CLINICAL PROTOCOL

PROTOCOL TITLE: Epidemiology of Priapism

CSCC PROTOCOL NUMBER: Version 6.3

DATE: February 10, 2006

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STUDY SITES

Southwestern Comprehensive Sickle Cell Center (CSCC); Duke-UNC CSCC; CSCC Statistics & Data Management Center (SDMC); Boston Medical Center CSCC; Bronx CSCC; Children's Hospital of Philadelphia CSCC; Northern California CSCC; University of Southern California CSCC; St. Jude Children's Research Hospital CSCC; Cincinnati CSCC; Marian Anderson Sickle Cell Anemia Care and Research Center.

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1 SYNOPSIS

Title: Epidemiology of Priapism

CSCC Protocol Date: February 10, 2006 Version 6.3

Overview: Priapism, a prolonged erection of the penis that may lead to impotence, is a specific type of painful crisis that commonly occurs in patients with sickle cell disease. The current treatment of priapism can be improved by comparing therapeutic strategies in prospective clinical trials, but first an assessment of the natural history of priapism is needed. This project will conduct an interview of 1,650 males with sickle cell disease in order to determine in which patients, how often, and under what circumstances priapism occurs.

CSCC Protocol Chair: Zora R. Rogers, M.D.

Intervention: Survey

Objectives:

1. Enumerate the cross-sectional prevalence, demographics, and common clinical characteristics of priapism in males with sickle cell disease among the CSCC patient population.
2. Identify patients eligible for randomized clinical trials of promising secondary prevention strategies.

This will be accomplished by completion of the following specific aim(s):

1. To conduct a questionnaire survey of 1,400 males with sickle cell anemia and sickle beta zero thalassemia 5 years of age or older in order to determine the prevalence (frequency) and characteristics (number and pattern of episodes, cause or precipitating event, treatment, and outcome) of priapism.
2. To survey 250 additional males with other forms of sickle cell disease with the same instrument and describe the occurrence and characteristics of priapism experienced.
3. To develop a structured educational brochure about priapism for patients with sickle cell disease.
4. To identify the number of patients with recurrent priapism potentially eligible for randomized clinical trials of secondary prevention strategies.

Hypotheses: Priapism is a common complication of sickle cell disease. In 5- to 10-year-old males with sickle cell anemia, it is hypothesized that the prevalence of priapism is 10%. In 10- to 15-year-old patients, it is hypothesized that the prevalence of priapism increases to 20%. In patients over 15 years old, it is hypothesized that the prevalence of priapism reaches 30%.

Primary Outcome:

Enumeration of the prevalence of priapism in males with sickle cell anemia and sickle beta zero thalassemia.

Secondary Outcome Measures:

1. Characterization of priapism in males with sickle cell anemia with reference to time of onset, duration of events, frequency of episodes, precipitating or associated activities, treatment modalities used, and outcome of treatments.
2. Descriptive comparison of the prevalence of priapism in males with sickle cell anemia to that described in older patients with other sickle hemoglobinopathies.
3. Assessment of general patient and parent understanding of priapism as a complication of sickle cell disease gained from completion of protocol.
4. Enumeration of patients available for clinical trials of secondary prevention.

Study Design: Standardized questionnaire survey of 1,400 male patients with sickle cell anemia and 250 additional patients with any other form of sickle hemoglobinopathy receiving care in any Comprehensive Sickle Cell Center.

Study Population: Males with sickle cell anemia and sickle beta zero thalassemia 5 years of age or older. Males with sickle beta plus thalassemia and sickle hemoglobin C disease 15 years of age and over.

Sample Size: 1,650 total; Each Center will be asked to survey a minimum number of male patients during a 7-month period, based on their patient population.

Human Subjects: Level of risk low. Patients may feel uncomfortable discussing priapism with their medical provider. The training manual will include suggestions for how to aide patients in feeling comfortable with this discussion. However, the educational benefit of learning about this complication of their hemoglobinopathy should outweigh the risk. Patients are free to not answer any question if they are too uncomfortable and to withdraw from the study without penalty at any time.

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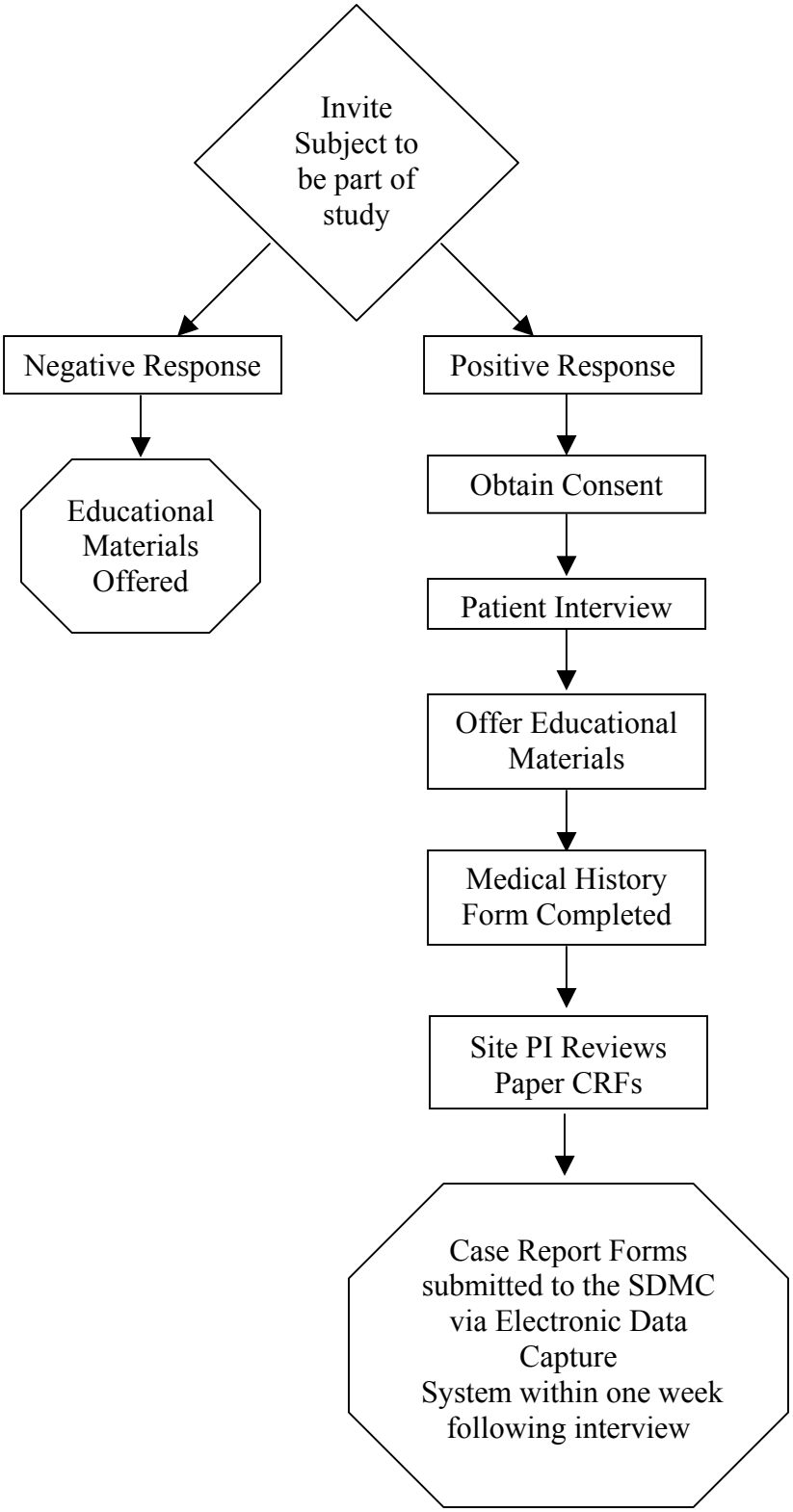
2 SUBJECT FLOW DIAGRAM



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4 ABBREVIATIONS

CSCC Comprehensive Sickle Cell Centers

CRF Case Report Form

EDC Electronic Data Capture

DSMB Data Safety Monitoring Board

GCP Good Clinical Practice

ICH International Conference on Harmonisation

HbSβ^0 Sickle Beta Zero Thalassemia

HbSβ^+ Sickle Beta Plus Thalassemia

HbSC Sickle Cell Hemoglobin C Disease

HbSS Sickle Cell Anemia

HIPAA Health Insurance Portability & Accountability Act

IRB Institutional Review Board

NHLBI National Heart, Lung, and Blood Institute

PRC Protocol Review Committee

SDMC Statistics and Data Management Center, located at Rho Federal Systems Division, Chapel Hill, NC

US United States

5 BACKGROUND AND RATIONALE

Priapism is an unwanted painful erection of the penis. It becomes more common with increasing age and vascular disease in the general population, and has been recognized as a complication of sickle cell disease since 1934. It occurs in two general patterns: (1) prolonged - an episode lasting 4 hours or more that carries with it a risk of permanent vascular damage and eventual impotence, and (2) stuttering - brief episodes that resolve spontaneously, often occur in clusters, but may herald a prolonged event.[1]

It is not known how many patients with sickle cell disease have experienced priapism. Historically, 5 to 10% of male sickle cell patients of any age were said to have had priapism.[2-5] Yet studies of adults with sickle cell disease now suggest that at least 30 to 45% of patients have a history of this complication.[6, 7] In a Jamaican survey of 104 patients with sickle cell anemia (HbSS), 42% (or 44 patients) had experienced at least one episode of priapism. The mean age at onset was 21 years, and no patient reported an episode before age 5 years.[7] Nigerian investigators, however, reported that 16% of male patients with sickle cell anemia and priapism were younger than 5 years of age.[8] A large review of published cases concluded that about half of all reported sickle cell patients with priapism had their first episode before they were 18 years old.[9] The systematic survey of male patients 5 to 20 years of age with sickle cell anemia reported from Dallas confirmed that the problem is common, with a cross-sectional prevalence of 27.5% and an actuarial incidence of 89% ± 9% by 20 years of age.[1] Thus, priapism is a common problem even in children.

There is also a wide variation in frequency of episodes (one time only to daily for months or years, with 2 to 50% of patients reporting recurrent episodes), age at onset (toddler to adult), associations that promote the occurrence or ending of episodes, and eventual outcome (spontaneous resolution or impotence).[1] Retrospective surveys indicate that priapism is most common in patients with sickle cell anemia (HbSS), who account for 80 to 90% of reported cases.[5, 6, 9, 10] However it may occur in persons with all forms of sickle cell disease, and has even been reported to be increased in individuals with sickle cell trait.[9] A single episode of priapism was reported by 31 to 64% of patients, a pattern that appears to be more common in childhood.[1, 5, 7] About half of all patients, however, have recurrent episodes from 2 to 50 times per year.[6] The pattern of recurrent episodes is also very individual. Stuttering spells may occur every few days for months before stopping abruptly or heralding a prolonged episode.[7] Other investigators noted no clustering and related patients with years of unpredictable recurrent events.

The occurrence of priapism has been associated with higher levels of hemoglobin S[11] and found to be inversely correlated with levels of fetal hemoglobin[12] in specific populations. This is also suggested by the 42% incidence of priapism reported in Jamaican patients[7] compared to 2% of patients from Saudi Arabia where, on average, fetal hemoglobin levels are higher in HbSS patients.[13] Other investigators have observed no relationship to fetal hemoglobin levels.[5] Priapism has been suggested by some authorities to be more common in patients experiencing a severe course[5] of their

sickle cell disease and by others to not be associated with overall severity.[6] In the Dallas survey, no significant difference was found in the baseline hematologic values or number of hospital admissions for painful events between patients with and without a history of priapism.[1]

In the literature, 77% of priapism episodes reported occurred during sleep, 17% were related to sexual activity, and 3% each were related to excessive alcohol intake or were called spontaneous.[9] Today, cocaine or other drug use would probably be a more significant factor, at least in older adolescent and adult patients. In the Dallas survey, half of the patients reported that urination or use of oral opioid analgesics terminated episodes, while about one-third mentioned that mild exercise or bathing in warm water was effective. Further, one-third of the boys described the pain of priapism as the worst complication of their sickle cell disease.[1] None of these associations or therapies have either been prospectively investigated or validated in a large clinical cohort from the United States. Priapism remains the most common complication of sickle cell disease not investigated by the Cooperative Study of Sickle Cell Disease or the Comprehensive Sickle Cell Center Clinical Trials Consortium, until now.

This protocol will investigate the epidemiology of priapism by a survey of males over 5 years of age with all forms of sickle cell disease. This questionnaire is patterned after the published Dallas survey. Patients will be asked about the frequency, time of onset, and precipitating causes of priapism as well as the type of interventions that they have utilized to terminate episodes. These data will be correlated with age, hemoglobinopathy, baseline hematologic values, current therapy if any (i.e., hydroxyurea or chronic transfusion), prior history of prolonged episodes requiring aspiration and irrigation or shunt procedures for priapism, other complications of their sickle cell disease (chest syndrome, avascular necrosis, history of obstructive sleep apnea and/or prior tonsillectomy or adenoidectomy, hospitalization for painful events, stroke, and subarachnoid hemorrhage), and center location. Data from this survey will provide important information on the characteristics and frequency of priapism that will be of use in the design of future intervention strategies. In addition, the questionnaire will aide in the initiation of discussion about priapism between patients and clinical staff as well as making patients aware of the subsequent clinical intervention trials should they then or subsequently become eligible.

This clinical trial will be conducted in compliance with the protocol, International Conference on Harmonization (IHC), Good Clinical Practice (GCP) guidelines, and other applicable regulatory requirements.

6 STUDY OBJECTIVES AND PURPOSE

Primary Hypothesis:

Priapism is a common complication of sickle cell disease. In 5- to 10-year-old patients, it is hypothesized that the prevalence of priapism is 10%. In 10- to 15-year-old patients, it is hypothesized that the prevalence of priapism increases to 20%. In patients over 15 years old, it is hypothesized that the prevalence of priapism reaches 30%.

Objectives:

1. Enumerate the cross-sectional prevalence, demographics, and common clinical characteristics of priapism in males with sickle cell disease among the CSCC patient population.

2. Identify patients eligible for randomized clinical trials of promising secondary prevention strategies.

Specific Aim(s):

1. To conduct a questionnaire survey of 1,400 males with sickle cell anemia (HbSS) and sickle beta zero thalassemia ($HbS\beta^0$) 5 years of age and older in order to determine the prevalence (frequency) and characteristics (number and pattern of episodes, cause or precipitating event, treatment, and outcome) of priapism.

2. To survey 250 additional males with other forms of sickle cell disease with the same instrument and describe the occurrence and characteristics of priapism experienced.

3. To develop a structured educational brochure about priapism for patients with sickle cell disease.

4. To identify the number of patients with recurrent priapism potentially eligible for randomized clinical trials of secondary prevention strategies.

7 STUDY DESIGN

7.1 Treatment Plan

1. A one-page, culturally-sensitive, face-to-face interview will be conducted by trained center staff to ascertain patients' awareness of priapism as a complication of sickle cell disease. Prior to administering the questionnaire to patients less than 15 years of age, an explicit discussion will be held with his parent(s) or guardian(s) regarding the sexual content of the survey. The words and phrases used to question their child will be reviewed at this point, and the parent/guardian signature on the pediatric consent form will document that the discussion occurred.

2. If the patient or parent indicates that priapism has occurred, approximately 18 additional questions will be asked in order to characterize the episode(s).

3. The principal investigator at each local site will review all of the questionnaires from subjects who report that they have had an episode of priapism and indicate they have done so by initialing each questionnaire. If there are health issues identified that could require treatment or referral, the physician or clinic medical staff will discuss options for care with the participant and/or make appropriate referrals. Such issues include drug use, harmful sexual behaviors, or impotence. Subjects who report that they have never had an episode of priapism do not complete the entire questionnaire, and do not answer questions regarding any issues that could require referral.

4. A brief demographic Case Report Form will be completed for all participants who have signed the consent forms, regardless of their experience with priapism.

5. An educational brochure containing information about priapism, including available clinical trials, and a check for participating will be given to the patient or parent/guardian at the conclusion of the interview.

7.1.1 Primary and Secondary Endpoints

Primary Outcome:

Enumeration of the prevalence of priapism in males with sickle cell anemia and sickle beta zero thalassemia.

Secondary Outcome Measures:

1. Characterization of priapism in males with sickle cell anemia with reference to time of onset, duration of events, frequency of episodes, precipitating or associated activities, treatment modalities used, and outcome of treatments.

2. Descriptive comparison of the prevalence of priapism in males with sickle cell anemia to that described in older patients with other sickle hemoglobinopathies.

3. Assessment of general patient and parent understanding of priapism as a complication of sickle cell disease gained from completion of protocol.

4. Enumeration of patients available for clinical trials of secondary prevention.

7.2 Rationale for Study Design

The estimates of the frequency of priapism in men and boys with sickle cell disease vary widely. The definitions of priapism used, age and location of the population surveyed, as well as the training and sensitivity of the interviewer clearly may influence reports. This is the first large-scale survey of males of all ages with sickle cell disease in well-organized sickle cell programs. As such, it should escape the obvious biases of prior surveys of men seeking urologic consultation for impotence, studies of patients with the same disease but in different cultural settings (i.e., the African surveys), or studies involving pediatric patients only. It is a vital first step in determining the magnitude of the problem for patients with sickle cell disease. A rational intervention trial for this complication cannot be designed without the information from this study, numbers of patients, frequency of episodes, and treatments received.

A randomly selected subset of all US males with sickle cell disease would provide an ideal study population to determine the most unbiased estimate of the prevalence of priapism. Clearly, privacy and logistical issues eliminate this as a realistic choice of study design. Such a list does not exist and HIPAA concerns prohibit this approach. A more probable design would be to identify a random subset of all males known to participating Centers from a patient list or census. Unfortunately, few Centers are able to maintain a database such as this, and those that do report that patient contact information is often inaccurate, outdated, or incomplete. More importantly, confidentiality and privacy regulations prohibit the use of patient information for such purposes.

For these reasons, adult and pediatric male patients presenting to a Comprehensive Sickle Cell Center for follow-up, scheduled laboratory or transfusion, emergency department visit, or hospitalization will serve as the target population. Prevalence estimates obtained in this manner may be subject to ascertainment bias, limiting generalizability of the findings. However, these are the patients who are seen in clinical centers and for that reason they are a truer representation of the patients that knowledgeable clinicians typically see. There is no current literature to suggest whether or not males who experience other sickle cell-related complications or events are more or less likely to experience priapism, making prediction of the extent and direction of this bias impossible

to assess. Further, lack of an acceptable, affordable alternative study design supports the use of this approach. All publications from this study will identify the study population in detail and acknowledge the possibility of this potential bias.

By utilizing the significant clinical resources of the CSCC Clinical Trials Consortium and the established research infrastructure of the CSCC SDMC, this study can be conducted in a standardized and efficient fashion. Centralized training should help interviewers of both sexes to increase their comfort level with questioning and educating patients about priapism. While it may be beneficial to have male, African-American interviewers, this may not be possible in every center. Participating sites will be encouraged to carefully consider such factors in deciding whom to select to be trained to administer the questionnaire in their center. Role-playing and information in cultural contexts of this complication, possible only during a centralized training session, will enhance this study, future research efforts about priapism in sickle cell disease, and the clinical care of patients. Centralized data collection will be conducted via a web-based form that mirrors the CRFs (included in Appendices 1-3), a format that all clinical centers should be comfortable with from prior CSCC studies.

The educational pamphlet about priapism developed for this survey will provide a benefit to patients and their families in consolidating their knowledge about sickle cell disease and priapism. Copies of the pamphlet will also be available to educate patients who decline to participate in the study but who may be eligible for later intervention trials. This study is a vital first step in the rational approach to the design of intervention studies in priapism.

8 ELIGIBILITY AND DISCONTINUATION OF SUBJECTS

All males over age 5 with access to care in a Comprehensive Sickle Cell Center (CSCC) or participating institution associated with a CSCC (for interval follow-up, scheduled laboratory or transfusion, emergency department visit, or hospitalization) will be eligible for recruitment without regard to known history of priapism. The interview will be administered face-to-face by trained staff at each CSCC site who are knowledgeable about and comfortable discussing priapism. A professional who understands the cultural aspects of this and similar sensitive health behavior subject matter will train the interview personnel to use culturally recognizable and appropriate language during the interviews. Written materials from that presentation will become part of the training manual for the study. If the patient is experiencing a stressful clinical event such as painful crisis, consent may be obtained for the interview to be conducted in the future. Clinical staff will record the responses on the interview form during the interview. Participation from all 10 CSCCs is desirable. Centers may have more than one designated study site; therefore, as many as 20 clinical sites from the nine participating Centers may serve as sources for study enrollment. It is hoped that expedited Institutional Review Board (IRB) review and use of a brief written consent form will be acceptable to local IRBs for participation in this survey.

8.1 Inclusion Criteria

Subjects who meet all of the following criteria are eligible for enrollment into the study:

1. Subject or parent/guardian gives written informed consent.
2. Male with or sickle cell anemia or sickle beta zero thalassemia 5 years of age or over

   - OR –

   Male with sickle beta plus thalassemia or sickle hemoglobin C disease 15 years of age or over.
3. Subject and/or parent/guardian able to communicate adequately with the interviewer.

Subjects currently taking hydroxyurea, undergoing chronic transfusion, or participating in other research trials including those involving agents such as arginine are eligible for the study if all other entry criteria are met.

8.2 Exclusion Criteria

Subjects who meet any of the following criteria are disqualified from enrollment in the study:

1. Patient or parent/guardian declines participation.
2. Female.
3. Subject or parent/guardian unable to communicate adequately with the interviewer.

8.3 Subject Discontinuation

Subjects may decide to discontinue participation at any time during the interview. Investigators may discontinue any subject at their discretion if, in their professional opinion, the subject's health, safety, and/or well-being is threatened by continued participation in the study. The following circumstances may require discontinuation of subjects:

1. Patient or parent/guardian becomes emotionally distressed by questions or discussion.
2. Patient or parent/guardian requests discontinuation of the study.

Adverse events caused by participation in the study may necessitate modifications to the level of participation of a subject or discontinuation of a subject from the study. Subjects who discontinue early from the study before a full questionnaire is completed or for whom demographics cannot be obtained will be replaced by recruitment of additional subjects up to a maximum of 1,650 subjects.

9 DATA COLLECTION AND DATA MONITORING

9.1 CRF and Source Documentation

The site study coordinator will complete interview and demographic case report forms (CRFs) for each subject (see Appendices 1-3). A detailed manual will be provided to each site to assist staff in: 1) obtaining sensitive information by face-to-face questioning; 2) ensuring appropriate coding of the questionnaire responses; and 3) ensuring correct completion of the CRF. Instructions for administration of interviews, completion of CRFs, and submission of data will be discussed at a training session prior to the beginning of the study.

All data recorded on the study forms must be legible and recorded in black ink or typed. Data errors are not to be erased, removed with "white out," or completely blackened over; rather, one line should be drawn through the error, the correction entered near by, and the entry initialed and dated by the Site Principal Investigator or study coordinator.

The paper questionnaire forms completed for each subject will be retained in a secure location in each clinical site as the primary source document.

When required information has not been provided, an explanation should be provided in a comments section of the CRF.

CRF data must be well maintained and up-to-date. The questionnaire portion of the CRF should be completed in hard copy during the interview, and the demographic portion of the CRF should be completed within one week of the interview.

Subjects will be identified by CSCC subject numbers assigned at enrollment. Names and other identifiers will not appear on any study documents.

9.2 Data Management

The Statistics and Data Management Center (SDMC), which is Rho Federal Systems Division, Inc., located in Chapel Hill, North Carolina, will provide statistical and data management support for this study. Responses to interview and demographic CRFs will be entered into a web-based data collection system by CSCC Center Staff within one week of the visit at which the data were collected. The data collection system will be developed and maintained by the SDMC.

9.3 Data Monitoring

After study initiation, individual sites will monitor CRFs and source documents for accuracy, protocol compliance, subject safety, and adherence to guidelines outlined in the CSCC Manual of Procedures.

9.4 Timeline

To PRC for review of study materials	October 2004
PRC approval	November 2004
Negotiate study budget	November 2004
To DSMB for review of study materials	January 2005
Final DSMB Approval	March 2005
Distribution of Informed Consent Templates to sites	April 2005
Negotiate study budget	May 2005
Interviewer Training	May 2005
Pilot testing	June 2005
Finalize Case Report Forms and EDC system	July 2005
EDC Training	July 2005
Enrollment begins	July 2005

It is anticipated that enrollment should be rapid. If most clinical Centers see 50 total patients per week, 40% of whom are male (as males may be less likely to present for comprehensive care), there will be 20 potential subjects per week per Center. Excluding the subjects under age 5 who may be half of all subjects in pediatric Centers, this allows 10 potential subjects per Center per week. Clinical time considerations, age/genotype stratification of the study, or patient preference may exclude half of the eligible subjects, allowing conservatively 5 subjects per Center per week. If all 10 Centers participate, this would allow 50 subjects into the study every week. This is especially true since there are 10 Centers in the CSCC, but several of the Centers have more than one site. Total planned accrual is 1,650 subjects, which should be achievable in 33 weeks of full enrollment. Given the realities of beginning a study in a large number of Centers, and the relative scarcity of older patients relative to younger ones, it is anticipated that it may take up to twice this long from the date of first subject enrollment to full accrual.

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10 STATISTICAL ANALYSIS

10.1 Sample Size

Approximately 1,650 questionnaires will be completed by patients cared for in all participating institutions. Fourteen hundred of these will be from subjects with sickle cell anemia (HbSS) or the clinically similar sickle beta zero thalassemia ($HbS\beta^0$). Prior studies of prevalence have suggested that priapism is most common in patients with HbSS, and this work has provided the data for the hypothesis of prevalence in this study. All statistical considerations detailed below apply to the 1,400 HbSS/$HbS\beta^0$ questionnaires.

An additional 250 questionnaires from males with sickle beta plus thalassemia ($HbS\beta^+$) and sickle hemoglobin C disease (HbSC) will also be obtained and evaluated descriptively. This sample will not allow for a statistical estimate of priapism prevalence; rather, this analysis will be descriptive and provide information for case study. It will also suggest a rationale for inclusion or exclusion of patients with these disorders in subsequent intervention trials.

Survey numbers will be stratified by age using previously reported[1,14] frequencies of priapism in different age groups. In a survey of pediatric sickle cell anemia patients whose methodology closely matches that of this study, the actuarial cumulative frequencies of priapism at different ages were reported as: 12.9%$\pm$4.1% by 10 years of age, 50.3%$\pm$8.5% by 15 years of age, and 89.3%$\pm$9.0% by 20 years of age[1]. A survey of adult patients with all genotypes of sickle cell disease disclosed a frequency of 35% of the population at a mean age of 22 years.[14] Clearly there is some recall bias in adult patients for an event that could have happened decades earlier.

Enrollment of patients from each center will be on a first-interviewed-and-demographic-form-completed basis. The 1,400 questionnaires from HbSS/$HbS\beta^0$ patients will be further divided into the following strata:

- 200 subjects ages 5 to 9.9 years
- 400 subjects ages 10 to 14.9 years
- 400 subjects ages 15 to 24.9 years
- 400 subjects age 25 years and older.

The 250 HbSC and $HbS\beta^+$ questionnaires will be from persons 15 years of age and older and in any proportion of those diagnoses. Each center will be encouraged to enroll all patients that they have available up to 25% of the total number of respondents in each age range until the total desired is reached. When a center enters 25% of the total patients in one age stratum, or the grand total of participants for an age stratum is reached, no further

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questionnaires will be accepted by the SDMC from that center in that age stratum. Centers will be encouraged to continue to enter patients in other age strata.

We will estimate the priapism prevalence and its 95% two-sided confidence interval for 4 age groups: 5 to 9.9 years, 10 to 14.9 years, 15 to 24.9 years, and 25 years and older. To estimate the necessary sample sizes for each age group, we used the formula:

$$n = \frac{(2 \cdot 1.96)^2 (p)(1-p)}{(w)^2}$$

where w is the total confidence interval width, and p is the expected prevalence.

If an age group has a priapism prevalence of 15%, then 196 completed interviews are needed for a 0.10 wide 95% two-sided confidence interval for the estimated proportion of patients with priapism among patients with sickle cell disease. A group that has a priapism prevalence of 30% will need 323 completed interviews; 385 completed questionnaires are needed for a group that has a priapism prevalence of 50%. We would like to conduct more interviews in each category than these predictions suggest to be sure of obtaining adequate data to achieve the aims of this study. Specifically, we seek to obtain 1,400 complete interviews with accompanying demographic data according to the age distribution noted earlier. With the planned sample size and anticipated observed proportion of patients with priapism in each age range, each of the 4 two-sided 95% confidence intervals should have a total width of 0.10. The specified sample sizes for the 15 to 24.9 years strata and 25 or older may not be reached, in such a case the two-sided 95% confidence interval will have a total width larger than 0.10.

Tabulation of the responses to the questions on the patient survey and correlation with information collected on the demographic sheet will provide the data necessary to accomplish the primary and secondary outcome measure #1. The responses from the 250 HbSC/HbSβ^+ participants will not be used to establish a prevalence of priapism per se, rather interesting characteristics including absence of episodes will be compared to those reported by the HbSS/HbSβ^0 group. Participation of patients in the questionnaire will allow attainment of secondary outcome measure #3. The combined sample size and division between participating centers will allow us to estimate prevalence aggregating across all sickle cell centers as well as look at differences between centers. With the planned sample size and anticipated observed proportion of patients with priapism in each age range, a two-sided 95% confidence interval based on a normal approximation will have a total width of 0.10.

Sites will be requested to track rates of and reasons for refusal and basic demographic data which will not be reported except in an aggregate format.

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10.2 Statistical Methods

In each age strata, an unadjusted 95% confidence interval of the priapism prevalence based on a normal approximation will be used to accomplish the primary outcome measure #1. Numerical summaries and frequency tabulation of the responses to the questions on the patient survey and information collected on the demographic sheet will provide the data necessary to accomplish the secondary outcome measure #1. Descriptive comparisons between the 1,400 HbSS/HbSβ^0 and the 250 HbSC/HbSβ^+ responses will accomplish secondary outcome measure #2. Tabulating the number of patients who did not know about priapism at start of study will accomplish the secondary outcome measure #3. The completed database will identify patients that are available for future clinical trials of secondary prevention and accomplish the secondary outcome measure #4. In addition to the primary objective and three secondary objectives, exploratory analyses will be completed to identify any differences between Ccenters and disease diagnoses.

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11 HUMAN SUBJECTS PROTECTION

11.1 Discontinuation of Study

Due to the single visit questionnaire nature of this study, it is not anticipated that early discontinuation will be required. While priapism can be a sensitive subject to discuss, care will be taken to encourage Centers to select appropriate interviewers and to provide appropriate training for interviewers to minimize participant and interviewer distress. Subjects may discontinue their participation at any point in the interview if they wish to do so, for any reason, at no risk to themselves. The National Heart Lung and Blood Institute (NHLBI) reserves the right to discontinue the study at any time for administrative reasons. Investigators will be reimbursed for reasonable expenses.

11.2 Ethics

11.2.1 Good Clinical Practice and IRB Review

Compliance with Good Clinical Practice (GCP) guidelines for the conduct and monitoring of this study will occur through observation of the ethical and regulatory requirements presented in ICH E6, Good Clinical Practice: Consolidated Guideline. By signing this protocol, the investigator agrees to adhere to these requirements. The study (protocol, informed consent, advertisements, subject information sheets, and Investigator CV and credentials) will be reviewed and approved by the IRB or ethics committee at each participating Center. Changes to the protocol may be initiated by the NHLBI and approved by the IRB. Subjects or their parents/guardians if appropriate, will be required to give verbal or written informed consent as required by local IRB standards. Sample IRB acceptable consents and HIPPA documents at the University of Texas Southwestern Medical Center are attached.

The investigators and institutions affiliated with this study will permit trial-related monitoring, audits, Data Safety Monitoring Board (DSMB)/IRB review, and regulatory inspection(s) by providing direct access to source documents.

11.2.2 Informed Consent

Subjects will be provided with a copy of the informed consent and printed materials that explain the purpose of the study, procedures, and assessments. Subjects will also be provided with the telephone numbers of the investigator and qualified personnel who can assist with their questions and/or concerns.

11.2.3 Confidentiality

Subject confidentiality will be maintained by the investigator, the investigator's associates and co-workers, and by all administrators who are part of the CSCC project.

Confidentiality will be maintained according to ICH E6; 4.8.10, part O: "Records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential."

11.3 Disclosure of Data

The investigator, his or her staff and associates, and the appropriate regulatory agencies may use the information included in this protocol as necessary for the conduct of the study and the safety of subjects. Data from the trial are confidential and may not be disclosed without the written permission of the NHLBI.

11.4 Publication of Research Findings

Manuscripts and abstracts prepared from the data collected during this trial will be prepared by the study investigators and the SDMC in accordance with the policies and procedures developed by the Publications Committee and approved by the CSCC Steering Committee.

11.5 Strategies to Protect Privacy and Confidentiality

Since participation in the Epidemiology of Priapism study only involves inclusion in a database, there are no potential risks to subjects that may result from clinical treatment or intervention. The risks to an individual's privacy or confidentiality due to unauthorized or inappropriate sharing or release of medical data are no greater than that encountered when participating in any other CSCC-supported investigation. However, since the subject matter and focus of this study address issues of a sensitive nature, it is especially important that the SDMC utilize several strategies to minimize this risk. These strategies include:

- SDMC provision of study-specific training for all CSCC Center staff prior to patient enrollment and initiation of the interview process and at regular intervals throughout the study period.
- Providing technical assistance related to all aspects of assuring patient privacy, confidentiality, and protection.
- Providing a data management system fully validated to 21CFR, Part 11 requirements.

12 COMMUNICATION

A well-developed and easily used communication system will facilitate successful achievement of the Epidemiology of Priapism study objectives. A web-based Network Communication System (RhoNET™) developed by Rho is currently being used to support CSCC work. The SDMC will establish and maintain a Priapism area of this CSCC website to facilitate ongoing day-to-day communication between the SDMC, Center data coordinators and data entry staff, the CSCC Steering Committee and Priapism Protocol Committee, and the NHLBI Project Officer. The Priapism area of the website will provide features currently available on the CSCC general site, with special emphasis on the following:

- A general information area for contact information for all CSCC Priapism Data Coordinators, other Center personnel, and SDMC Priapism study staff;
- Priapism Protocol Committee and DSMB meeting materials including meeting schedules, agendas, and minutes;
- Priapism Project materials including training documents, the study protocol, case report forms, and informed consent materials; and,
- A weekly enrollment tracking report and graph showing the number of subjects enrolled by site.

Conference calls for Center Data Coordinators and/or Center Directors will be scheduled as needed, to discuss Priapism Project progress and issues.

13 SUBJECT COMPENSATION

Subjects will receive $25 to cover some of the costs incurred while participating in the study (e.g., prolonged parking fees) and to compensate them for their time.

14 LIST OF INVESTIGATOR(S) AND CLINICAL LABORATORY(S)

This section lists the name(s) and title(s) of the investigator(s) who is/are responsible for conducting the trial, and the address(es) and telephone number(s) of the trial center(s).

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5	Marilyn Telen, MD	Duke-UNC CSCC Division of Hematology Box 2615 Duke Univ Medical Center Rm 333 Durham, NC 27710 (919) 684-5378
6	Marie Stuart, MD	Marian Anderson Sickle Cell Anemia Care and Research Center Thomas Jefferson University 1025 Walnut Street College Bldg., Suite 727 Philadelphia, PA 19107 (215) 955-9820
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9	Winfred Wang, MD	St. Jude Children's Research Hospital CSCC Department of Hematology/Oncology 332 North Lauderdale Bldg R-6010 Mail Stop Code 763 Memphis, TN 38105 (901) 495-3497
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