in SCD,[75] and establishment of prevention and treatment guidelines; (6) risk factors for sickle nephropathy in older children and adults and the role of renal-modifying therapies; (7) factors underlying the sharp increase in mortality in young adults, as compared to children; and (8) how biomarkers can be used to monitor treatment response and disease severity.[76]

A major long-term goal of SCCRIP is to utilize genomic studies to predict SCD outcomes and guide treatment. Biomarkers of SCD severity, including fetal Hb level and hemolysis indices have a high heritability and numerous genetic variants are associated with these traits.[77,78] Organ-specific problems, such as sickle nephropathy[79] and susceptibility to red blood cell alloimmunization[80] are influenced by genetic information that will likely be used prospectively for therapeutic decisions. We use pharmacogenetics data routinely to guide codeine use in SCD.[81] Thus, we plan to obtain genetic information on SCCRIP participants in order to interpret their clinical course in the context of variants known to influence SCD outcomes, plan prospective studies using this information, and elucidate new genetic modifiers of SCD through phenotype-genotype correlations.

The strengths of the study design are enrollment of a large unselected population, near complete coverage of the total local population for each participating institution (i.e. all site patients are approached), systematic ascertainment of multilevel health outcomes, and a robust data management infrastructure and plan. In addition, because clinical and laboratorial events are classified according to established phenotype (PhenX), it allows for cross analysis between SCCRIP and

other studies. Another major strength is how the cohort will serve as a resource to the broader SCD research community in the future. Non-SCCRIP investigators will be able to request access to SCCRIP data by developing concept proposals that are vetted by the Steering Committee, in addition to combining their own datasets with that of SCCRIP to bolster sample size, whenever applicable. Limitations of the study include the exclusion of subjects not treated by the participating institutions, limiting generalization beyond the geographical location of the participating sites. In addition, if subjects join the cohort, but were previously treated by other institutions, complete past health records may be unavailable. However, participants without complete retrospective records are a minority (<1%) of the study population, minimizing the risk of incomplete retrospective data ascertainment. Finally, because SCCRIP initiated in 2014, and participants joined the cohort at different ages, the observation time for the period prior to study enrollment was greater than that post enrollment, that is, 10,077.4 and 1,837.4 person-years, respectively. However, except for the optional research activities that only occur after enrollment, the methodology for data abstraction form the EMR for the period prior to and after enrollment is the same.

SCCRIP is a contemporary natural history cohort study of SCD that provides data on disease progression, education outcomes, and healthcare utilization throughout the lifespan of patients with SCD, some exposed to current and future disease-modifying therapies, such as the newly approved L-glutamine.[82–84] The detailed and standardized characterization of the disease phenotype in SCCRIP, coupled with future genetic, socio-environmental-behavioral, and proteomic studies will be a unique resource for advancing the understanding of SCD. Elucidation of predictors of disease progression from SCCRIP studies may accelerate efforts to develop and improve precision medicine in the SCD population.

## CONFLICT OF INTEREST

J.H.E. receives research support from Pfizer and Eli Lilly and Co. and serves as a consultant for Daiichi Sankyo and Global Blood Therapeutics. W.C.W. receives research support from Global Blood Therapeutics. J.S.H. receives research support from Novartis and Global Blood Therapeutics and consultant fees from bluebird bio. K.L.S. receives financial support from Molina Healthcare Clinical Quality Improvement Committee to conduct quality improvement projects, and owns Pfizer stocks. P.C.B. receives research support and speaker fees from Novo Nordisk. M.J.W. is a consultant for Glaxo SmithKline and Novartis and an advisory board member for Rubius, and receives research funding from Biogen. The other authors have no financial relationships relevant to this article to disclose.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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