Sickle Cell Disease Patient Registry Protocol

Sickle Cell Disease Implementation Consortium (SCDIC)

Sponsors and Partners

National Heart, Lung, and Blood Institute
National Institute for Minority Health and Health Disparities

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ABSTRACT

The purpose of the Sickle Cell Disease Implementation Consortium (SCDIC) is to use implementation science to identify and address barriers to quality care in sickle cell disease (SCD). Implementation science examines study methods that promote the adoption of research findings into healthcare. SCDIC is a cooperative research program of eight Clinical Centers, a data coordinating center (DCC), and the National Heart, Lung, and Blood Institute (NHLBI) that will promote the development and evaluation of strategies that take a multi-modal, multi-sector approach across two phases and six years. In Phase I, the Consortium will 1) systematically assess barriers to ongoing care at all points of entry into the local health care systems as part of needs-based community assessments; 2) develop implementation interventions to address these barriers and plan clinical studies that will test the efficacy of these interventions; and 3) design and develop a SCD Registry of at least 2,400 patients. During Phase II the SCDIC will carry out the implementation research studies and continue to enhance the SCD Registry with additional patients and follow-up data collection.

1. BACKGROUND AND RATIONALE

1.1 Sickle Cell Disease

Sickle cell anemia (SCA) refers to the clinically similar disorders Hb SS or Hb $S\beta^0$-thalassemia. Sickle cell disease (SCD) refers to all disease genotypes, including SCA and compound heterozygous disorders, such as Hb SC, Hb $S\beta^+$-thalassemia, and other less common variants. The carrier state for hemoglobin S (Hb AS or sickle cell trait) is not a form of SCD.

Hb A, the predominant hemoglobin after the newborn period, consists of two α and two β globin chains. Hemoglobin with two mutated β^s-globin chains is designated Hb S, sickle hemoglobin. The predominant hemoglobin during intrauterine development, Hb F (fetal hemoglobin), contains two γ-globin chains rather than two β-globin chains. Individuals with SCD-SS produce predominantly Hb S with some Hb F, and those with other forms of SCD produce both Hb S and another hemoglobin. When the Hb S is deoxygenated, it can aggregate into stiff rod-like structures. These structures make the RBCs less deformable and result in abnormally shaped RBCs that rupture easily, stick to other blood cells and vascular endothelial cells, occlude blood vessels, and interrupt blood flow in the tissues. These characteristics increase hemolysis and cause vaso-occlusion, which produce clinical symptoms of SCD.

The most common complications of SCD result from damaged blood vessels and entrapment of the sickled cells and other blood cells. Ischemia, tissue damage and hemolysis cause much of the morbidity and mortality associated with SCD, including episodic pain, splenic dysfunction and associated vulnerability to bacterial infections, strokes, renal dysfunction, acute and chronic lung injury, retinal damage, and skin ulcerations. The size of the U.S. SCD population is unknown but is estimated to be as high as 122,900 of which 99,888 (81%) have Hb SS. Minorities are disproportionately affected, occurring in roughly one of every 500 African American births and one of every 36,000 Hispanic births.

1.1.1 Treatment and Management of Sickle Cell Disease

Bone marrow or stem cell transplantation is the only cure available for SCD. Best outcomes are achieved in those with matched related donors which are available for a minority of the eligible population. Some patients and providers perceive the risks of the transplant-related mortality and morbidity to outweigh the potential for a cure. For most individuals with SCD, health care is a matter of preventing and treating its complications. Hydroxyurea increases the level of Hb F in RBCs of people with SCD, making the cells less likely to sickle. This reduces the amount of cellular injury and extends RBC survival, corresponding to improvements in anemia and lower rates of vaso-occlusive complications such as pain and acute chest syndrome. Blood transfusions are the only proven way to prevent some of the major complications of SCD, especially recurrent stroke. They are also used frequently to help manage some of the acute complications of SCD. In the absence of a widely accessible cure, treatment for SCD is usually aimed at avoiding crises, relieving symptoms, and preventing complications.

1.1.2 Barriers to Care

Fifty years ago, it was rare for individuals with SCD to live beyond childhood. Advances in care delivery and treatment have more than doubled the life expectancy of individuals with sickle cell disease (SCD) since 1972. Beginning in the 1970s, measures such as newborn screening, prophylactic administration of penicillin and immunization against bacterial infections decreased complications and morbidity, increasing the length and quality of life of children with SCD. More recently, the use of hydroxyurea as a therapeutic agent to increase fetal hemoglobin has been shown to further reduce the debilitating symptoms of and improve survival in SCD. However, many of these advances have not translated into an increase in longevity or quality of life for adolescents and adults because of disparities in access to routine primary health care.

Individuals with SCD experience a markedly increased mortality beginning in the second decade of life. The third and later decades of life are frequently associated with severe chronic pain, progressive organ damage and frequent hospitalizations. The provision of evidence-based and expert opinion-based care in SCD is complicated by the difficulties that many patients experience in obtaining access to the health care system and in receiving long-term care from knowledgeable providers. The disparities in the health care of individuals with SCD are due to multiple, overlapping factors that are common to many underserved populations at the individual, community and health care services levels. As demonstrated in the approach to care of other chronic diseases affecting underserved populations, maximal effectiveness in implementation of optimal care is achieved through multi-level and multi-modal interventions. The literature on disparities in health care has emphasized that equity can best be achieved by addressing barriers that exist at multiple levels (patient, community, provider/health care, organizational), and in considering the specific needs and resources that exist in care settings.

1.2 Rationale

Implementation science is the study of methods for improving the uptake (adaptation), implementation and translation of research findings into routine and common practice. The process of ensuring that evidence-based medical practices can be delivered to the appropriate group of subjects must consider the societal contexts of the health care system, as well as institutional cultures, and the availability of appropriate providers. The SCDIC proposes to approach these issues through the implementation of systems-wide interventions to improve the health and well-being of adolescents and adults with sickle cell disease through geographically based consortia consisting of community and academic health care institutions. A multi-level approach to implementation research will be established that takes advantage of community, governmental and academic institutions as well as sources of support from family, friends, school, work and social services. The project will have two phases: in Phase I, the Consortium will 1) systematically assess barriers to ongoing care at all points of entry into the local health care systems as part of needs-based community assessments; 2) develop implementation interventions to address these barriers and plan clinical studies that will test the efficacy of these interventions; and 3) design and develop a SCD Registry of at least 2,400 patients. During Phase II the SCDIC will carry out the implementation research studies and continue to enhance the SCD Registry with additional patients and follow-up data collection.

2. REGISTRY OBJECTIVES

2.1 Objectives

The Sickle Cell Disease Implementation Consortium (SCDIC) is the first research program to use implementation science to identify and address barriers to quality care in SCD. Patients enrolled in the implementation research studies may be selected from the SCD Registry. The Registry is designed during Year 1 and begins recruitment in Year 2. The goal is to enroll at least 2,400 patients (300 per Center) between the ages of 15 and 45 years by the end of January 2019 or the time that recruitment for the implementation research studies begins. To achieve these goals, the Registry will:

a. Develop standard data collection tools and methods which will be used to characterize the SCD population leading to the development and implementation of research studies;
b. Identify gaps in research;
c. Conduct data queries and analyze data collected;
d. Provide access to these resources to Registry investigators who are interested in advancing the understanding of the SCD population; and
e. Publish and disseminate results.

The overall timeline for the Registry is shown below. In Phase I, the Registry will be designed, and the data collection instruments and protocol will be developed. Once IRB approval has been obtained at each of the eight Centers, the Registry will begin enrollment. Enrollment began in late summer 2017 with a minimum of 300 patients enrolled at each Center by the end of January 2019. In Phase II, which will commence in 2019, additional subjects may be enrolled as well as retention of the original cohort. The Registry will also collect follow-up data, including patient reported outcomes, data abstracted from medical records, and vital status at the end of the study.

	PHASE I											PHASE II				
	YEAR 1				YEAR 2				YEAR 3			YEAR 3		YEARS 4 - 6		
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2		Q3	Q4	YR 4	YR 5	YR 6
SCDIC REGISTRY											ADMINISTRATIVE REVIEW					
Finalize Core Measures		X														
Develop Procedures		X	X													
Design Data Forms		X	X													
Protocol Development			X	X												
IRB Approvals				X	X											
Develop Data Systems				X	X											
Manual of Operations				X	X											
Train Coordinators					X											
Recruit 300 Pts/Center					X	X	X	X	X	X						
Recruitment/Follow-Up												X	X	X	X	X
Monitoring						X	X	X	X	X		X	X	X	X	X
Data Analysis/Publications												X	X	X	X	X

3. RESEARCH QUESTIONS

3.1 Research Questions

The data collection forms were developed to answer, either directly or with ancillary studies, the following research questions, although it is not meant to be an exhaustive list of questions that might be answered with Registry data. The organization that proposed the research question is in brackets after each question.

Complications/Co-morbidities

1. What is the incidence and prevalence of certain complications (pain crises, acute chest, avascular necrosis, priapism, deep vein thrombosis, hydroxyurea use etc.) for patients enrolled in the SCD Registry? Can we interact with EMR to get at incidence? [Augusta]
2. Can the diagnosis of chronic kidney disease from medical records be confirmed by laboratory data?

Treatment

1. What is the prevalence and history of transfusions for patients in the Registry by age and what are the indications for stopping? What are the adverse effects of cessation? [UCSF]
2. How many patients are on anti-coagulants?
3. What is the prevalence of hydroxyurea use in children and adults in different areas of the country, and what is the association of hydroxyurea utilization with age, insurance status, access to a hematologist, access to a cell phone, health literacy, and quality of life? [St. Jude]
4. What is the empiric use of hydroxyurea in persons with Hb SC or Hb S-beta Thal? Little is known about Hb SC or Hb S-beta Thal patients on hydroxyurea. Which persons with Hb SC or Hb S-beta Thal are on HU and why, and what are the barriers to other Hb SC or Hb S-beta Thal patients with similar indications being on HU? [UCSF]
5. Pregnancy outcomes associated with use of hydroxyurea during pregnancy. How many subjects became pregnant or fathered a child while on hydroxyurea? Were there any birth defects, intrauterine growth retardation, etc. in infants born of pregnancies when father or mother was on hydroxyurea at the time of conception? Were there any pregnancy complications, losses, pre-term births, etc.? For women, how long did the pregnancy go before stopping hydroxyurea and did this length of time correlate with any complications? [Chicago]
6. Does use of hydroxyurea negatively impact fertility? [Chicago]

Access to Care

1. After adjusting for patient-level effects, are "outcomes" better for individuals who receive care at tertiary centers with SCD expertise vs. those cared for in low-density settings (i.e. with fewer numbers of people with SCD)? The outcomes that we choose would depend upon what data the Registry is capable of collecting (measures of organ function like proteinuria could be useful, patient-reported outcomes like ASCQ-Me and PROMIS would be great, as would acute care utilization). This addresses the issue of whether sickle cell care should be regionalized. [Mt. Sinai]
2. In young adults who have become disconnected from longitudinal care, what factors are associated with adults who ultimately reconnect to longitudinal care vs. those who do not? This would allow us to further target scarce resources towards the highest risk individuals. [Mt. Sinai]

Quality of Life and Patient Reported Outcomes

1. What is the spectrum and distribution of educational attainment and employment status of adults with SCD? How does lower SES contribute to lower adherence, lower levels of QOL, and morbidity and mortality? [St. Louis]

2. What are the clinical and sociodemographic factors that most affect quality of life for patients with SCD? [DCC]
3. Does self-report of pain frequency correspond to acute healthcare utilization by age? [Chicago]
4. Does sickle cell disease have greater impact on females than males, where impact is defined as (A) pain frequency, (B) health related quality of life, and (C) disability measures? [Chicago]
5. What is the disability attributable to sickle cell disease? What are the actual vs predicted levels by zip code or address for (A) educational level (B) employment status (C) marital status? Use census analyses that provide information on many socioeconomic metrics and assign each zip code a "Distress Score" for the general population of that neighborhood. Compare sickle cell patients to this background of distress. [Chicago]
6. What longitudinal changes over time can be identified from ASCQ-Me? [UCSF]
7. Validate ASCQ-Me in the population age 15-17 years. [UCSF]

3.2 Longitudinal Research Questions

The data collection forms were developed to answer, either directly or with ancillary studies, the following research questions, although it is not meant to be an exhaustive list of questions that might be answered with follow-up Registry data. The organization that proposed the research question is in brackets after each question.

Pregnancy/Fertility

1. How does hydroxyurea use affect patient fertility? Is there a time dependence to infertility after a patient stops taking hydroxyurea? [Chicago]
2. What medical, clinical, and social factors impact the outcome of pregnancies in women with sickle cell disease? [UCSF]

Acute/Chronic Pain

1. Is there a relationship between chronic pain development over the period of observation and hydroxyurea use? [St. Jude]
2. Is there a relationship between chronic pain development over the period of observation and depression? [St. Jude]
3. Is lower baseline hemoglobin associated with increase proteinuria? Do these patients have LESS pain than age-matched other patients? [MUSC]

Organ Function

1. Kidneys: Does proteinuria predict worsening creatinine clearance over a 3-year period? If so, are patients on ACE-I or ARB protected from this change? [MUSC]
2. Heart: Do patients with lower baseline hemoglobin develop high output cardiac failure? [MUSC]
3. Heart: Is lower baseline hemoglobin associated with worsening atrial dilation? Does it get worse over a two-year period? Are hydroxyurea or blood transfusions protective? [MUSC]
4. Heart: Do patients with history of a blood clot have an increased risk of developing pulmonary hypertension? [MUSC]
5. Heart: Are right and left ventricle cardiac strain associated with the development of cardiac insufficiency over the period of observation? [St. Jude]
6. Lung: Do patients with acute chest syndrome develop R heart failure more rapidly than those who do not? [MUSC]
7. What surgical procedures are common for Registry patients? [Chicago]

Hydroxyurea vs. Non-Hydroxyurea Patients and SCD Diagnosis Comparisons

1. Is there a difference in renal disease progression among hydroxyurea versus non-hydroxyurea patients with Hb SS or Hb S-beta zero thal over the period of observation? Disease progression defined as decreased GFR, increased microalbuminuria, and increased prot/creat ration. [St. Jude]
2. Is there a difference in TRjet change among hydroxyurea versus non-hydroxyurea patients with Hb SS or Hb S-beta zero thal over the period of observation? [St. Jude]
3. Is there a difference in left ventricle mass change among hydroxyurea versus non-hydroxyurea patients with Hb SS or Hb S-beta zero thal over the period of observation? [St. Jude]
4. Is there a difference in left atrium size change among hydroxyurea versus non-hydroxyurea patients with Hb SS or Hb S-beta zero thal over the period of observation? [St. Jude]
5. Does left right and left ventricle cardiac strain change over time (over the period of observation) in patients with Hb SS or Hb S-beta sero thal? [St. Jude]
6. Is there a difference in cognitive function change among hydroxyurea versus non-hydroxyurea patients with Hb SS or Hb S-beta zero thal over the period of observation? We can use memory and other variables collected in the survey (ASCQ-me cognitive questions). [St. Jude]
7. Do Hb SC and Hb S-beta plus thal patients treated with hydroxyurea have fewer acute events leading to admission or ED visits than those with Hb SC and Hb S-beta plus thal who are not treated with hydroxyurea over the period of observation? [St. Jude]
8. Was mortality lower among patients treated with hydroxyurea over the period of observation? [St. Jude]
9. Describe the change in hydroxyurea prescribing patterns by age. [Duke]

Adherence/Access to Care

1. Evaluate adherence differences based on insurance. [Chicago]
2. How does the quality of care depend upon the insurance status and the provider availability? [Chicago]
3. Evaluate adherence differences based on insurance and consistent primary care and/or hematologist, and/or case manager or community health worker? [Chicago]

Other

1. What is the impact of other registries on the enrollment in the SCDIC Registry? [Chicago]
2. What social determinants influence later health status for patients with sickle cell disease [UCSF]
3. What is the incidence and prevalence of any cancers in SCD patients? [UCSF]

3.3 Other Uses of the Registry

In addition to collecting baseline and longitudinal data that will be used for cross-section analyses, patients in the Registry may be identified for clinical trials or cohort studies based on eligibility criteria found in the Registry data. In addition, Registry patients may serve as the basis for selection of subjects into the implementation research studies to be conducted in Phase II.

4. REGISTRY ORGANIZATION

4.1 Overview

The Registry leverages the availability of common data elements (CDEs) in sickle cell disease developed in such sources as the PhenX Toolkit, ASCQ-Me, and PROMIS to collect standard clinical measures, laboratory values, lifestyle factors, medical history, treatment, healthcare utilization, and patient reported outcomes associated with pain, co-morbidities, quality of life, physical functioning, mental health and barriers to care. The Registry is a resource for identifying gaps in research, conducting data queries and analyses that lead to development and implementation of research studies, and dissemination of research findings.

4.2 Organization and Participating Institutions

The following sections describe the organizations that are participating in the SCDIC Registry including the study sponsor, data coordinating center, study chair, and the eight SCDIC Clinical Centers.

Sponsor

The Sickle Cell Disease Implementation Consortium (SCDIC) was established in 2016 and funded by the National Heart, Lung, and Blood Institute (Dr. Sharon Smith, Program Official) and the National Institute for Minority Health and Health Disparities (NIMHD) of the National Institutes of Health (NIH). The NHLBI's Division of Blood Diseases and Resources (DBDR) is responsible for organizing the overall program, providing oversight to the various components of the Consortium, overall monitoring of interim data and safety issues, and collaborating with the Data Coordinating Center (DCC) and the SCDIC investigators in the development and implementation of the Registry.

Data Coordinating Center

RTI International serves as the DCC for the SCDIC Registry (Dr. Barbara Kroner, PI). As the DCC, RTI is responsible for the data capture and management, coordination of training, logistics and communications, study website, and statistical design and analysis. In concert with the Registry Committee, the DCC is responsible for development of the protocol, data collection forms, manual of operations, and assistance with the preparation of manuscripts and presentations.

Steering Committee Chair

Dr. Alexis Thompson serves as the chair of the SCDIC Steering Committee. Dr. Thompson is the Medical and Scientific Director of Hematology at the Ann & Robert H. Lurie Children's Hospital of Chicago and Associate Professor of Pediatrics at the Northwestern University Feinberg School of Medicine.

Clinical Centers

The eight Clinical Centers participating in the SCDIC Registry represent academic and medical institutions and research teams that are multi-disciplinary in sickle cell disease, pediatrics and adult care, hematology, community-based research, and implementation science. The leadership at each Clinical Center is provided by the Principal Investigator (PI), who assumes responsibility for all aspects of the Center's participation in the Consortium and the Registry. Each Center provides care to patients from a wide geographic catchment area.

1. Augusta University
2. University of Illinois at Chicago and Sinai Health System
3. St. Jude Children's Research Hospital
4. Washington University School of Medicine
5. Icahn School of Medicine at Mount Sinai
6. Duke University

7. UCSF Benioff Children's Hospital Oakland
8. Medical University of South Carolina

4.3 Committees

The **Registry Committee** is responsible for developing the data collection forms and procedures that constitute the basis and content of the Registry. The Committee and DCC provide guidance for standardization of methods of data collections and the provision of common electronic data systems. The Registry Committee identifies individuals with requisite expertise in standardized data collection among the Clinical Centers and is empowered to draw upon those individuals' expertise when necessary. The Registry Committee monitors the Centers' progress in establishing the individual Center data collection protocols, enrollment of study subjects, and timely entry of clinical and patient-reported data.

The **Executive Committee** meets regularly to manage the day-to-day operations of the Consortium and to update the status and ensure timely completion of activities in Phase I and Phase II. The Executive Committee membership consists of an independent Steering Committee Chairperson, the NHLBI Program Officer, the Principal Investigator and Co-PI from the DCC and one investigator from a Clinical Center who serves on a 9-month rotating basis.

The **Steering Committee** is the governing body of the SCDIC and has primary responsibility for the scientific direction of the Consortium, including conduct of timely data collection for the Registry and dissemination of research findings through presentations and publications. The Steering Committee membership consists of one Investigator from each Clinical Center, the Principal Investigator from the DCC, and the NHLBI Program Officer. The Steering Committee Chairperson, who is not participating as a Principal Investigator, is appointed by the NHLBI.

The **Publications Committee** is responsible for prioritization, assignment, and the timely completion of all publications emanating from the scientific activities of the SCDIC. The Committee is the final arbiter of authorship disputes and facilitates the approval of all manuscripts prior to submission.

4.4 Project Website

The SCDIC website serves as a source of information for the public and the Consortium members. Its content will be closely monitored and kept up-to-date so that the most current information is available to visitors.

Public Website

The public side of the project website, http://scdic.rti.org, will be used most notably to disseminate information about the Registry to the research public. The public pages include 1) project description and rationale, 2) participating institutions and contact information, 3) links to project news, and (4) list of publications and copies of abstracts.

Private Website

The restricted area of the study website provides a secure, unified communication channel for all SCDIC activities and will consolidate access to the data capture and management systems, as well as maintain the repository of study documents. This ensures that all research staff have one place to access SCDIC information, enter data and track progress. Access to information will be authenticated for users based on the definition of study roles. These roles allow access only to those systems needed by a user to carry out the responsibilities of his/her role. Role-based access protects data confidentiality and security and increases data integrity.

5. ELIGIBILITY, RECRUITMENT AND INFORMED CONSENT

5.1 Inclusion and Exclusion Criteria

The SCDIC Registry will enroll at least 2,400 patients (300 per Center) who meet inclusion criteria in Phase I of the SCDIC program. Additional patients may be enrolled during Phase II. Women and children will be included in the SCDIC Registry to the extent that they exist in the population being studied and meet eligibility criteria set forth for study participation. In addition to parental/guardian consent, adolescent assent will be obtained from children 15-17 years of age, or as determined by the local IRB. Patients or guardians must agree to complete the Patient Enrollment Survey in order to be considered a Registry participant. Availability of medical records is not required for participation.

Inclusion Criteria

- Age 15 years up to and including 45 years
- English speaking
- Confirmed SCD diagnosis. Confirmed is defined as supported by documentation in the medical record of a positive test for one of the following: Hb SS, Hb SC, Hb Sβ-thalassemia, Hb SO, Hb SD, Hb SG, Hb SE, Hb SF. If no medical record is available, the enrolling Center may conduct its own laboratory test as confirmation.
- Willing and cognitively able to give informed consent and complete the Patient Enrollment Survey

Exclusion Criteria

- Unwilling or unable to give consent/assent or complete the Patient Enrollment Survey
- Sickle cell trait (i.e., Hb AS)
- Successful bone marrow transplant

5.2 Recruitment and Enrollment

Recruitment for the SCD Registry will occur at each participating Clinical Center as well as within its respective geographic catchment area. All recruitment materials will be approved by the Center IRBs, as appropriate, prior to implementation.

SCDIC Clinical Center infrastructure allows efficient access to the proposed study population. Eligible subjects may be identified and recruited in different ways. People may be contacted in person (e.g. in clinic, Emergency Department), by phone, or via electronic media (e.g. chat rooms, text) about enrolling in the study. Informed consent will occur in the following ways, with appropriate IRB approval:

1. In-person (e.g., in clinic or hospital, at SCD community events, in Emergency Departments, at home)
2. Mail
3. Telephone

The SCDIC Centers will enroll at least 2,400 eligible participants (at least 300 per center) who meet inclusion criteria for the Registry. A participant will be considered enrolled when consent is obtained and inclusion criteria have been confirmed. The SCDIC enrolling Center will maintain a local log of consented participants and will also confirm enrollment status in the data management system (DMS). SCDIC clinic staff will identify eligible patients using the eligibility criteria developed and approved by the Steering Committee. They will both screen their current patient population as well as identify new patients that attend the clinic. Eligible patients will be solicited during clinic visits according to protocols approved by the local IRB. Depending on the geographic area covered by the SCDIC, patients may also be recruited during outreach visits to outlying areas or through other outreach efforts within the community. This flexibility on the part of the SCDIC will

insure inclusion of the greatest number of eligible patients for the Registry, including patients not currently in care.

Screening, approaching, consenting and verifying eligibility of potential study participants will be conducted by designated study staff. If the patient (and parent/guardian of minors) agrees, the designated study staff will meet with the patient for a more comprehensive explanation of the Registry. If there is continued agreement, the designated study staff will proceed with the consent and enrollment process. Signed informed consent will be obtained prior to any data collection. Patients will receive a hard-copy of the completed and signed consent form to keep. Patients will be able to ask questions at any time. Literacy in English will be required of the consenting patient or parent/guardian. Adolescent assent will be obtained from children 15-17 years of age, or as determined by the local IRB. A signed HIPAA Research Authorization is also required of all participants.

Some Centers will provide Registry participants with monetary compensation for their time and participation in the Registry. The appropriate amount and schedule of payment(s) will be determined by local SCDIC Clinical Centers and approved by local IRBs.

5.3 Human Subjects and Informed Consent

No data collection activities will begin at an individual SCDIC participating Clinical Center until approvals from RTI and the Center IRBs have been granted. The SCDIC Clinical Centers and RTI will concurrently submit the protocol, consents, and data collection forms to their respective IRBs for review. The RTI IRB will focus on data security (receipt, storage, sharing, protection of breach) and defer to the Center IRBs for procedures related to direct patient interaction and those conducted locally. All participating SCDIC Clinical Centers and RTI have a Federal Wide Assurance issued through the US Office of Human Research Protections which assures that the organizations are complying with all federal regulations to protect research subjects.

Confidentiality of Data and Use of Identifying Information

Full names and other identifying information, excluding date of birth, will be retained only by the Centers. Participants' data will be labeled and stored with coded identification numbers that can be linked to names only by the corresponding Center. All collected data will be kept confidential to the extent permitted by law. The DCC will not be able to link an individual to their identifying information.

Risks and Benefits

The data collected for this Registry are from medical record abstraction and self-reported information. The patient surveys are not considered greater than minimal risk but may trigger uncomfortable feelings about one's lifestyle, quality of life or personal or family history of disease. There are no direct benefits to the participants in this Registry. Some patients may benefit from knowing that they are helping to advance knowledge for future patients with their condition.

Unbiased Recruitment

All eligible participants will be recruited without bias. Adolescents, women and minorities will be included as they represent the patient population of each Center.

Inclusion of Children

Children aged 15-17 will be included in the SCDIC Registry to the extent that they exist in the population being studied and meet eligibility criteria set forth for study participation. In addition to parental/guardian consent, adolescent assent will be obtained from children at 15-17 years of age, or as determined by the local IRB. The Center will also obtain a signed adult consent from minors who turn 18 years of age while participating in the Registry.

Inclusion of Women and Minorities

This Registry's selection criteria include all individuals that fit the inclusion criteria, without regard to sex, race, or ethnic group. We recognize the importance of having all eligible persons participate in this study, and we are particularly conscious of the need to include women and minorities in the study population. Sickle cell disease occurs in people with African ancestry or identify themselves as black, as well as people who come from Hispanic, southern European, Middle Eastern, or Asian Indian backgrounds. We expect the demographics of enrolled subjects to reflect the patient population seen by each Center. The DCC will monitor data collection to assure recruitment of women and minorities who meet eligibility criteria.

Rights of Refusal and Withdrawal

Patients will be free to refuse enrollment or withdraw from the study at any time. Participants may refuse to answer individual questions on the self-administered questionnaires. If they refuse the Patient Enrollment Survey entirely, they cannot be part of the Registry.

6. DATA COLLECTION

6.1 Overview

Patients enrolled in the SCDIC Registry will be assigned a unique identification number which will be used to identify them throughout the life of the Registry. The unique identification number scheme will be developed by the DCC and will be Center specific. The identification number will be assigned by the designated study staff after a patient provides consent to participate in the Registry. The link between the patient and the associated identification number will remain at the enrolling Center under restricted access. Required forms for all enrolled participants include the Patient Enrollment Survey and at least the first half page of the Enrollment Medical Record Abstraction Form. The remaining Enrollment Medical Record Abstraction Form and the Enrollment Laboratory Form will be completed on those with available medical records. Participants may refuse to answer some of the Patient Enrollment Survey questions but not the entire form to be considered enrolled in the Registry. Follow-up data will be collected in Phase II.

6.2 Enrollment Data

After assent or consent is obtained and enrollment is confirmed, collection of data can begin. Several data forms will be completed. They include:

1. Patient Registration Form (completed for all subjects)
2. Patient Enrollment Survey (completed by all enrolled participants)
3. Enrollment Pregnancy and Conception Form [Female and Male versions] (completed by all enrolled and willing participants)
4. Enrollment Medical Records Abstraction Form (completed for all enrolled subjects, with only limited data for those without available medical records)
5. Enrollment Laboratory Reporting Form (completed if medical records are available)

6.2.1 Patient Registration Form

This form is completed by the study coordinator after signed informed consent or assent has been obtained and the eligibility criteria for enrollment has been confirmed. This form provides basic patient demographics and geocode. It is the first form entered in the DMS for all new subjects and creates a record of all subjects in the SCDIC Registry. The Registry is interested in enrolling a cross-section of people with sickle cell disease who receive and do not receive regular medical care for their condition. To identify these people, the form collects additional information from subjects to ascertain unaffiliated patients and patients receiving care. Unaffiliated patients are those who have NOT been seen by a sickle cell provider (non-acute setting) as an outpatient in the past two years (for new patients, this excludes the visit during which they were enrolled).

6.2.2 Patient Enrollment Survey

This is a self-administered form to be completed by the participant, either as self-administered or interviewer administered. It provides baseline information about the patient's health at the time of enrollment. Completion of this form will provide demographic and diagnosis information, pain experience, social and mental health information, transfusion history and treatment. Patients may refuse to answer some of the questions but not the entire form. The survey may be taken home for completion, but every effort should be made to have the patient complete it in the enrollment setting (clinic, community).

6.2.3 Enrollment Pregnancy and Conception Form

This is a self-administered form to be completed by the participant, either as self-administered or interviewer administered. Completion of this form will provide information about the pregnancy and conception history of the participant at the time of enrollment, including information about each live birth. There are different

versions for female and male participants. The survey may be taken home for completion, but every effort should be made to have the patient complete it in the enrollment setting (e.g. clinic, community).

6.2.4 Enrollment Medical Record Abstraction Form

This form will be completed to the extent possible by research staff for all enrolled participants. For those without available medical records, the first half page will record the method used to confirm the diagnosis and an indication that records are not available for review. For those with medical records available for review, the entire form will be completed with baseline information about the patient's medical history and health at the time of enrollment. Completion of this form will provide demographic and diagnosis information, anthropometric measurements, organ systems review, and treatment.

6.2.4.1 Transitioning Patients

The Registry is interested in identifying young adults with sickle cell disease who are transitioning from pediatric to adult care. Some of these patients do not seek adult care and become unaffiliated. Clinic staff will provide additional information on transition of care from patient medical records for people age 15-25 at the time of enrollment. Those that are unaffiliated may be recruited for an implementation research study targeted at this population.

6.2.4.2 Supplemental Medical Record Abstraction Forms

Additional data may be collected for enrolled subjects based on select conditions reported on the Enrollment Medical Record Abstraction Form. The two supplemental forms will collect additional data from medical records and be completed for select subjects.

Cardiology and Pulmonary Supplemental Form

This form is completed for enrolled subjects who have either pulmonary hypertension or LV dysfunction reported on the Enrollment Medical Record Abstraction Form. It collects data from medical records about recent procedures to assess the subject's heart function.

Renal Supplemental Form

This form is completed for enrolled subjects who have chronic kidney disease or end stage renal disease reported on the Enrollment Medical Record Abstraction Form. It collects data from medical records about albuminuria, proteinuria, estimated GFR, end stage renal disease, and other medical conditions.

6.2.5 Enrollment Laboratory Reporting Form

This form will be completed by research staff for all enrolled participants for whom medical records and/or laboratory records are available at the time of enrollment. All test results recorded are the most recent at the time the patient was in steady state. The Enrollment Laboratory Reporting Form will not be completed if no laboratory data is available for when the patient was last in steady state.

6.2.6 Data Capture

Completed forms will be keyed by the Center coordinator into a secure web-based data entry system accessible through the project website. RTI will monitor the promptness of data entry and quality of data on an ongoing basis, working closely with SCDIC research staff to address any problems with data collection.

6.3 Follow-up Data

The Registry will collect follow-up data in Phase II, including annual patient surveys, data from patients' medical records, and vital status at the end of the study.

Enrolled patients will be asked to complete self-reported questionnaires annually. Patients will complete the annual Patient Follow-Up Survey and provide get information about their current pain, medical conditions, medication use, barriers to care and their social and mental health. Patients will complete the annual Follow-Up Pregnancy and Conception Form. Questions on the Patient Follow-Up Survey and Follow-Up Pregnancy and Conception Form are a subset of those on the Patient Enrollment Survey and Enrollment Pregnancy and Conception Form.

The Registry will also obtain data from the subject's medical records once during Phase II which covers the period between enrollment and the second time the records are abstracted.

6.4 Coordinator Training

To ensure consistent and standardized data collection across the 8 Centers and affiliated sites, the DCC will develop and implement a training program for the research coordinators based on the training manual and manual of operations. This training will be either web-based and will review the detailed instructions on subject enrollment, study procedures, data collection, and data management procedures. Specifically, the training will include:

- Purpose of study
- Enrollment criteria (inclusion/exclusion)
- Strategies for outreach and enrollment
- Completion and editing of hardcopy forms
- Question by question specifications
- Review of the data entry and data management systems
- Privacy and data security policies
- Abstraction of information from medical records
- Communications with the DCC
- Data entry and access to monitoring reports

If there is attrition, the DCC will train new study coordinators as necessary. In addition to DCC training, each site is responsible for providing supervision and oversight of the local Registry coordinators and assuring quality control of data collected including review and sign-off of record abstractions and a 10% reabstraction.

7. DATA MANAGEMENT

7.1 Overview

There are complexities in handling data from multiple centers. Data management and quality control systems will be implemented to ensure the timely receipt of all clinic data and resolutions of data discrepancies and duplications.

7.2 Data Management System

Data will be entered into a password protected, secure web-based data management (DMS) system. Within this system, the DCC will build in edit, range and validity checks on the data as they are being entered. In addition to data entry, the DMS will allow SCDIC staff to produce data management reports to monitor their performance. The DCC will train Center staff in data collection and management in accordance with the protocol and manual of operations.

To monitor enrollment, data flow, delinquent data, and data quality, the DCC project managers will run reports that monitor the performance of the individual Centers. These reports will also be distributed and reviewed regularly by the Center staff and the Executive and Steering Committees. The reports will show the number of patients enrolled, the number and type of forms submitted through the DMS, the number of incomplete and delinquent forms, and the number of unresolved data edits. The DCC will collaborate with the Center staff to design reports that are helpful in monitoring the conduct of the study and producing high quality data for analysis.

7.3 Data Edits

Quality control checks will be programmed into the web-based entry system developed for collection of data from Centers. Checks for internal consistency with respect to dates, acceptable ranges, required items, and skip patterns will be set up as validation at the time of data entry. In batch, the data will undergo additional automated, electronic edits that could not efficiently be included in the data entry screens, such as cross-form editing. Edit checks that are performed in real time will be replicated by the DCC in batch. In addition, complex within-form and across-form consistency and logic checks will be applied at the DCC. These checks will be based upon the specifications appropriate to each of the data collection forms. Any failures will be reported to the Center as error resolution reports. Center personnel will enter the corrections for the keyed data into the electronic file, and an audit trail of corrections will be maintained. The error resolution will be done online via the data entry system or externally, using an MS Excel or MS Access database file format.

7.4 Monitoring Reports

To monitor enrollment, data flow, delinquent data, and data quality, reports will be generated regularly from the accumulating database at the DCC and distributed to Center staff and the Executive and Steering Committees. Reports will show the number of patients enrolled by diagnosis at each Center, as well as the number and type of forms received by the DCC, the number of delinquent forms, and the number of unresolved data edits. The DCC will collaborate with the Center coordinators and investigators to design reports that are meaningful and assist in monitoring the conduct of the study and producing high quality data for analysis.

8. STATISTICAL ANALYSIS

8.1 Overview

The SCDIC Registry cohort will consist of approximately 2,400 patients with confirmed sickle cell disease. In general, the analyses of the Registry data will be descriptive and exploratory in nature and are for hypothesis-generating rather than hypothesis testing. With a sample size of 2,400, there is sufficient power to detect differences among treatment or outcome groups. The SCDIC Registry will also be used as a resource for identification of well-characterized patients for the implementation research studies to be conducted in Phase II.

The Registry research questions can be summarized into the following categories: 1) Treatment, 2) Comorbidities and Complications, 3) Quality of Life, and 4) Access to Care. Additional new research questions may be developed as the Registry progresses.

8.2 Primary Outcomes

There will be several outcomes of interest for the Registry depending on the analysis. Outcomes of interest are the use and compliance to hydroxyurea therapy, pain and pain treatment, and prevalence of comorbidities related to SCD.

8.3 Approach to Analysis

Patients enrolled in the Registry will be characterized by their demographics (e.g. age, gender), clinical conditions, treatment procedures, and self-reported health status. Categorical or ordinal variables such as conditions and treatments will be summarized by frequency distribution. Continuous variables such as blood chemistry results will be summarized by mean, median, standard deviation, minimum and maximum value. Outliers and possible data errors will be detected for further formal statistical analysis.

Regression methods may be used to examine the relationship between specific factors and an outcome of interest while controlling for potential confounding factors. According to the nature or measurement of outcome variables, linear regression, logistic regression, multinomial logistic regression, or time-dependent covariate analysis, such as Cox proportional hazards will be performed. Random effects models may also be used because the Registry is conducted through multiple Clinical Centers. Outcome variables such as disease severity or use of hydroxyurea may vary by site because of recruitment procedures or physician practice. Ignoring this effect in the regression analysis may result in underestimated standard errors of parameter estimates.

There is a likelihood of missing data which can seriously affect the results. Ignoring missing data, or assuming that excluding missing data is sufficient, will increase the risk of reaching invalid and insignificant results. Also, missing data may reduce the precision of calculated statistics because there is less information than originally planned. Another concern is that the assumptions behind many statistical procedures are based on complete cases, and missing values can complicate the theory required. We will review mean, standard deviation, frequencies, number of missing and non-missing values, number of extreme values for all variables to understand the missing data. We will conduct missing value analysis to find if the cases with missing values are systematically different from cases without missing values. Based on our initial missing value analysis, we will employ appropriate ad-hoc imputation methods (such as, last observation carried forward, minimum value replacement, maximum value replacement, estimates based on different regressing models) or multiple imputations to impute the missing values.

8.4 Statistical Methods

Statistical analysis of the Registry data will require a variety of methods. Different statistical techniques will be employed to answer specific research questions. The selection of statistical methods will be based on the research question and the type of outcome variables used (categorical or continuous). The following are a few examples of statistical methods we will use to explore the specific type of scientific relationship between variables.

Descriptive and Bivariate Analyses

Descriptive analysis will be performed to examine the distribution of data and detect possible error. To explore the crude association of an outcome variable with a single factor we will use bivariate analysis. Selection of statistical methods will depend on the measurements of two variables. Cross-tabulation will be used when both variables are categorical. Chi-square, or Fisher's exact test in the case of sparse cells, will be performed to test the significance of the associations. T-test and analysis of variance (ANOVA) will be used to compare continuous variables such as age, number of transfusions and lab values among different outcomes. Simple correlation coefficient may be used to describe the association between two continuous or interval variables such as age and pain severity.

Regression Analysis

To examine the relationship between a continuous outcome of interest and a group of factors that may be significantly associated with that outcome variable, multiple linear regressions will be used. Multiple regression will also be used to test the relationship between outcome variables while controlling for potential confounding factors. Logistic regression will be used to analyze binary outcomes, such as whether an individual patient was using hydroxyurea and whether the patient experienced certain comorbidities. Logistic regression will be used to analyze those binary outcomes in relation to predictors such as insurance status, gender, barriers to care, age, pain severity and measures of quality of life. Multinomial logistic regression will be used to analyze categorical outcomes such as type of stroke and transfusion.

Time to Event Analysis

To analyze the survival type data, also known as time to event(s) data, we will use Kaplan-Meier survival analysis. To examine the relative risk for specific factors while adjusting for other covariates and potential confounding factors we will use Cox-proportional hazard model. If the proportional hazard assumption isn't valid for the Cox model, we will use Exponential regression and Weibull regression. If the survival or failure data have multiple failure events, then we will use Multiple decrement life table analysis to calculate the cumulative incidence rate.

Other advance statistical analysis methods such as Mixed models, GEE, competing risk survival model, factor analysis, principal component analysis, and discriminant analysis may be also employed to answer scientific questions utilizing the Registry data. Analyses will mainly be implemented using SAS and other statistical packages such as R, Stata, and MLwin.

9. DATA USE AND DISSEMINATION

9.1 Overview

Sharing of research data expedites the translation of research results into knowledge and procedures to improve human health. Data from well-characterized population samples constitute an important scientific resource. It is the view of the NHLBI that their full value can only be realized if they are made available, under appropriate terms and conditions consistent with the informed consent provided by individual participants, in a timely manner to the largest possible number of qualified investigators. The definition of "timely release and sharing" is three years after the completion of the enrollment phase of the study. Ancillary studies conducted concurrently with the Registry must also abide by the Data Sharing Policy.

9.2 Data Sharing Policy

The primary goal of the SCDIC Registry is to establish a data repository that will be shared with Registry investigators and qualified researchers outside the Registry interested in studying additional aspects of SCD that are not being addressed by this protocol. De-identified patient-level data will be made available to researchers outside the Registry through an application and approval process as part of the study's Ancillary Studies Policy and Data Dissemination Plan. To protect the confidentiality and privacy of the subjects, investigators granted access to the limited access data and biologic specimens must adhere to strict requirements incorporated into a standard Data Use Agreement. In accordance with NHLBI policy, outside researchers will also be required to submit an approval from their Institutional Review Board (IRB).

9.3 Ancillary Studies Policy

An ancillary study is one that proposes to use the existing data or to collect new data and derives support from funds other than the SCDIC Cooperative Agreement. The Ancillary Studies Committee will develop a policy for the submission, review and approval of ancillary studies. SCDIC investigators are encouraged to consider ancillary studies and to involve other investigators within their institutions in this process. Ancillary study proposals will also be considered from non-SCDIC investigators and institutions.

APPENDICES

Appendix A **Adult Consent Form Template**

Appendix B **Patient Registration Form**

Appendix C **Patient Enrollment Survey**

Appendix D **Pregnancy and Conception Form – Female**

Appendix E **Pregnancy and Conception Form – Males**

Appendix F **Medical Record Abstraction Form**

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Appendix I **Laboratory Reporting Form**

APPENDIX A: ADULT CONSENT FORM TEMPLATE

SICKLE CELL DISEASE IMPLEMENTATION CONSORTIUM (SCDIC) REGISTRY
ADULT INFORMED CONSENT FORM TEMPLATE

Name of Study
Sickle Cell Disease Implementation Consortium (SCDIC) Patient Registry

Sponsors
National Heart, Lung and Blood Institute (NHLBI) and National Institute for Minority Health and Health Disparities (NIMHD)

Invitation to take part in research
You are being asked to participate in a research study titled "Sickle Cell Disease Implementation Consortium (SCDIC) Registry" (the "Registry") because you have been diagnosed with sickle cell disease. The SCDIC is a group of clinical centers working together to identify and address outcomes related to sickle cell disease and obstacles that some patients may experience with receiving appropriate care for their sickle cell disease. The SCDIC also includes a data coordinating center that will receive the data and help analyze it.

Why is this study being done?
The Registry will collect information on the medical history, management and access to care for people with sickle cell disease. The Registry will enroll over 2,400 people from across the country who have sickle cell disease. This information will help to better understand the medical and quality of life issues of people with sickle cell disease.

What will be done in this study?

Collection of Medical Chart Information
We will collect information from your medical records. Members from the study team will review your medical record and will record demographic information, physical exam findings, medication use, hospital admissions, laboratory test results, and other evaluations. Your records will be reviewed when you enroll and then they may be reviewed once or twice a year over the next six years or when the funding for the Registry ends.

Quality of Life and Reproductive Health Questionnaires
At enrollment, you will be asked to complete a survey which asks questions about your medical history, use of medicines, transfusions, quality of life and pregnancies or fatherhood. These questions will take about 30 minutes of your time. You have the right to refuse to answer any or all the questions. You may be asked to complete one or two additional surveys each year over the next six years or when the funding for the Registry ends. These surveys may be given to you in person or mailed to your home.

How could I benefit from being in this study?
You might not benefit directly from this study. However, a possible benefit of this study is the improvement of care and health outcomes for individuals and families living with and affected by sickle cell disease.

Will researchers tell me if they learn something new that may affect my decision to participate?

You will be informed of any new findings, such as changes to the risks or benefits, or new alternatives to participation, that might cause you to change your mind about continuing in the study.

What are my other choices if I do not take part in this study?
Your choices are either to participate in the study or not participate in the study. If you choose not to participate, it will not affect your medical care at this institution in any way.

Will I be paid for enrolling in this study?
[**ALT WORDING, MAY VARY BY CENTER**: You will not receive payment for taking part in this study. / You will be paid $XX for enrolling in this study.] There is no cost to you for participating in this study.

Future Contacts
A Registry team member may contact you about once a year to verify that we have your most current contact information, including your address and telephone numbers.

We would like your permission to invite you to participate in other research studies in the future that you are eligible for. You would have the opportunity to learn more about any other studies before you agree to participate. Please check one of the boxes below

I agree to be contacted for future research studies: ❒ Yes ❒ No

Can I stop taking part in the study?
You may withdraw from the study at any time. If you decide to stop being in the study, please contact the research staff. If you do leave the study, you will still receive the same services and care you normally would.

What are the possible risks or discomforts?
There is the risk for loss of privacy of your personal information. However, to avoid this from happening we will:

- Assign a unique code number to your data before it is sent to the data coordinating center.
- Only allow members of the study team to see your medical records.
- Store electronic data only on computers protected with a password and encryption software.
- Report study results on the whole group and never identify one single person in any reports.

Who will see my research records and medical information?
Only information needed for the study is recorded by the study staff under the direction of the Principal Investigator. Your study data will be sent to the data coordinating center at RTI International through a secure website. The website is protected by a login and password and secure socket layer (SSL) technology. This technology scrambles the data as it is being keyed, and is the industry standard for protecting personal information during transfer.

We will keep your medical records private to the degree allowed by law. Your health data, without identifiers, may be given to other investigators for other research projects not listed in this form. We will not identify you personally in any text published from this study, nor will your personal information ever be used in any published report.

The study information will be kept in your research record indefinitely. Research information from this study will be kept in a research file and will not intentionally be placed in the official medical records by

research staff. Research data from which you may be identified will not be given or sold to third parties except with your permission or as required by law.

Confidentiality

Study records that identify you will be kept confidential as required by law. Federal privacy regulations provided under the Health Insurance Portability and Accountability Act (HIPAA) provide safeguards for privacy, security, and authorized access of your records. This includes such things as your name, full address, telephone number, medical record number, insurance number or social security number. These regulations require participating institutions to obtain an authorization from you for the use and disclosure of your protected health information. By signing this consent form, you are authorizing the use and disclosure of your protected health information for completing the research study. As part of this study, the Principal Investigator, study team and others at INSERT NAME OF INSTITUTION may disclose your protected health information to the following people or organizations:

- Other research centers collaborating with us on this project;
- RTI International and/or their representative(s) who are responsible for collecting data from all the centers;
- The sponsoring government agency and/or their representative who need to confirm the accuracy of the results submitted to the government or the use of government funds;
- A Data Safety Monitoring Board or other committee that will monitor the study on an ongoing basis for safety; and
- The United States Department of Health and Human Services and the Office of Human Research Protection.

For data disclosed to those institutions listed above, you will not be identified by your name, social security number, full address, phone number or any other direct personal identifier unless disclosure of the direct identifier is required by law. Your data will be identified only by a unique code number (subject ID). The key to the code will be kept in a password-protected database on an internal server at INSERT NAME OF INSTITUTION.

Your data may be requested for research by Principal Investigators who are not part of this study. In these instances, your data will be de-identified, which means that there is link between you and your data.

At the end of this study, all data will be de-identified so that there are no direct personal identifiers remaining. The de-identified data will be stored at the NHLBI data repository or other NIH data storage facility. Your data will also be stored at the center at which you were enrolled.

If you sign this form, you are giving us permission to collect, use, and share your protected health information. If you decide not to let us collect, use and share your protected health information, you should not sign this form and you cannot be in the registry. Your decision to participate or not participate in this study will not affect the care you receive here.

This authorization for the use and disclosure of your health information as described above expires upon the conclusion of the research study.

Contact Person(s)

If you have any questions, concerns, or complaints at any time about this research study, please contact any member of the research team and/or [NAME OF PRINCIPAL INVESTIGATOR] at [PRINCIPAL INVESTIGATOR PHONE NUMBER (after normal office hours at PHONE NUMBER). ADD IN ANY ALTERNATE CONTACT DETAILS.

STATEMENT OF CONSENT

I have read this document or it was read to me. I have been giving an opportunity to ask questions and all my questions have been answered to my satisfaction. I agree to participate in this research study and to the use and disclosure of my health information for the research. I will be given a copy of this signed and dated form.

_____	_____
Printed name of participant	Date
_____	_____
Signature of participant	Time
_____	_____
Printed name of legally authorized representative *(if applicable)*	Date
_____	_____
Signature of legally authorized representative *(if applicable)*	Time
_____	_____
Printed name of person obtaining consent	Date
_____	_____
Signature of person obtaining consent	Time

(My signature indicates that I was present during the informed consent process and signing of this form and that informed consent was given freely by the participant or their legally authorized representative.)

APPENDIX B: PATIENT REGISTRATION FORM

Patient Registration Form

Version 2 (7/2/2018)

Subject ID Label

By entering this form into the DMS, you are entering this subject into the SCDIC Registry database. The REDCap survey is accessible after the SCD diagnosis status is entered. Demographics should be completed for eligible subjects only.

Registration Checklist:

- ☐ The subject provided signed consent to participate in the Registry on _____.
  (DATE)
  - ☐ Assent form signed (minors only)
- ☐ The subject completed the patient survey via the following mode (check one):
  - ☐ Interview; hard copy
  - ☐ Interview; online entry
  - ☐ Interview: phone
  - ☐ Self-administered; hard copy
  - ☐ Self-administered; online entry

Diagnosis Status:

- ☐ Confirmed (with documentation) by newborn screening, hemoglobin fractionation, hemoglobin electrophoresis or DNA sequencing
- ☐ Pending – DO NOT ENTER DEMOGRAPHICS INTO DMS UNTIL CONFIRMED
- ☐ Unable to Confirm, subject not eligible – FORM COMPLETE

*******PATIENT SURVEY IS NOW ACCESSIBLE IN REDCap*******

Subject Demographics for Confirmed Diagnoses Only:

1. Date of birth |___|___|/|___|___|/|___|___|___|___|
   (mm/dd/yyyy)
2. Race (check all that apply)
   - ☐ American Indian or Alaska Native
   - ☐ Asian
   - ☐ Black or African American
   - ☐ Native Hawaiian or Pacific Islander
   - ☐ White
3. Ethnicity (check one)
   - ☐ Hispanic or Latino
   - ☐ Not Hispanic or Latino
4. Sex
   - ☐ Male
   - ☐ Female
5. Zip code of primary residence |___|___|___|___|___|

Unaffiliated patients have NOT been seen by a sickle cell provider (non-acute setting) as an outpatient in the past 2 years [for new patients, this excludes the visit during which they were enrolled].

6. Is this patient unaffiliated?
   - ☐ Yes
   - ☐ No

APPENDIX C: PATIENT ENROLLMENT SURVEY

Patient Enrollment Survey

Version 1.1 (11/28/2017)

Subject ID

We are interested in learning more about people who have sickle cell disease. As you complete this form, answer the questions as best as you can. If you don't know the answer or do not want to answer a question, you may leave it blank.

1. What is today's date? |__|__|/ |__|__|/ |_2_|_0_|___|___|
   Month Day Year

2. What is your year of birth? |___|___|___|___|
   Year

3. How old are you today? _____ years

4. How old were you when you were diagnosed with sickle cell disease? |___|___| years

5. What type of healthcare professional has been providing the majority of care for your sickle cell disease in the past 2 years?
   - ❒ Sickle cell specialist or hematologist (including all care providers in the SCD clinic)
   - ❒ Primary care or general practice
   - ❒ Emergency department
   - ❒ I don't currently receive care for my sickle cell disease

A. YOUR PAIN HISTORY

6. Do you take pain medicine every day for your sickle cell disease?
   - ❒ Yes
   - ❒ No

7. In the past 12 months, how many sickle cell pain attacks (crises) did you have?
   - ❒ I did not have a pain attack in the past 12 months
   - ❒ 1
   - ❒ 2
   - ❒ 3
   - ❒ 4 or more

8. When was your last pain attack (crisis)?
   - ❒ I've never had a pain attack (crisis)
   - ❒ More than 5 years ago
   - ❒ 1-5 years ago
   - ❒ 7-11 months ago
   - ❒ 1-6 months ago
   - ❒ 1-3 weeks ago
   - ❒ Less than a week ago
   - ❒ I have one right now

9. How severe was your pain during your last pain attack (crisis)? **Circle a number from 0 to 10 below**, where 0 is no pain and 10 is the worst pain imaginable.

0	1	2	3	4	5	6	7	8	9	10

No pain Worst pain imaginable

10. How much did your last pain attack (crisis) interfere with your life?

- ❒ I've never had a pain attack (crisis)
- ❒ Not at all, I did everything I usually do
- ❒ I had to cut down on some things I usually do
- ❒ I could not do most things I usually do
- ❒ I could not take care of myself and needed some help from family or friends
- ❒ I could not take care of myself and needed constant care from family, friends, doctors, or nurses

11. About how long did your most recent pain attack (crisis) last?

- ❒ I've never had a pain attack (crisis)
- ❒ Less than 1 hour
- ❒ 1-12 hours
- ❒ 13-23 hours
- ❒ 1-3 days
- ❒ 4-6 days
- ❒ 1-2 weeks
- ❒ More than 2 weeks

12. Think about your pain in the **past 7 days**, and answer the following questions.

		Never	Rarely	Sometimes	Often	Always
a.	How often did you have very severe pain?	❒	❒	❒	❒	❒
b.	How often did you have pain so bad that it was hard to finish what you were doing?	❒	❒	❒	❒	❒

13. Now think about your pain in the **past 6 months**, and answer the following questions.

		Never	Rarely	Sometimes	Often	Always
a.	How often did you have very severe pain?	❒	❒	❒	❒	❒
b.	How often did you have pain so bad that it was hard to finish what you were doing?	❒	❒	❒	❒	❒

14. Think about how your pain felt in the **past 7 days**, and answer the following questions.

		Not at all	A little bit	Somewhat	Quite a bit	Very much
a.	Did your pain feel like pins and needles?	❒	❒	❒	❒	❒
b.	Did your pain feel sore?	❒	❒	❒	❒	❒

B. YOUR HISTORY OF HYDROXYUREA USE

15. Did a doctor **ever** suggest you take hydroxyurea?

- ❒ Yes
- ❒ No

16. What makes it difficult for you to take hydroxyurea or is there a reason why you do not take hydroxyurea? Please select one or more from the list below whether or not you have ever taken hydroxyurea.

- ❒ I have no difficulties or concerns using hydroxyurea
- ❒ I don't know enough about the medicine
- ❒ Sometimes I forget to take the medicine
- ❒ I am worried about side effects
- ❒ I don't like the frequent blood tests or clinic visits
- ❒ I'm feeling well and I don't think I need it
- ❒ The cost is more than I can afford
- ❑ I have heard that hydroxyurea may cause cancer
- ❑ I have heard that hydroxyurea may cause problems with having healthy children
- ❒ Other difficulty, specify_____

17. Have you **ever** taken hydroxyurea?

- ❒ Yes
- ❒ No → ***skip to Question 23***

18. Have you experienced any side effects related to hydroxyurea?

- ❒ Yes
- ❒ No → ***skip to Question 20***

19. What side effects have you experienced while you were taking hydroxyurea?

- ❒ Hair loss/thinning
- ❒ Nail blackening or discoloration
- ❒ Lowered blood counts (e.g., platelets, white count, hemoglobin)
- ❒ Low sperm count or other fertility problems
- ❒ Nausea/vomiting
- ❒ Skin ulcers
- ❒ Weight gain
- ❒ Headaches or dizziness
- ❒ Fatigue/drowsiness
- ❒ Other, specify_____

20. Are you **currently** on hydroxyurea?

- ❒ Yes
- ❒ No → ***skip to Question 22***

21. How many days did you take hydroxyurea in the PAST WEEK?

- ❒ 0 days
- ❒ 1 day
- ❒ 2 days
- ❒ 3 days
- ❒ 4 days
- ❒ 5 days
- ❒ 6 days
- ❒ 7 days

Skip to Section C, Question 23 after answering this question

22. What is the reason you discontinued or stopped taking hydroxyurea?

- ❒ Side effects
- ❒ Yours/your family's preference
- ❒ Other reason, specify_____

C. YOUR HISTORY OF BLOOD TRANSFUSIONS

23. Do you get regular blood transfusions for your sickle cell disease?

- ❒ Yes
- ❒ No

24. Estimate the number of units (pints) of blood that you have **ever** received.

- ❒ none
- ❒ 1 to 10
- ❒ 11 to 20
- ❒ 21 to 50
- ❒ 50-100
- ❒ more than 100
- ❒ Don't Know

25. Are you on iron chelation treatment **at this time**?

- ❒ Yes
- ❒ No

26. Have you **ever** been told that it is difficult to find blood for you (i.e., you have antibodies or react to other people's blood red blood cells)?

- ❒ Yes
- ❒ No
- ❒ Don't Know

27. Have you **ever** been referred for a bone marrow transplant?

- ❒ Yes
- ❒ No

D. YOUR MEDICAL HISTORY

28. Has a doctor or nurse ever told you that you have or had any of the following conditions? Please check YES or NO for each condition.

	Condition	**YES**	**NO**
a.	Lung problems such as pneumonia or acute chest syndrome	❒	❒
b.	Kidney damage	❒	❒
c.	Eye damage called retinopathy	❒	❒
d.	Damage to your hip or shoulder due to sickle cell disease	❒	❒
e.	High blood pressure in your lungs (also called pulmonary hypertension)	❒	❒
f.	Heart failure	❒	❒
g.	Blood clots in your legs or arms or that went to your lung	❒	❒
h.	A stroke	❒	❒
i.	Asthma	❒	❒
j.	Diabetes	❒	❒

29. Have you ever had open sores on your legs or feet (leg ulcers)?

- ❒ Yes
- ❒ No

30. Has your spleen either been removed or seriously damaged due to sickle cell disease?

- ❒ Yes
- ❒ No

E. MEDICATIONS YOU ARE TAKING AT THE PRESENT TIME

31. Please list all medications you are **currently** taking.

Name of Medication	Name of Medication
1.	6.
2.	7.
3.	8.
4.	9.
5.	10.

F. BARRIERS TO YOUR MEDICAL CARE

32. During the past 12 months, was there any time when you didn't get the medical care you needed or had delays in getting the care you needed?

- ❒ Yes
- ❒ No → ***skip to Question 34***

33. Did you not get the medical care you needed or have delays getting medical care you needed for any of the following reasons?

- ❒ Worry about the cost
- ❒ The doctor or hospital wouldn‘t accept your health insurance
- ❒ Your health plan wouldn‘t pay for the treatment
- ❒ You couldn‘t get an appointment soon enough
- ❒ You couldn‘t get there when the doctor‘s office or clinic was open
- ❒ It takes too long to get to the doctor‘s office or clinic from your house or work
- ❒ You couldn‘t get through on the telephone
- ❒ You were too busy with work or other commitments to take the time
- ❒ You didn‘t think the problem was serious enough
- ❒ You had previous bad experiences with the health care system
- ❒ People at the doctor’s office or clinic don’t speak the same language I do
- ❒ Some other reason not listed above, please specify _____

G. YOUR SOCIAL AND MENTAL HEALTH

34. Think about your sleep in the **past 7 days**, and answer the following questions.

		Never	Rarely	Sometimes	Often	Always
a.	How often did you stay up most of the night because you could not fall asleep?	❒	❒	❒	❒	❒
b.	How often did you have a lot of trouble falling asleep?	❒	❒	❒	❒	❒

35. In the **past 7 days**, how often did the following happen?

		Never	Rarely (Once)	Sometimes (2-3 times)	Often (once a day)	Very often (several times a day)
a.	I had to read something several times to understand it.	❒	❒	❒	❒	❒
b.	My thinking was slow.	❒	❒	❒	❒	❒
c.	I had to work really hard to pay attention or I would make a mistake.	❒	❒	❒	❒	❒
d.	I had trouble concentrating.	❒	❒	❒	❒	❒

36. How much DIFFICULTY do you **currently** have doing the following things?

		None	A little	Somewhat	A lot	Cannot do
a.	Reading and following complex instructions (e.g., directions for a new medication)?	❒	❒	❒	❒	❒
b.	Planning for and keeping appointments that are not part of your weekly routine (e.g, a therapy or doctor appointment, a social gathering with friends or family)?	❒	❒	❒	❒	❒
c.	Managing your time to do most of your daily activities?	❒	❒	❒	❒	❒
d.	Learning new tasks or instructions?	❒	❒	❒	❒	❒

37. Think about how you felt in the **past 7 days**, and respond to each question or statement.

		Never	Rarely	Sometimes	Often	Always
a.	I felt worthless.	❒	❒	❒	❒	❒
b.	I felt helpless.	❒	❒	❒	❒	❒
c.	I felt depressed.	❒	❒	❒	❒	❒
d.	I felt hopeless.	❒	❒	❒	❒	❒
e.	How often did you feel completely hopeless because of your health?	❒	❒	❒	❒	❒
f.	How often were you very worried about needing to go to the hospital?	❒	❒	❒	❒	❒
		Not at all	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
g.	I felt tired.	❒	❒	❒	❒	❒

38. Have you ever been treated for depression?

- ❒ Yes, currently receiving treatment
- ❒ Yes, treated in the past but not now
- ❒ No, never received treatment

39. In the **past 30 days**, how much did the following happen?

		Not at all	A little bit	Somewhat	Quite a bit	Very much
a.	How much did you rely on others to take care of you because of your health?	❒	❒	❒	❒	❒
b.	How much did your health make it hard for you to do things with your friends?	❒	❒	❒	❒	❒

H. TELL US ABOUT YOURSELF

40. Are you male or female?

- ❒ Male
- ❒ Female

41. Do you consider yourself Hispanic/Latino or not Hispanic/Latino?

- ❒ Hispanic or Latino
- ❒ Not Hispanic or Latino

42. Which of the following five racial designations best describes you? More than one choice is acceptable.

- ❒ American Indian or Alaska Native
- ❒ Asian
- ❒ Black or African American
- ❒ Native Hawaiian or Pacific Islander
- ❒ White

43. In what language do you feel most comfortable speaking with your doctor or nurse?

- ❒ English
- ❒ Spanish
- ❒ Another language

44. What is your current marital status?

- ❒ Not Applicable (subject is a child)
- ❒ Married
- ❒ Living as married (including living with a partner)
- ❒ Divorced or separated
- ❒ Widowed
- ❒ Never married

45. How many children and adults, including yourself, live in your household at least 4 nights a week?

_____ # of children _____ # of adults

46. What is your approximate yearly household income? Include income from all sources.

- ❒ $25,000 and under
- ❒ $25,001 - $50,000
- ❒ $50,001 - $75,000
- ❒ $75,001 - $100,000
- ❒ >$100,000

47. What is the highest grade or level of school you have completed or the highest degree you have received?

- ❒ Less than High School
- ❒ Some high school
- ❒ High school graduate or GED equivalent
- ❒ Some college or vocational training
- ❒ College graduate
- ❒ Some graduate school or professional school
- ❒ Graduate or professional degree

48. We would like to know about what you do -- are you working, looking for work, retired, keeping house, or what?

- ❒ Working now
- ❒ Only temporarily laid off, sick leave, or maternity leave
- ❒ Looking for work, unemployed
- ❒ Retired
- ❒ Disabled, permanently or temporarily
- ❒ Keeping house
- ❒ Student
- ❒ Other (Specify):_____

This is the END of the survey. Please return it to the study coordinator.
Thank you for your participation.

APPENDIX D: PREGNANCY AND CONCEPTION FORM – FEMALE

SUBJECT ID

PREGNANCY AND CONCEPTION FORM

For Females

Final Version 1.1, 11/28/2017

This form asks questions about pregnancies you have had.

1. Have you ever been pregnant?

   ☐ No → **SKIP TO QUESTION 13 ON THE BACK OF THIS FORM**
   ☐ Yes

2. How many times have you been pregnant? Please be sure to include any pregnancies that ended in a live birth, miscarriage, stillbirth, or abortion. Enter the total number on the line below.

   _____ total number of pregnancies in your lifetime

INSTRUCTIONS FOR PAGES 2-3:

As you answer the questions on the following 2 pages, please think about each of the pregnancies that you have had. Start with the earliest pregnancy, listing it in the first column labeled "1st pregnancy". From there, work forward until you have provided information about all of the pregnancies you listed in question 2 above. Then go to the back page and answer the remaining questions. Tell the study coordinator if you have had more than 6 pregnancies.

		1st pregnancy	2nd pregnancy	3rd pregnancy
3.	In what month and year did this pregnancy end (enter due date if currently pregnant)?	_____ / _____ Month / Year	_____ / _____ Month / Year	_____ / _____ Month / Year
4.	What was the outcome of this pregnancy?	☐ Live birth ☐ Still birth ☐ Miscarriage ☐ Abortion ☐ Currently pregnant	☐ Live birth ☐ Still birth ☐ Miscarriage ☐ Abortion ☐ Currently pregnant	☐ Live birth ☐ Still birth ☐ Miscarriage ☐ Abortion ☐ Currently pregnant
5.	Were you taking hydroxyurea at the time of conception (when the pregnancy started) or within the month before conception?	☐ No ☐ Yes ☐ Don't remember	☐ No ☐ Yes ☐ Don't remember	☐ No ☐ Yes ☐ Don't remember
6.	During this pregnancy were you taking hydroxyurea? *If yes, check all trimesters that apply or that you can remember.*	☐ No, did not take HU ☐ Yes, during 1st trimester ☐ Yes, during 2st trimester ☐ Yes, during 3rd trimester ☐ Don't remember	☐ No, did not take HU ☐ Yes, during 1st trimester ☐ Yes, during 2st trimester ☐ Yes, during 3rd trimester ☐ Don't remember	☐ No, did not take HU ☐ Yes, during 1st trimester ☐ Yes, during 2st trimester ☐ Yes, during 3rd trimester ☐ Don't remember
7.	Did you take any fertility drugs or receive any procedure from a health care worker to help you get pregnant with this pregnancy?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

**** Answer Questions 8 – 12 below only if the pregnancy ended in a live birth**

		1st pregnancy	2nd pregnancy	3rd pregnancy
8.	How many babies were born with this pregnancy?	_____ # of babies	_____ # of babies	_____ # of babies
9.	Was the baby (or babies) born prematurely?	☐ No, not born prematurely ☐ Yes → enter how many weeks of gestation _____	☐ No, not born prematurely ☐ Yes → enter how many weeks of gestation _____	☐ No, not born prematurely ☐ Yes → enter how many weeks of gestation _____
10.	Did any of the babies in this pregnancy weigh **less than 5.5 pounds** at the time of birth?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
11.	Did a doctor ever say a baby from this pregnancy had low birth weight, a birth defect, a genetic condition, or another serious medical problem related to birth?	☐ No ☐ Yes → What condition?	☐ No ☐ Yes→ What condition?	☐ No ☐ Yes→ What condition?
12.	Did you have any significant medical complications during this pregnancy? *Check all that apply*	☐ No complications ☐ Pain crisis ☐ Acute chest syndrome ☐ Preeclampsia ☐ Maternal diabetes ☐ Transfusion required ☐ Blood clots ☐ Other specify _____	☐ No complications ☐ Pain crisis ☐ Acute chest syndrome ☐ Preeclampsia ☐ Maternal diabetes ☐ Transfusion required ☐ Blood clots ☐ Other specify _____	☐ No complications ☐ Pain crisis ☐ Acute chest syndrome ☐ Preeclampsia ☐ Maternal diabetes ☐ Transfusion required ☐ Blood clots ☐ Other specify _____

		4th pregnancy	5th pregnancy	6th pregnancy
3.	In what month and year did this pregnancy end (enter due date if currently pregnant)?	_____ / _____ Month / Year	_____ / _____ Month / Year	_____ / _____ Month / Year
4.	What was the outcome of this pregnancy?	☐ Live birth ☐ Still birth ☐ Miscarriage ☐ Abortion ☐ Currently pregnant	☐ Live birth ☐ Still birth ☐ Miscarriage ☐ Abortion ☐ Currently pregnant	☐ Live birth ☐ Still birth ☐ Miscarriage ☐ Abortion ☐ Currently pregnant
5.	Were you taking hydroxyurea at the time of conception (when the pregnancy started) or within the month before conception?	☐ No ☐ Yes ☐ Don't remember	☐ No ☐ Yes ☐ Don't remember	☐ No ☐ Yes ☐ Don't remember
6.	During this pregnancy were you taking hydroxyurea? *If yes, check all trimesters that apply or that you can remember.*	☐ No, did not take HU ☐ Yes, during 1st trimester ☐ Yes, during 2st trimester ☐ Yes, during 3rd trimester ☐ Don't remember	☐ No, did not take HU ☐ Yes, during 1st trimester ☐ Yes, during 2st trimester ☐ Yes, during 3rd trimester ☐ Don't remember	☐ No, did not take HU ☐ Yes, during 1st trimester ☐ Yes, during 2st trimester ☐ Yes, during 3rd trimester ☐ Don't remember
7.	Did you take any fertility drugs or receive any procedure from a health care worker to help you get pregnant with this pregnancy?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

**** Answer Questions 8 – 12 below only if the pregnancy ended in a live birth**

		4th pregnancy	5th pregnancy	6th pregnancy
8.	How many babies were born with this pregnancy?	_____ # of babies	_____ # of babies	_____ # of babies
9.	Was the baby (or babies) born prematurely?	☐ No, not born prematurely ☐ Yes → enter how many weeks of gestation _____	☐ No, not born prematurely ☐ Yes → enter how many weeks of gestation _____	☐ No, not born prematurely ☐ Yes → enter how many weeks of gestation _____
10.	Did any of the babies in this pregnancy weigh **less than 5.5 pounds** at the time of birth?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
11.	Did a doctor ever say a baby from this pregnancy had low birth weight, a birth defect, a genetic condition, or another serious medical problem related to birth?	☐ No ☐ Yes → What condition?	☐ No ☐ Yes→ What condition?	☐ No ☐ Yes→ What condition?
12.	Did you have any significant medical complications during this pregnancy? *Check all that apply*	☐ No complications ☐ Pain crisis ☐ Acute chest syndrome ☐ Preeclampsia ☐ Maternal diabetes ☐ Transfusion required ☐ Blood clots ☐ Other specify _____	☐ No complications ☐ Pain crisis ☐ Acute chest syndrome ☐ Preeclampsia ☐ Maternal diabetes ☐ Transfusion required ☐ Blood clots ☐ Other specify _____	☐ No complications ☐ Pain crisis ☐ Acute chest syndrome ☐ Preeclampsia ☐ Maternal diabetes ☐ Transfusion required ☐ Blood clots ☐ Other specify _____

13. Has there ever been a time in your life during which you didn't become pregnant despite 12 or more months of regular unprotected intercourse?

    - ☐ No → **SKIP TO END**
    - ☐ Yes

14. Did you ever go to a doctor or other medical care provider to talk about ways to help you have a baby?

    - ☐ Yes
    - ☐ No → **GO TO QUESTION 16**

15. Which of the services did you have to help you have a baby? Check all the apply.

    - ☐ Advice
    - ☐ Infertility testing
    - ☐ Drugs to improve ovulation
    - ☐ Surgery to correct blocked tubes
    - ☐ Artificial insemination
    - ☐ Other types of medical help

16. Has a doctor or other medical care provider ever told you that you had fibroid tumors or myomas in your uterus?

    - ☐ Yes
    - ☐ No

17. Has a doctor or other medical care provider ever told you that you had endometriosis?

    - ☐ Yes
    - ☐ No

THIS IS THE END OF THE FORM. THANK YOU FOR YOUR PARTICIPATION.

PLEASE RETURN THE FORM TO THE STUDY COORDINATOR.

APPENDIX E: PREGNANCY AND CONCEPTION FORM – MALES

PREGNANCY AND CONCEPTION FORM
For Males

Final Version 1.1, 11/286/2017

Subject ID

This form asks questions about pregnancies where you have been the father.

1. Have you ever fathered a baby?

   ☐ No → **SKIP TO QUESTION 10 ON THE BACK OF THIS FORM**
   ☐ Yes

2. How many times have you fathered a baby? Please be sure to include any pregnancies that are current or ended in a live birth, miscarriage, stillbirth, or abortion. Enter the total number on the line below.

   _____ total number of pregnancies where you have been the father

INSTRUCTIONS FOR QUESTIONS 3-9:
As you answer the questions on the following 2 pages, please think about each of the pregnancies where you have been the father. Start with the earliest pregnancy, listing it in the first column labeled "1st pregnancy". From there, work forward until you have provided information about all of the pregnancies you listed in question 2 above. Then go to the back page and answer the remaining questions. Tell the study coordinator if you have fathered more than 8 pregnancies.

		1st pregnancy	2nd pregnancy	3rd pregnancy
3.	In what month and year did this pregnancy end (or due date if currently pregnancy)?	_____ / _____ Month / Year	_____ / _____ Month / Year	_____ / _____ Month / Year
4.	What was the outcome of this pregnancy?	☐ Live birth ☐ Still birth ☐ Miscarriage ☐ Abortion ☐ Currently pregnant	☐ Live birth ☐ Still birth ☐ Miscarriage ☐ Abortion ☐ Currently pregnant	☐ Live birth ☐ Still birth ☐ Miscarriage ☐ Abortion ☐ Currently pregnant
5.	Were you taking hydroxyurea at the time of conception (when the pregnancy started) or within the month before conception?	☐ No ☐ Yes ☐ Don't remember	☐ No ☐ Yes ☐ Don't remember	☐ No ☐ Yes ☐ Don't remember

**** Answer Questions 6 – 9 below only if the pregnancy ended in a live birth**

		1st pregnancy	2nd pregnancy	3rd pregnancy
6.	How many babies were born with this pregnancy?	_____ # of babies	_____ # of babies	_____ # of babies
7.	Was the baby (or babies) born prematurely?	☐ No, not born prematurely ☐ Yes → enter how many weeks of gestation _____	☐ No, not born prematurely ☐ Yes → enter how many weeks of gestation _____	☐ No, not born prematurely ☐ Yes → enter how many weeks of gestation _____
8.	Did any of the babies in this pregnancy weigh **less than 5.5 pounds** at the time of birth?	☐ No ☐ Yes ☐ Don't know	☐ No ☐ Yes ☐ Don't know	☐ No ☐ Yes ☐ Don't know
9.	Did a doctor ever say a baby from this pregnancy had low birth weight, a birth defect, a genetic condition, or another serious medical problem related to birth?	☐ No ☐ Yes → What condition?	☐ No ☐ Yes→ What condition?	☐ No ☐ Yes→ What condition?

		4th pregnancy	5th pregnancy	6th pregnancy
3.	In what month and year did this pregnancy end (or due date if currently pregnant)?	_____ / _____ Month / Year	_____ / _____ Month / Year	_____ / _____ Month / Year
4.	What was the outcome of this pregnancy?	☐ Live birth ☐ Still birth ☐ Miscarriage ☐ Abortion ☐ Currently pregnant	☐ Live birth ☐ Still birth ☐ Miscarriage ☐ Abortion ☐ Currently pregnant	☐ Live birth ☐ Still birth ☐ Miscarriage ☐ Abortion ☐ Currently pregnant
5.	Were you taking hydroxyurea at the time of conception (when the pregnancy started) or within the month before conception?	☐ No ☐ Yes ☐ Don't remember	☐ No ☐ Yes ☐ Don't remember	☐ No ☐ Yes ☐ Don't remember

**** Answer Questions 6 – 9 below only if the pregnancy ended in a live birth**

		4th pregnancy	5th pregnancy	6th pregnancy
6.	How many babies were born with this pregnancy?	_____ # of babies	_____ # of babies	_____ # of babies
7.	Was the baby (or babies) born prematurely?	☐ No, not born prematurely ☐ Yes → enter how many weeks of gestation _____	☐ No, not born prematurely ☐ Yes → enter how many weeks of gestation _____	☐ No, not born prematurely ☐ Yes → enter how many weeks of gestation _____
8.	Did any of the babies in this pregnancy weigh **less than 5.5 pounds** at the time of birth?	☐ No ☐ Yes ☐ Don't know	☐ No ☐ Yes ☐ Don't know	☐ No ☐ Yes ☐ Don't know
9.	Did a doctor ever say a baby from this pregnancy had low birth weight, a birth defect, a genetic condition, or another serious medical problem related to birth?	☐ No ☐ Yes → What condition?	☐ No ☐ Yes→ What condition?	☐ No ☐ Yes→ What condition?

10. Have you ever had a painful continuous erection, which is also called priapism?

    ☐ No
    ☐ Yes

11. Has there ever been a time in your life during which you weren't able to get your partner pregnant despite 12 or more months of regular unprotected intercourse?

    ☐ No → **FORM COMPLETE**
    ☐ Yes

12. Did you ever go to a doctor or other medical care provider to talk about ways to help you father a baby?

    ☐ No → **FORM COMPLETE**
    ☐ Yes → **GO TO QUESTION 13**

13. Which of the following services did you have to help you father a baby? Check all the apply.

    ☐ Advice
    ☐ Infertility testing
    ☐ Surgery to reverse a vasectomy
    ☐ Treatment for varicocele
    ☐ Other types of medical help

14. When you went for medical help to father a baby, were you ever told that you had any of the following male infertility problems? Check all that apply.

    ☐ Sperm or semen problems
    ☐ Varicocele
    ☐ Other
    ☐ None of the above

This is the END of the survey. Thank you for your participation. Please return the form to the study coordinator.

APPENDIX F: MEDICAL RECORD ABSTRACTION FORM

Medical Record Abstraction Form

Subject ID Label

If date or age is not available, enter '99'. Name of Abstractor: _____

1. DATE OF ENROLLMENT: |___|___|-|___|___|-|___|___|___|___|

2. Location where person enrolled:

- ☐ Routine visit--main SCDIC center
- ☐ Routine visit--satellite SCDIC center
- ☐ Emergency Department
- ☐ Acute Pain Center
- ☐ Hospital in-patient
- ☐ Primary Care offices
- ☐ Community event (e.g. SCD walk)
- ☐ Other _____

3. Confirmed enrollment diagnosis: (CHECK ONLY ONE). DIAGNOSIS MUST BE SUPPORTED BY SOURCE DOCUMENTATION.

Diagnosis	
a. Hb SS or sickle cell anemia	☐
b. Hb SC disease	☐
c. Hb S beta^0 thalassemia	☐
d. Hb S beta$^+$ thalassemia	☐

Diagnosis	
e. Hb S hereditary persistence of fetal Hb (S/HPFH)	☐
f. Hb SE	☐
g. Hb SD	☐
h. Hb SO	☐

a. What was the basis for diagnosis?

- ☐ Newborn screening
- ☐ Hemoglobin fractionation
- ☐ Hemoglobin electrophoresis
- ☐ DNA sequencing

4. Approximate age of first diagnosis (physician confirmed): _____ AGE IN YEARS **OR** ☐ NEWBORN SCREENING **OR** ☐ UNKNOWN

For subjects age 15-25 at time of enrollment:

a. Date of most recent visit to pediatric sickle cell provider. |__|__|-|__|__|-|__|__|__|__| ☐ DATE UNAVAILABLE

Date of first visit to adult sickle cell provider. |__|__|-|__|__|-|__|__|__|__| ☐ DATE UNAVAILABLE ☐ HAS NOT SEEN ADULT PROVIDER

☐ **FORM COMPLETE, MEDICAL RECORDS NOT AVAILABLE**

5. Ever tested for alpha-thalassemia?

- ☐ Yes—single alpha globin gene deleted
- ☐ Yes—two alpha globin genes deleted
- ☐ Yes-–negative
- ☐ No—not evaluated
- ☐ Unknown

Basic Measurements (most recent)	Not in Record	Measurements	Date (mm/yyyy)	Steady state?
6. Height	☐	|___|___|___| CM		Y N
7. Weight	☐	|___|___|___|.|___| KG		Y N
8. Temperature	☐	|___|___|.|___| Celsius		Y N
9. Heart Rate	☐	|___|___|___| BEATS/MINUTE		Y N
10. Respiration Rate	☐	|___|___|___| BREATHS/MINUTE		Y N
11. Oxygen saturation (SpO_2)	☐	|___|___|___| %		Y N
12. Blood Pressure	☐	|___|___|___| / |___|___|___| ON ANTI-HYPERTENSIVE MEDS? ☐ Yes ☐ No		Y N

13. Has the subject ever used hydroxyurea? ☐ Yes ☐ No ➔ SKIP TO MEDICATION TABLE ON NEXT PAGE

a. Start date (mm/yyyy) _____/_____

b. Stop/last date (mm/yyyy) _____/_____

c. Total duration of use _____ ☐ Months or ☐ Years ☐ Unknown

d. Current dose _____ Mg/kg or _____ Mg

14. Please list all medications the subject is **currently** taking (at time of enrollment). ☐ NONE CURRENTLY BEING USED

Name of Medication	Name of Medication
a.	k.
b.	l.
c.	m.
d.	n.
e.	o.
f.	p.

Most recent visit to ….	Not in record	Visit/Admission Date (mm/yyyy)	Length of stay (in days)	Was visit for acute pain?	# of total visits in past year for acute pain/crisis
15. Acute Pain/Infusion Center (not admitted)	☐			☐ Yes ☐ No	
16. Emergency Department (not admitted)	☐			☐ Yes ☐ No	
17. Hospitalization	☐			☐ Yes ☐ No	

Most recent visit to…	Not in record	Visit Date (mm/yyyy)	Most recent visit to….	Not in record	Visit Date (mm/yyyy)
18. Primary care physician (i.e. family/internal medicine, pediatrician)	☐		19. Behavioral medicine/psychiatrist	☐	
20. Hematologist	☐		21. Orthopedic surgeon	☐	
22. Nephrologist	☐		23. Ophthalmologist	☐	
24. Cardiologist	☐		25. Neurologist	☐	
26. Pulmonologist	☐		27. OB/GYN	☐	

Transfusion History at Clinic Site

	None	# ever had	# total units	First time (mm/yyyy)	Last time (mm/yyyy)	Reason stopped	Frequency	Type
28. Episodic, simple	☐						☐ Less than once/year ☐ About once a year ☐ More than once/year ☐ Unknown	
29. Chronic, simple	☐					☐ Hemochromatosis ☐ Alloimmunization ☐ Other ☐ Unknown	☐ Once every 4 weeks ☐ Once every 6 weeks ☐ Once every 8 weeks ☐ Unknown	
30. Episodic, exchange	☐						☐ Less than once/year ☐ About once a year ☐ More than once/year ☐ Unknown	☐ Automated ☐ Manual ☐ Unknown
31. Chronic, exchange	☐					☐ Hemochromatosis ☐ Alloimmunization ☐ Other ☐ Unknown	☐ Once every 4 weeks ☐ Once every 6 weeks ☐ Once every 8 weeks ☐ Unknown	☐ Automated ☐ Manual ☐ Unknown

SCD Complications Indicate whether the subject has ever had each condition and the date it was most recently diagnosed.	**No**	**Not in record**	**Yes**	**Most recent dx (record age OR date)**	
				Age	**Date (mm/yyyy)**
Musculoskeletal					
32. Avascular necrosis *(check all that apply)*	☐	☐	☐		
a. Hip	☐	☐	☐		
b. Shoulder	☐	☐	☐		
c. Knee	☐	☐	☐		
33. Dactylitis	☐	☐	☐		
34. Osteomyelitis	☐	☐	☐		
Genitourinary					
35. Chronic kidney disease	☐	☐	☐		
36. End stage renal disease	☐	☐	☐		
a. Kidney transplant	☐	☐	☐		
37. Priapism	☐	☐	☐		
Nervous system					
38. Stroke (*check all that apply*)	☐	☐	☐		
a. Ischemic	☐	☐	☐		
b. Hemorrhagic	☐	☐	☐		
c. Transient ischemic attack (TIA)	☐	☐	☐		
d. Silent	☐	☐	☐		
39. Intracranial bleeding	☐	☐	☐		
Cardiovascular					
40. Pulmonary arterial hypertension	☐	☐	☐		
a. Mean pulmonary artery pressure > or = to 25 mm Hg	☐	☐	☐		
b. Tricuspid regurgitation velocity (TRV) > or = to 3.0 m/sec	☐	☐	☐		
41. Left ventricular dysfunction	☐	☐	☐		
Respiratory					
42. Acute chest syndrome	☐	☐	☐		
43. Asthma	☐	☐	☐		
Digestive					
44. Gallstones/cholelithiasis, cholecystitis	☐	☐	☐		
45. Splenomegaly *(check all that apply)*	☐	☐	☐		
a. Splenic sequestration	☐	☐	☐		
b. Splenic infarcts	☐	☐	☐		
c. Hypersplenism	☐	☐	☐		
d. Splenectomy	☐	☐	☐		
Other Autoimmune/Inflammatory					
46. Deep vein thrombosis (DVT)	☐	☐	☐		
a. Pulmonary embolism	☐	☐	☐		
b. Venous thromboembolism (VTE)	☐	☐	☐		
47. Lupus	☐	☐	☐		
48. Rheumatoid arthritis	☐	☐	☐		
49. Gout	☐	☐	☐		
50. Sarcoidosis	☐	☐	☐		
51. Other autoimmune or inflammatory, specify:	☐	☐	☐		

Other Conditions	No	Not in record	Yes	Most recent dx (record age OR date)	
				Age	Date (mm/yyyy)
52. Multi-organ failure *(check all that apply)*	☐	☐	☐		
a. ICU	☐	☐	☐		
b. Intubation	☐	☐	☐		
c. Simple transfusion	☐	☐	☐		
d. Exchange transfusion	☐	☐	☐		
e. Hemodialysis	☐	☐	☐		
f. Peritoneal dialysis	☐	☐	☐		
53. Pneumococcal sepsis (Pulmonary)	☐	☐	☐		
54. Skin ulcers (Integumentary)	☐	☐	☐		
55. Retinopathy (Ocular)	☐	☐	☐		
56. Diabetes mellitus (other systemic)	☐	☐	☐		
57. Iron overload (Other)	☐	☐	☐		
58. Chronic refractory pain (Other)	☐	☐	☐		
59. Anxiety (Mental health)	☐	☐	☐		
60. Depression (Mental health)	☐	☐	☐		
61. Other psychiatric disorder (Mental health) Specify:	☐	☐	☐		

62. Has the subject ever been diagnosed with cancer?

- ☐ Yes
- ☐ No ➔ GO TO Q 63
- ☐ Don't know ➔ GO TO Q 63

IF YES: For each primary cancer, complete a row in the table:

	Cancer Type & Location	Stage	When diagnosed? (record age or date)	
			Age	Date (mm/yyyy)
a.				
b.				

63. What kind of health insurance or health care coverage does the subject have at the time of enrollment? (Choose all that apply.)

- ☐ None
- ☐ Private health insurance
- ☐ Medicare
- ☐ Medicaid, Medical Assistance (MA), the Children's Health Insurance Program (CHIP), or any kind of state or government-sponsored assistance.
- ☐ TRICARE or other military health care, including VA health care
- ☐ Other type of health insurance, specify:_____

64. Year of first visit in medical record: |___|___|___|___| ☐ Subject not seen at this institution

PI review and sign-off: _____

APPENDIX G: CARDIOLOGY AND PULMONARY SUPPLEMENTAL FORM

Pulmonary hypertension and LV dysfunction Form

Subject ID Label

DATE FORM COMPLETED: |___|___|-|___|___|-|___|___|___|___|

Complete this form if there is a YES response to Q40. pulmonary hypertension OR Q41. LV dysfunction on the Enrollment Medical Record Abstraction Form. Use the most recent results available in the 5 years prior to the date of consent for the Registry.

Date of most recent ECHO: |___|___|-|___|___|-|___|___|___|___| ☐ ECHO not available

Measurement from ECHO		Qualitative data	Quantitative data
1.	Mitral regurgitation	☐ none ☐ trivial ☐ moderate ☐ mild ☐ severe	
2.	Tricuspid regurgitation	☐ none ☐ trivial ☐ moderate ☐ mild ☐ severe	
3.	TR jet velocity		_____m/s
4.	Tricuspid Annular Plane Systolic Excursion		_____mm
5.	Ejection fraction, left ventricle		|__|__|.|__| %
6.	Left Atrial Volume	☐ normal ☐ moderate ☐ mild ☐ severe	(LAESVI in ml/sq.m) = _____ml/m^2
7.	Right Atrial Volume	☐ normal ☐ moderate ☐ mild ☐ severe	(RAESVI in ml/sq.m) = _____ml/m^2
8.	Left ventricular volume	☐ normal ☐ moderate ☐ mild ☐ severe	Left ventricular end systolic dimension LVIDs =_____mm LVESVI= ____ mL/m2 Left ventricular end diastolic dimension LVIDd=_____mm Left ventricular posterior wall mm thickness at end-diastole LVPwD=_____mm
9.	Right ventricular volume	☐ normal ☐ moderate ☐ mild ☐ severe	Right ventricular end systolic dimension RVIDs=_____mm Right ventricular end diastolic dimension RVIDd=_____mm Mention of interventricular septal flattening Y/N
10.	RV hypertrophy	☐ normal ☐ moderate ☐ mild ☐ severe	

Date of most recent EKG: |___|___|-|___|___|-|___|___|___|___| ☐ EKG not available

Measurement from EKG		Diagnosed?
11.	Arrhythmia	☐ Yes ➔ type _____ ☐ No ☐ Unknown
12.	Ventricular rate	_____ bpm ☐ NA
13.	PR Interval	_____ ms ☐ NA
14.	QRS duration	_____ ms ☐ NA
15.	QT/QTc	____ /____ ms ☐ NA
16.	P-R-T axes	____ ____ ____ ☐ NA

Date of most recent right heart catheterization: |___|___|-|___|___|-|___|___|___|___| ☐ Report not available

Target		Measurement
17.	RA pressure (mean)	_____ mm/hg ☐ NA
18.	RV pressure (mean)	_____ mm/hg ☐ NA
19.	PA pressure (mean)	_____ mm/hg ☐ NA
20.	Pulmonary artery saturation	_____ % ☐ NA
21.	Pulmonary vascular resistance	_____ dynes-sec-cm^{-5} ☐ NA
22.	Pulmonary capillary wedge pressure (PCWP or PAWP)	_____ mm/hg ☐ NA
23.	Cardiac output and index	_____ L/min ☐ NA

Notes:

1) Right atrial pressure: This is usually present in the echo report and is reported based on IVC collapsibility (might be under heading of IVC/Hepatic veins)

2) Right atrial size: qualitatively (as normal, mildly, moderately or severely dilated) vs. quantitatively (RA area or RAESVI). The numerical values are all usually reported at the bottom of the report.

3) Left ventricular size (qualitative - normal, mild, mod, severely dilated) vs quantitative (LVEDVI , LVESVI)

4) Any comment of **interventricular septal flattening** indicates RV pressure or volume overloading and points to significant pulmonary hypertension.

5) Left atrial dimensions reported qualitatively (as normal, mildly, moderately or severely dilated) vs. quantitatively (LAESVI in ml/sq.m). The numerical values are all usually reported at the bottom of the report.

APPENDIX H: RENAL SUPPLEMENTAL FORM

Renal Form

Subject ID Label

DATE FORM COMPLETED: |___|___|-|___|___|-|___|___|___|___|

This form should be completed if YES to either Q35 (chronic kidney disease) or Q36 (end stage renal disease) on the enrollment Medical Record Abstraction Form.

	1. Albuminuria	**2. Proteinuria**
a. When did it start?	|__|__|-|__|__|-|__|__|__|__| **OR** ☐ Less than 1 year ago ☐ Between 1 and 2 years ago ☐ More than 2 years ago ☐ Unknown/NA ☐ Has not had albuminuria **GO TO Q2**	|__|__|-|__|__|-|__|__|__|__| **OR** ☐ Less than 1 year ago ☐ Between 1 and 2 years ago ☐ More than 2 years ago ☐ Unknown/NA ☐ Has not had proteinuria **GO TO Q3**
b. Date of most recent measurement	|__|__|-|__|__|-|__|__|__|__| ☐ Unknown/NA ☐ No measurement available **GO TO Q2**	|__|__|-|__|__|-|__|__|__|__| ☐ Unknown/NA ☐ No measurement available **GO TO Q3**
c. Type of measurement *(check one)*	☐ Spot ☐ 24-hour urine **GO TO Q2** ☐ Unknown/NA **GO TO Q2**	☐ Spot ☐ 24-hour urine **GO TO Q3** ☐ Unknown/NA **GO TO Q3**
d. Spot urine sample	_____ mg/L (milligram albumin per liter of urine)	_____ mg/L (milligram protein per liter of urine)
e. Spot urine [albumin/protein]/ creatinine ratio	_____ mg/mmol (milligram albumin per millimole creatinine) _____ µg/mg (microgram albumin per milligram creatinine)	_____ mg/mmol (milligram protein per millimole creatinine) _____ µg/mg (microgram protein per milligram creatinine)

	3. eGFR <60
a. When did it start?	|__|__|-|__|__|-|__|__|__|__| **OR** ☐ Less than 1 year ago ☐ Between 1 and 2 years ago ☐ More than 2 years ago ☐ Unknown/NA ☐ Has not had albuminuria **GO TO Q4**
b. Date of most recent measurement	|__|__|-|__|__|-|__|__|__|__| ☐ Unknown/NA ☐ No measurement available **GO TO Q4**

4. Has the subject had:	Yes	No	Unknown
a. History of acute kidney injury (AKI*)	☐	☐	☐
b. History of >1 episode of AKI*	☐	☐	☐
c. Hemodialysis	☐	☐	☐
d. Peritoneal dialysis	☐	☐	☐
e. Kidney disease/ESRD	☐ Date: |_|_|-|_|_|-|_|_|_|_| **OR** ☐ Less than 1 year ago ☐ Between 1 and 2 years ago ☐ More than 2 years ago ☐ Unknown/NA	☐	☐
f. Kidney transplant	☐ Date: |_|_|-|_|_|-|_|_|_|_| ☐ Unknown/NA Rejection? ☐ Yes ☐ No ☐ Unknown/NA	☐	☐

*Must meet Acute Kidney Injury Network (AKIN) criteria, with a minimum of stage 1: an increase in serum creatinine of ≥26.4 µmol/L or increase to ≥150–200% from baseline.

APPENDIX I: LABORATORY REPORTING FORM

Laboratory Reporting Form

Subject ID Label

Complete using medical records, using values from the subject in steady state. **Abstractor**: _____

Test Name	Units	Date of Most Recent	NA
1. Nucleated RBC	|___|___|.|___| $10^3/mm^3$	_____/_____/_____	☐
2. White Blood Cells	|___|___|.|___| $10^3/mm^3$	_____/_____/_____	☐
3. RBC	|___|___|.|___| $10^6/mm^3$	_____/_____/_____	☐
4. Hemoglobin	|___|___|.|___|g/dL	_____/_____/_____	☐
5. Hematocrit	|___|___|.|___| %	_____/_____/_____	☐
6. MCV	|___|___| micrometer^3	_____/_____/_____	☐
7. MCH	|___|___|.|___| pg	_____/_____/_____	☐
8. MCHC	|___|___|.|___| g/dL	_____/_____/_____	☐
9. Platelets	|___|___|___| $10^3/mm^3$	_____/_____/_____	☐
10. Neutrophils (segmented and band together)	|___|___| %	_____/_____/_____	☐
11. Lymphocytes	|___|___| %	_____/_____/_____	☐
12. Monocytes	|___|___| %	_____/_____/_____	☐
13. Reticulocytes	|___|___|.|___| % AND/OR |___|___| 10^3/microliter	_____/_____/_____	☐
14. Serum BUN	|___|___|.|___| mg/dL	_____/_____/_____	☐
15. Serum Creatinine	|___|.|___| mg/dL	_____/_____/_____	☐
17. Estimated creatinine clearance	|___|___|___| mL/min	_____/_____/_____	☐
18. Total Cholesterol	|___|___|___| mg/dL	_____/_____/_____	☐
19. Non-Fasting HDL	|___|___|___| mg/dL	_____/_____/_____	☐
20. Fasting HDL	|___|___|___| mg/dL	_____/_____/_____	☐
21. Non-Fasting LDL	|___|___|___| mg/dL	_____/_____/_____	☐
22. Fasting LDL	|___|___|___| mg/dL	_____/_____/_____	☐
23. Triglyceride	|___|___|___| mg/dL	_____/_____/_____	☐
24. Non-Fasting Blood Glucose	|___|___|___| mg/dL	_____/_____/_____	☐
25. Fasting Blood Glucose	|___|___|___| mg/dL	_____/_____/_____	☐
26. CRP	|___|___|.|___| mg/dL	_____/_____/_____	☐
27. Bilirubin serum, total	|___|___|.|___| mg/dL	_____/_____/_____	☐
28. Bilirubin, serum, direct	|___|___|.|___| mg/dL	_____/_____/_____	☐
29. AST	|___|___|.|___| U/L	_____/_____/_____	☐

Test Name	Units	Date of Most Recent	NA
30. ALT	|___|___|.|___| U/L	_____/_____/_____	☐
31. Alkaline Phosphatase	|___|___|___|.|___| U/L	_____/_____/_____	☐
32. Total Protein (plasma)	|___|___|.|___| g/dL	_____/_____/_____	☐
33. Albumin	|___|___|.|___| g/dL	_____/_____/_____	☐
34. LDH (serum)	|___|___|___| U/L	_____/_____/_____	☐
35. NT-pro-BNP	|___|___|___|___| pg/mL	_____/_____/_____	☐
36. BNP	|___|___|___|___| pg/mL	_____/_____/_____	☐
37. Serum iron	|___|___|___| ug/dL	_____/_____/_____	☐
38. Total iron binding capacity (TIBC)	|___|___|___| ug/dL	_____/_____/_____	☐
39. Serum transferrin	|___|___|___| mg/dL	_____/_____/_____	☐
40. Ferritin	|___|___|___| ng/mL	_____/_____/_____	☐
41. 25-Hydroxy Vitamin D	|___|___| ng/mL	_____/_____/_____	☐
42. Erythropoietin (EPO)	|___|___| mU/ml	_____/_____/_____	☐
43. Urine albumin	|___|___|___|.|___| mg/g	_____/_____/_____	☐
44. Urine albumin / creatinine	|___|.|___|___| mcg/mg	_____/_____/_____	☐
45. Urine protein (dipstick)	|__| 0/negative |__| trace |__| 1+ |__| 2+ |__| 3+ |__| 4+ |__| positive	_____/_____/_____	☐
46. Urine protein/creatinine	|___|.|___|___| mg/g	_____/_____/_____	☐
47. Urine dipstick heme	|__| 0/negative |__| trace |__| 1+ |__| 2+ |__| 3+ |__| 4+ |__| positive	_____/_____/_____	☐
48. Urine microscopic RBCs	|___|___|.|___| $10^3/mm^3$ (if < 100, enter exact value) OR |__| ≥ 100 $10^3/mm^3$	_____/_____/_____	☐
49. Urine microscopic WBCs	|___|___|.|___| $10^3/mm^3$ (if < 100, enter exact value) OR |__| ≥ 100 $10^3/mm^3$	_____/_____/_____	☐
50. Hemoglobin fractionation, baseline (before HU use)	Hb A |___|___|% Hb A2 |___|___|% Hb C |___|___|% Hb D |___|___|% Hb E |___|___|% Hb F |___|___|% Hb O |___|___|% Hb S |___|___|% Other, _____ |___|___|%	_____/_____/_____	☐
51. Hemoglobin fractionation, most recent	Hb A |___|___|% Hb A2 |___|___|% Hb C |___|___|% Hb D |___|___|% Hb E |___|___|% Hb F |___|___|% Hb O |___|___|% Hb S |___|___|% Other, _____ |___|___|%	_____/_____/_____	☐
52. Hemoglobin fractionation, maximum dose HU	Hb A |___|___|% Hb A2 |___|___|% Hb C |___|___|% Hb D |___|___|% Hb E |___|___|% Hb F |___|___|% Hb O |___|___|% Hb S |___|___|% Other, _____ |___|___|%	_____/_____/_____	☐