Cooperative Study of Sickle Cell Disease
Phase 1 Extension Protocol
1983-1988

COOPERATIVE STUDY OF SICKLE CELL DISEASE (CSSCD)

PROTOCOL

A. Background

Even though sickle cell disease has been known for many years and many of its clinical manifestations have been described, the natural history or clinical course of the disease from birth to death and the impact of the disease on the patient have been poorly understood largely because of its clinical variability. To correct the deficiency in understanding of this disorder, the National Sickle Cell Disease Advisory Committee and the Blood Diseases and Resources Advisory Committee recommended, and the National Heart, Lung, and Blood Advisory Council approved in 1976, the implementation of a 5-year, multi-institutional, prospective, longitudinal study of the "natural history" of sickle cell disease, the Cooperative Study of Sickle Cell Disease (CSSCD).

During the first 18 months of planning, 23 centers were organized into a cooperative group and, with active statistical input, a protocol was developed aimed at achieving the following objectives:

- To study the effects of sickle cell disease on growth and development of children from birth through early childhood.
- To study conditions or events which may be related to the onset and nature of the "painful crisis," and to record therapeutic interventions.
- To obtain cross-sectional data regarding selected major complications of sickle cell disease, for example, renal, ocular, neural, and pulmonary.
- To determine the prevalence and incidence of organ damage.
- To study the role of sickle cell disease in complicating other health events, for example, pregnancy, and surgery and inhalation anesthesia.
- To examine the economic impact on, and the educational and vocational achievement of, patients with sickle cell disease.
- To develop a data base that will permit a rational approach to establishing patient criteria for potential therapeutic interventions.

Patient recruitment began in 1979 and has resulted in a substantial study population in four age groups: newborns, pediatric (first decade), adolescents (second decade), and adults (over 20 years of age).

The sickle cell patient study population of over 3,600 is clinically evaluated at regular intervals and during periods of illness. Retention of patients has been excellent, with an overall study attrition of only 6 to 7 percent (10 percent attrition was initially anticipated). Over the past 4 years, the study group has completed the following operational goals:

- Organization of the clinical centers for gathering and transferring data to the Statistical Coordinating Center for entry onto the database.
- Development and implementation of the study protocol with standardized forms, manual of operations, training of key personnel, standardized and quality controlled laboratory procedures.
- Establishment of central laboratories for specialized tests such as globin-chain synthesis ratios, alloantibodies, and vesiculated red blood cells.
- Organization of the patients around scheduled visits at predetermined intervals and clinical documentation of acute and chronic events.
- Establishment of quality-control procedures for clinical and laboratory data.
- Design and implementation of ancillary studies such as iron metabolism in sickle cell disease, cardiac function, and prevalence of lead intoxication.
- Formulation of testable hypotheses addressing the objectives of the study and designing statistically valid procedures for analysis to answer specific questions.

As data accumulated, preliminary analysis began in year 03 with the combined efforts of statisticians and clinical investigators. From the initial assessment of clinical and laboratory data, important tasks have been accomplished:

- Description of the demographic characteristics of the study patient population.
- Documentation of patterns of growth and sexual development.
- Assessment of physical findings in over 3,500 individuals with sickle disease.
- Documentation of splenic function and correlation of vesiculated cells with spleen scans.
- Documentation of the incidence of infections and mortality in the first 3 years of life.
- Establishment of patters of alloantibody production in transfused patients.
- Description of the course of the acute chest syndrome.

- Observation of the outcome and complications of over 150 pregnancies.

Despite the substantial accomplishments after 4 years, it is evident that the current data base is not adequate to permit elucidation of the course of this disease in several important areas because of the short observation period and the unpredictable infrequent occurrence of certain events. Therefore, an additional 5 years has been approved to permit accomplishment of the following objectives:

B. Objectives:

1. To follow prospectively newborns with sickle cell disease for a minimum of 10 years, and elucidate issues relating to development, infections, efficacy of prophylactic regimens, and onset and course of acute and chronic complications.

2. To accurately determine incidence rates and obtain data on the nature, duration and outcome of selected acute special events.

3. To determine the prevalence and incidence, age of onset, rate of progression, and outcome of chronic organ damage.

4. To study the role of sickle cell disease and its interaction with selected health events.

5. To continue to examine the economic, educational and vocational levels, and obtain data on other psychosocial aspects including self-concept, coping, and intra-family relationships.

6. To continue to develop a data base which will be used:

   a. to evaluate treatment modalities currently used in the care of patients with sickle cell disease;

   b. to describe the spectrum of disease severity in patients with sickle cell disease; and

   c. to establish criteria for potential therapeutic interventions based upon the knowledge gained in the study.

7. To further elucidate previously unrecognized clinical manifestations and their sequelae.

8. To conduct in-depth investigations relating to the wide variability of clinical manifestations in sickle cell disease and delineate factors contributing to the spectrum of mild to severe disease.

9. To continue a prophylactic penicillin trial in the pediatric age group to evaluate its efficacy in preventing severe overwhelming infections.

C. Rationale:

1. Objective: To follow prospectively newborns with sickle cell disease for a minimum of 10 years, and elucidate issues relating to development, infections, efficacy of prophylactic regimens, and onset and course of acute and chronic complications.

   Newborns constitute the true patient population of a study of the natural history of a genetic disease, and only through long-term follow-up can there be a complete understanding of factors influencing survival and testing the severity/risk concept. Data derived from the young pediatric population will provide the best knowledge base to evaluate the continuum of disease.

   The prevalence of abnormal pulmonary function and gallstones appears higher at younger ages than predicted. A longer period of observation, spanning the first decade of life, will permit an assessment of the onset and progression of these complications. Screening of newborns will continue through year 03 of the extension.

2. Objective: To accurately determine incidence rates and obtain data on the nature, duration and outcome of selected acute special events.

   Published incidence data provided the basis for initial statistical calculations of the number of clinical events needed to answer specific questions. Many acute events occur less frequently in the study patients than has been reported in the literature and additional observation years are needed to acquire sufficient data to permit analysis. Data collection has been discontinued for hospital based painful episodes, and other areas will be discontinued as the data becomes sufficient.

3. Objective: To determine the prevalence and incidence, age of onset, rate of progression, and outcome of chronic organ damage.

   One of the most serious consequences of sickle cell disease is the impairment of organ function. Many of these impairments have been anecdotally reported, e.g., renal failure, cardiac failure, and pulmonary disease. However, in most instances, patients are studied at a time when organ damage is already severe and accurate assessment of time of onset and rate of progression of organ damage cannot be made from such investigations. This information is of vital importance for designing a realistic approach to medical management, including both treatment and prevention of organ damage. The additional period of observation will permit elucidation of the age of onset, rate of progression, and outcome.

   In addition, previously undescribed clinical findings have been documented: (a) the incidence of abnormal pulmonary function tests is higher and occurs at earlier ages than anticipated; and (b) a high incidence of chronic liver disease in older patients.

4. Objective: To study the role of sickle cell disease and its interaction with selected health events.

Data will continue to be collected on pregnancy, surgery with general anesthesia, and infection.

5. Objective: To continue to examine the economic, educational and vocational levels, and obtain data on other psychosocial aspects including self-concept, coping, and intra-family relationships.

   Sickle cell disease, like other chronic illnesses, has a negative impact on the psychosocial well-being of individuals and their families. While there is a large body of knowledge on the general nature and specific features of the psychosocial effects of many chronic illnesses, there is a paucity of information related to this aspect of sickle cell disease and none which provides a systematic approach to social intervention. Most of the information on this population of patients is anecdotal, extrapolated from clinical observations or made on theoretical generalizations. Information to be collected will focus on self-concept, anxiety, coping strategies, relationships, and outlook on life.

6. Objective: To continue to develop a data base which will be used to evaluate treatment modalities, describe the spectrum of diseases and establish criteria for potential therapeutic interventions.

   A better understanding of the clinical course will augment our understanding of the mild and moderately ill patient, allow an examination of possible “risk” factors and provide data for a statistical determination of an index of severity. This will aid in the establishment of specific criteria for future therapies and should improve the quality of life of patients with sickle cell disease.

7. Objective: To further elucidate previously unrecognized clinical manifestations and their sequelae.

   Based on preliminary data analysis, unanticipated trends have emerged with respect to abnormal pulmonary function and aseptic necrosis. Specifically, the occurrence of abnormal pulmonary function in the 12-year old population and an increased number in the adult population was unexpected. The possible association with a history of repeated pulmonary infection is not clear and the exact prevalence of this abnormality and age at onset should be clarified. Preliminary evaluations show an unexplained association of aseptic necrosis and gallstones in the young population, and a low incidence of hypertension in the adult population. To determine if these trends are real or apparent requires further exploration, and additional time is needed to investigate these findings prospectively.

   In addition, an unanticipated large number of patients present a clinical picture of chronic liver disease. Initial study plans did not include data collection for this complication.

8. Objective: To conduct in-depth investigations relating to the wide variability of clinical manifestations in sickle cell disease and delineate factors contributing to the spectrum of mild to severe disease.

It is clear from current data that sickle cell disease is highly variable in its manifestations, and the CSSCD database will enable the development of a system or systems for the classification of the severity of disease. It will then be essential to determine the reasons for this clinical heterogeneity. New technological advances, not available at the initiation of the study, will permit more in-depth investigation of the clinical heterogeneity being documented by the CSSCD. Selected studies will be prioritized from the following areas:

- Gene mapping – In the last 5 years, techniques have become available which permit precise delineation of the composition and activity of hemoglobin gene clusters for accurate diagnosis of concommitant thalassemic states and genetic conditions resulting in increased fetal hemoglobin. Both thalassemia and increased Hgb F have been reported to ameliorate the clinical severity of sickle cell disease. It is intended to obtain this information on all patients.

- Investigations will include, on a subset of patients (i.e., patients over 40 years, sib-sib pairs, parent –child pairs), cellular heterogeneity, quantitation of Hb S polymerization, kinetics of Hb S gelation, and adherence of erythrocytes to vascular endothelium.

9. Objective: To institute a prophylactic penicillin trial in the pediatric age group to evaluate its efficacy in preventing severe overwhelming infections.

   The mortality in children remains high despite improved diagnosis and care and prophylactic use of pneumococcal vaccine. Preliminary evidence suggests some benefit from prophylactic penicillin and a number of patients in the study have recently been placed on this regimen. Evaluation of this approach will have a significant effect on future care of children with sickle cell disease.

D. Impact of Cooperative Study of Sickle Cell Disease (CSSCD)

The impact of this large-scale cooperative investigation should be realized in two areas: (1) providing a data base which will extend our understanding of the clinical aspects and thereby improve the management of this illness; and (2) providing general and specific information on which future research may proceed.

Impact on Health Care

A major outcome of the CSSCD has been the establishment of a framework and model for comprehensive care of patients with sickle cell disease. The results of this large-scale cooperative study will significantly affect the care of patients with sickle cell disease. Specifically, knowledge of risk factors, rates of progression of organ damage, and incidence and outcome of complications will positively alter the approach by the practicing physician in managing this patient population. In the absence of a cure for sickle cell disease, a systematic approach to the management as documented by this study offers the most favorable outlook for the patient.

The increased clinical awareness of the development of problems early in the course of this illness, many previously undocumented, and appropriate intervention should ultimately reduce the costs of medical care for these patients. The multisystem

morbidity of sickle cell disease frequently leads to excessive and expensive diagnostic testing by the physician who lacks knowledge of the clinical course of this disease, thereby tremendously increasing costs for patient care. The present study will provide the basis upon which more rational clinical judgments can be made.

The use of blood transfusions as a routine therapeutic regimen has gained wide practice over the last 10 years. However, data from this study indicate that 15 percent of patients transfused are sensitized to minor group antigens. This increases the problem of recruiting suitable donors for these patients. More prudent use of blood for specific indications and the judicious selection of blood donors, using guidelines derived from the CSSCD, should assist in conserving blood resources and improve standards of transfusion therapy for sickle cell patients.

Information as to current management practices and optimal outcomes should emerge from the study even though it is not designed as a clinical intervention trial. From the assessment of therapeutic approaches currently used and documented in study patients, effective measures can be identified, as well as areas where therapy is inadequate, and complications where intervention does not lead to improved outcome.

Accurate knowledge of the effects of the disease on the economic, educational, vocational, social, and psychosocial status of the patient will provide a firm basis for making policy decisions concerning the delivery of health care and social services to these patients. Greater knowledge about the disease will allow health educators and physicians to counsel families and patients more accurately and enhance the ability of patients and families to make more informed decisions about their health care.

An ultimate impact of the clinical course study on health care should be the development of a sickle cell population with an improved quality of life, an enhanced self-image, and the ability to make a contribution to society.

Impact on Research

Data obtained from the cooperative study will advance research in sickle cell disease by identifying needs and opportunities for basic and clinical investigations in the future.

Baseline data will be available to evaluate the effectiveness of pharmacologic agents and other approaches proposed for patient management. Current therapeutic evaluations are primarily subjective and focus on the presence, frequency, and intensity of painful episodes. Clinical severity indices established from a large series of sickle cell patients will provide objective criteria for assessing the benefits, or lack thereof, of specific therapies.

E. Project Design

a. General:

1. The purpose of the extension is to provide an adequate observation period to better elucidate the clinical course in the areas specified by the objectives.

Therefore, only patients presently enrolled will be followed with the exception of newborns diagnosed over the next three years and entered into the study as new patients.

2. In addition, no initial evaluations related to chronic organ damage will be performed. Only repeat "special tests" will occur (i.e., ophthalmic, gallbladder, shoulder and hip films).

3. As data becomes sufficient and specific objectives are met, various aspects of the investigation will be discounted.

b. Recruitment and Entry of Patients:

There will be no entry of new patients into the study beyond the newborn period (6 months of age).

Entry of Newborns:

Newborns will be diagnosed and entered as previously, but without matched newborn controls. Newborn diagnosis and entry will continue throughout year 03 of the extension. (October 1985-1986) Infants born at other hospitals and referred to study centers for care will also be recruited for entry if they are less than 6 months of age.

c. Retention of CSSCD Patients:

All patients currently in the CSSCD will be followed for an additional 4-5 years according to the study protocol. Centers will be responsible for follow-up on patients who missed visits through letters, telephone visits and home visits as necessary to maintain adequate follow-up.

Transfer of Patients:

Pediatric patients who graduate to the adult protocol will be transferred to the corresponding adult CSSCD program.

Patients who move from the vicinity of the original study center will be transferred to another study center if at all possible. Centers will be responsible for maintaining an address file on patients who move, for purposes of long-term follow-up.

The Recruitment and Retention Committee will continue to be responsible for the monitoring of compliance by Centers and will recommend needed action in the event that compliance needs to be improved.

d. Exit of Patients:

Patients completing eight years of follow-up will be closed out beginning in the 04 year (1986-1987). Other patients will be exited in 1987.

e. Routine Scheduled Visits:

1. Newborns and Infants will be followed every 2 months until the age of 6 months, and every 3 months from 6 months to 2 years of age.

2. Pediatric patients:

   - 2 years – 9 years will be followed yearly.

3. Adolescent Patients – 10-19 – yearly.
4. Adults – 20+ - yearly.

Routine visits will involve a history, physical examination, routine laboratory tests, and special tests as outlined on the composite flow sheet.

f. Special Events

Data will be collected on all special events except hospital-based painful episodes where only the face sheet is completed. Collection of data involving other special events will be discontinued as the data becomes sufficient.

g. Special Tests

1. Special evaluations of the eye, gallbaladder, shoulder, and hips will only be performed as repeat evaluations. The schedule for the repeat test is determined by wheter the initial evaluation was normal or abnormal.

2. Ocular – The following clinical centers will perform eye evaluations during the first and third year of the extension:

   Yale, University of Miami, Philadelphial Children's, Interfaith, St. Louis Children's, University of Mississippi, San Francisco General, Harlem Hospital, Michael Reese, and Wyler. The patients to be evaluated are as follows:

   SS 20+ - repeat 1/3 of the patients
   SC 20+ - repeat all patients
   SC 10-19 - perform on all patients whether previously seen or not

3. New or initial evaluations of lung function (PFT's) will be performed on children 6-10 years of age and adult patients over the age of 40 with SS disease.

4. Summary of Special Tests

A. Repeat Evaluations	Normal	Abnormal

1. X-rays – shoulder	4 years after last. (not performed if <10 years of age)	See every 6 mos. without x-ray
– hip	4 years after last	See every 6 mos. without x-ray
2. Gallbladder (Sonogram) (only adults)	4 years after last	
3. Ocular	See g.2.	See g.2.
4. Pulmonary Function Tests	4 years after last. All cardiac patients	4 years after last

B. New Evaluations

1. PFT's: SS – children 6-10 years of age.
SS – adults over 40 years.

h. Special Evaluations

Special evaluations such as gene mapping and density gradients will be obtained as a "one-time" determination during the first and second years of the extension.

1. Gene mapping – will be obtained on every SS study patient. This determination will be performed by a central laboratory.

2. Density gradients will be collected on only approximately 500 patients from the following institutions:

   Philadelphia Children's, St. Louis Children's, Boston Children's, George Washington University, Duke University, Children's Hospital, D.C., Howard University and Oakland Children's.

   The determinations will be performed at the local institutions.

i. Ancillary Studies

1. Prophylactic Penicillin Trial

   This trial involving children with SS disease less than 3 years of age will continue through the first 2 years of the extension according to the project-specific protocol.

2. Cardiac Function

   This evaluation will be repeated in the 04 year of the extension on the same patients who received the initial evaluation. New patients will not be entered for evaluation. This ancillary study will be conducted in only 4 centers according to the cardiac protocol.

3. Psychosocial Evaluation

   This evaluation will be conducted in all centers utilizing a randomly selected subset of patients (approximately 20 per center) during the first year of the extension. This study is to be conducted according to the project-specific protocol, forms, and manual of operations.

COMPOSITE FLOW SHEET

EVALUATION	NEWBORN AND PEDIATRIC	ADOLESCENT	ADULT
Routine Visit History Physical Exam	Every 2 months til 6 months Every 3 months til 2 years Yearly >2 years	Yearly (with Tanner)	Yearly
<u>Hematology</u> cbc	Every visit	Yearly	Yearly
Hgb F	2 years of age 5 years of age Exit if <5 years of age	--	--
Hgb Evaluation	Confirm diagnosis at 2 years of age	--	--
<u>Liver</u> SGOT Bilirubin Alkaline Phos.	12 months, 24 months of age and then every other year	Every other year	Every other year
<u>Spleen</u> Vesiculated (pocked) rbc	Every visit til 24 months, then yearly til >5%	--	--
<u>Gallbladder</u> Sonogram	--	--	4 years after last

COMPOSITE FLOW SHEET (continued)

EVALUATION	NEWBORN AND PEDIATRIC	ADOLESCENT	ADULT
Renal U/A Creatinine	Yearly (Start age 3)	Yearly	Yearly
X-rays Chest Shoulder Hips	-- --	-- 4 years after last 4 years after last	Exit 4 years after last 4 years after last
Ophthamology		See g.2	See g.2
Pulmonary Function	a. New evaluation only 55, beginning at age 6.	a. 4 years after last one b. All cardiac patients	a. 4 years after last one b. All cardiac patients c. New evaluation—SS 40+ years

EXTENSION

YEAR	01 83-84	02 84-85	03 85-86	04 86-87	05 87-88
Routine Visits (6-12 months)	→	→	→	→	6 months →
Special Events	→	→	→	→	→
Repeat Evaluation on Abnormals	→	→	→	→	→
Newborn Screening	→	→	→	D/C	
Gene Mapping, etc.	→	→	D/C		
Psychosocial	→	D/C			
Prophylactic PCN	→	→	D/C		
Diary	→	D/C			
Editing	→	→	→	→	→
Clarification of Existing Data	→	→	→	→	→
Cardiac				→	
Close-Out				→	→
					Close-out patients with 8 years.