Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH)

PROTOCOL

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CHAPTER 1

BACKGROUND AND STUDY RATIONALE

1.1 HISTORICAL BACKGROUND

Sickle cell anemia affects nearly one in every five hundred black newborns in the United States. To date, there is no effective treatment for the patient with sickle cell anemia to prevent recurrent, vaso-occlusive (painful) crises. There are an estimated 50,000 people in the United States with sickle cell anemia. Of these 50,000 at least 10% (5,000) of the adults have more than three crises per year based on projections from the Study of the Cooperative Study of Sickle Cell Disease (CSSCD).

The first indication that Hb F interfered with sickling was Watson's observation that children with sickle cell anemia did not begin to develop symptoms until Hb F levels had dropped to those seen in adults.[1] Much stronger clinical evidence was provided some years later by description of the asymptomatic compound heterozygous condition sickle cell/hereditary persistence of fetal hemoglobin[2] and patients with relatively mild sickle cell anemia in eastern Saudi Arabia and India.[3] Most recently, data from 3,578 American patients studied by the CSSCD show that Hb F level is a significant predictor of pain rate, over the entire range of values encountered, without a threshold, predicting that any increase in Hb F would be beneficial.[4]

1.2BIOPHYSICAL STUDIES

Concentrated solutions of Hb S "gel" when deoxygenated, and Hb F interfered with that process.[5] The effect of Hb F is twofold, for neither the intact Hb F molecule nor the hybrid tetramer $\alpha_2\gamma\beta^S$ could polymerize.

1.3RATIONALE FOR THE CHOICE OF AGENT

De Simone and his coworkers administered 5-azacytidine to anemic baboons, and produced striking increases in their F cell production.[6] Administration of 5-azacytidine increased Hb F in SS patients[7], but 5-azacytidine has unacceptable side effects. Hydroxyurea is probably a safer drug than 5-azacytidine. Hydroxyurea has also been shown to increase Hb F in SS patients and uncontrolled observations have associated hydroxyurea administration with decreased frequency of vaso-occlusive (painful) crises.[8] The mechanism of drug action in stimulating fetal hemoglobin synthesis in patients with sickle cell anemia is unknown.

1.4 REFERENCES

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CHAPTER 2

OVERVIEW OF OBJECTIVES AND DESIGN OF THE TRIAL

2.1 INTRODUCTION

The Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) is a double-blind, placebo controlled study designed to determine if treatment with orally administered hydroxyurea, in maximal tolerated doses, can decrease the frequency of vaso-occlusive (painful) crises in patients with sickle cell anemia by at least 50%. Patients with sickle cell anemia enrolling in the study will have had at least three vaso-occlusive (painful) crises in the 12 months preceding study entry.

The primary analysis in the MSH will be the comparison of rates of vaso-occlusive (painful) crises between patients assigned to treatment with hydroxyurea and patients assigned to treatment with placebo. Vaso-occlusive (painful) crises will be classified according to defined criteria by an independent Crisis Review Committee. The Crisis Review Committee members will be blind to study treatment assignment.

Measurements of fetal hemoglobin production, blood counts and serum chemistries will be made along with clinical observations to evaluate the role that fetal hemoglobin production plays in the pathophysiology of sickle cell crises, and as surveillance for toxicity due to hydroxyurea.

2.2 OBJECTIVES

The primary objective is to determine whether or not treatment with hydroxyurea titrated to maximum tolerated doses will reduce by at least 50% the frequency of vaso-occlusive (painful) crises. The principal end point is the occurrence of a vaso-occlusive (painful) crisis, defined as pain not due to another cause, lasting at least

four hours and requiring parenteral (or equivalent doses of oral narcotics at clinics not dispensing parenteral narcotics) narcotics or non-steroidal anti-inflammatory drugs for relief. Occurrences of chest syndrome will be counted as crises. Pain due to chronic conditions such as ankle ulcers, osteomyelitis or aseptic necrosis of bone will not be counted as crises.

Secondary objectives are to establish the relationship of fetal hemoglobin levels and other patient or treatment characteristics to the occurrence of vaso-occlusive (painful) crises, and the effect of treatment on the quality of patients' lives.

2.3 DESIGN FEATURES

2.3.1 Eligibility

Men and women with sickle cell anemia, aged 18 or over, may be eligible for the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (for a detailed description of eligibility criteria see Chapter 3).

2.3.2 Allocation of Treatment

The study is a randomized, double-blind, placebo-controlled clinical trial. Patients meeting all of the eligibility criteria will be asked to give informed consent. After obtaining informed consent, and successful completion of a "run-in" period during which pre-treatment data will be collected, the enrolling Clinical Center staff will request a treatment allocation from the Data Coordinating Center. If the Data Coordinating Center staff confirm the potential participant's eligibility, they will issue a treatment allocation. The treatment assignments will be made using separate randomization schedules for each participating Clinical Center. These schedules will be prepared by the Data Coordinating Center prior to the initiation of patient recruitment and will be designed to allocate eligible patients

equally to the two treatment groups after specified numbers of participants are enrolled. The study will be conducted double-blind, that is, neither the Clinical Center staff nor the patient will be informed of the patient's treatment assignment. This will be accomplished by packaging active study medication and placebos so they are identified only by a code number.

2.3.3 Dose Titration

All patients assigned to hydroxyurea will begin with an initial dose of 15 mg/kg which will be incremented by 5 mg/kg every twelve weeks but never to a daily dose of greater than 35 mg/kg. Every two weeks blood specimens will be obtained from each patient and shipped to the Core Laboratory. Blood counts (performed in the Core Laboratory) and other Core Laboratory analyses will be used to monitor for bone marrow depression (toxicity). The Data Coordinating Center will receive blood counts from the Core Laboratory daily as Core Laboratory staff process blood specimens. On a daily basis, the Data Coordinating Center will run a computer program that will be specifically designed to review the previously accumulated blood cell counts for all patients who have had new complete blood cell counts or Core Laboratory data entered. Patients will be classified on the basis of their laboratory data as pre-toxic, toxic or non-toxic. Based on the patient's history in the study and classification as pre-toxic, toxic or non-toxic, a dose recommendation will be made for each patient on hydroxyurea. Dosage adjustments will be made for the patients assigned to placebo therapy in order to keep patients and clinic coordinators blind to treatment assignments. Treatments Distribution Center (TDC) staff will ship 12-week supplies of hydroxyurea or placebo to Clinical Centers for each patient.

2.3.4 Ascertainment of End Points

Four methods will be used to obtain the complete ascertainment of all vaso-occlusive (painful) crises: first, the importance of reporting crises will be explained to all patients; second, patients will keep a daily diary of attacks of pain; third, every two weeks the diary will be reviewed with the patient by the clinic coordinator; and fourth, the assistant coordinator in the Central Office will call each patient monthly to inquire about crises. Information from other sources such as the patient's family, the patient's physician or medical center staff who learn of hospitalization or out-patient treatments for the patients will be used as prompts for potential reports.

All episodes of acute medical care provided will be identified. For those episodes which could be associated with vaso-occlusive (painful) crises, copies and/or abstracts of medical records and narrative summaries will be submitted to the Crisis Review Committee (CRC) for classification. All cases presented to the CRC will be reviewed independently by two of its members. The members of this committee will also review data collected on each study patient who dies. An outline of the study design is presented in Exhibit 2-1 and the two week cycle of study procedures and data collection is presented in Appendix III.

2.3.5 Size of Study and Duration of Follow-Up

The overall recruitment goal for the Multicenter Study of Hydroxyurea in Sickle Cell Anemia is 296 patients with 148 patients assigned to each of the two treatment groups. It is expected that it will take one year to achieve this recruitment goal.

Dose titration to maximum tolerated doses of hydroxyurea will take approximately one year for each patient. Each patient will be followed

for at least two years from the time of study entry. Every effort will be made to maintain contact with the patients so that all participants will have a complete two years of follow-up after study entry. When a participant fails to keep a scheduled appointment, the Clinical Center staff will be expected to contact the participant immediately to reschedule the appointment. If a participant stops returning for scheduled visits, every effort will be made to obtain minimum follow-up information regarding morbidity including, at least, his or her vital status.

Patients who have cerebral vascular accidents or other serious complications of sickle cell anemia will have the clinical outcome completely documented and may undergo additional necessary therapy as indicated.

2.3.6 Data Monitoring and Patient Safety

During the Multicenter Study of Hydroxyurea in Sickle Cell Anemia, the specific primary and secondary end points as well as other information concerning the effects of hydroxyurea therapy will be reviewed by the Data and Safety Monitoring Board (DSMB). Every six months from the beginning of enrollment, the DSMB will review safety monitoring data. The DSMB will review accumulated data on efficacy at 18, 24, 30 and 36 months after the start of study treatment and follow-up, for a total of four interim looks. These reviews will determine whether the accumulated data indicate that protocol changes are warranted by evidence of adverse effects or overwhelming beneficial effects in one of the treatment groups.

Individual cases of serious (requiring medical intervention) or unexpected adverse effects possibly related to the study drugs will be

reported immediately by the study physician by submitting reports to the Central Office with a copy to the Data Coordinating Center.

2.4 RESPONSE VARIABLES TO BE MONITORED

The main objective of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia is the assessment of efficacy of hydroxyurea for the reduction of the frequency of occurrence of vaso-occlusive (painful) crises in sickle cell anemia. For that purpose, the primary response variable will be the occurrence of vaso-occlusive (painful) crises from the time of study entry to the time of study closeout for each patient in the study. Patients who are taken off their study treatments because of the development of conditions which make continuation of study treatments unacceptable will continue in follow-up and will contribute all events observed to the primary analysis. Some secondary analyses may include only those events observed while the patient was receiving study medicines.

Measures of hemoglobin-F production, such as hemoglobin-F level, and % F cells, will be measured every four weeks in the Core Laboratory and analyzed for changes in relation to treatment assignment. Occurrence of crises as a function of hemoglobin-F measures will be included among the secondary analyses.

The frequency of clearly definable complications of sickle cell anemia and potential complications of hydroxyurea therapy such as infection, hair loss, gastrointestinal disturbance, and bone marrow depression will be ascertained at each follow-up visit. Compliance and reasons for non-compliance will be recorded at each follow-up visit.

An independent Crisis Review Committee will have responsibility for reviewing and classifying all fatal events as well as complications of sickle cell anemia and vaso-occlusive (painful) crises. Each event

will be classified using predetermined definitions without knowledge of study treatment assignments.

2.5 STUDY SIZE CONSIDERATIONS

The proposed number of patients enrolled in the Multicenter Study of Hydroxyurea in Sickle Cell Anemia is 296 (148 assigned to each of the two study therapies). Estimates of power to detect differences between these two groups have been calculated. These power estimates are given in Exhibit 2-2, and derivations of these power calculations are presented in Appendix V. With 148 patients in each treatment group, the primary analysis would have power of almost 0.90 to detect a 50% reduction in vaso-occlusive (painful) crisis attack rates between the two treatments. Recruitment of 296 patients in the Clinical Centers is, thus, appropriate for the proposed study.

Interim assessment of the primary outcome measure will be carried out at four points -- at 18, 24, 30 and 36 months of follow-up -- before the final analysis is conducted in order for the Data and Safety Monitoring Board to determine whether early termination of the study is warranted. To maintain the overall Type I error rate at the desired level, account must be taken of the multiple looks at the data when conducting interim analyses. The critical test statistic, Z, will be 3.29 for each interim analysis (nominal p-value equals 0.001), and for the final analysis 1.99 (nominal p-value equals 0.046). The final comparison is very close to the critical value of z ($\pm$ 1.96) corresponding to α = 0.05 which would have been used if no interim monitoring had been conducted, but it will be possible to end this study early if initial results show one treatment greatly superior to the other.

EXHIBIT 2-1

MSH STUDY DESIGN

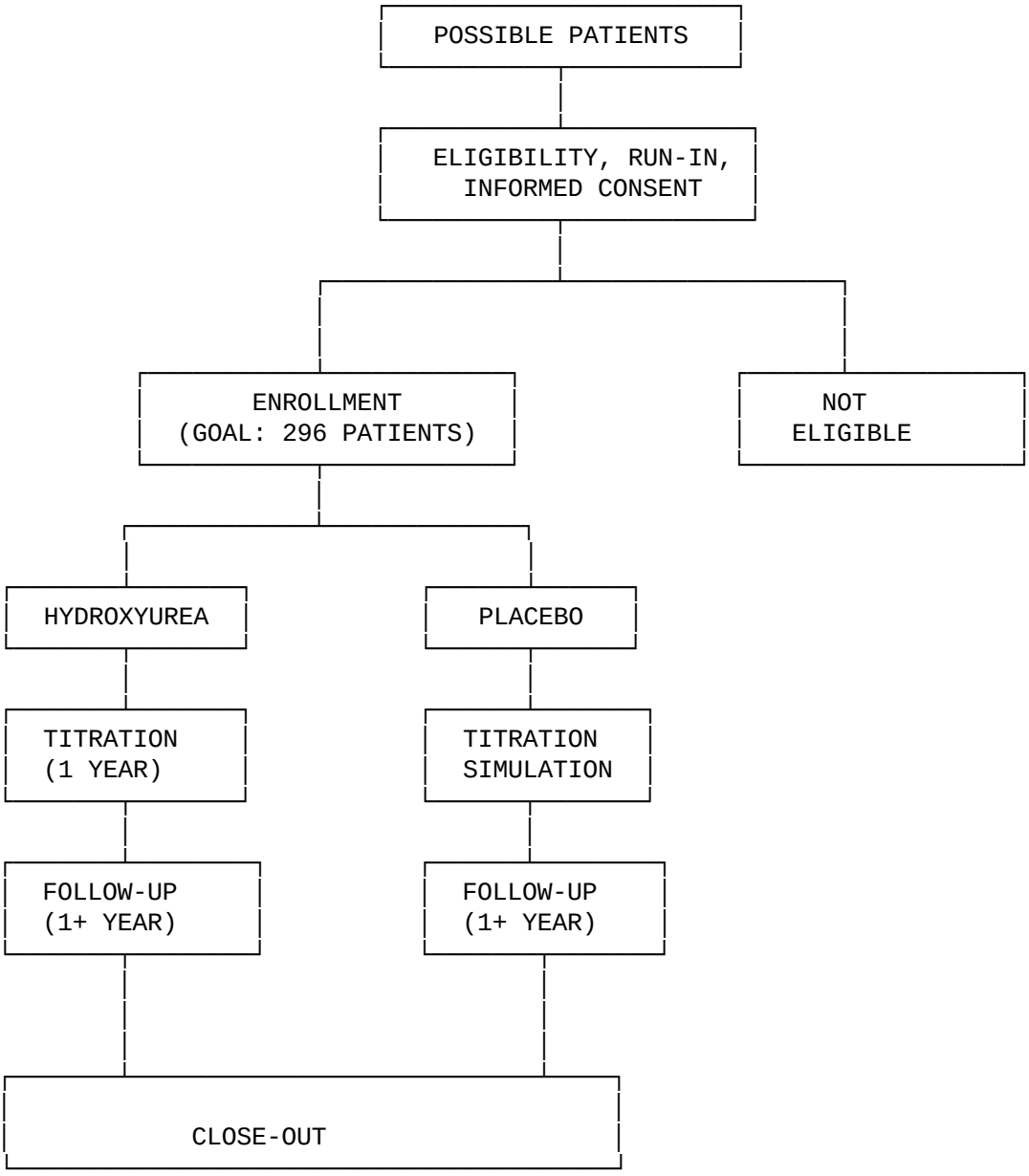

EXHIBIT 2-2

STUDY SIZE CONSIDERATIONS

Sample sizes needed in each treatment group for a clinical trial of hydroxyurea (HU) versus placebo, depending on reduction in rate relative to placebo at maximum HU dose and proportion lost to follow-up, for $\alpha = 0.05$, power = 0.70, 0.80, 0.90.

Proportion lost	Power	Reduction in rate at maximum HU dose 70%	60%	50%
0.00	0.70	37	53	80
	0.80	47	67	101
	0.90	63	89	135
0.05	0.70	39	56	84
	0.80	49	70	106
	0.90	66	94	142
0.10	0.70	41	59	89
	0.80	52	74	112
	0.90	70	99	150

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CHAPTER 3

PATIENT ELIGIBILITY AND PATIENT ORIENTATION

3.1 INTRODUCTION

There is a genuine uncertainty in the medical community as to whether or not there are benefits of hydroxyurea therapy for sickle cell anemia which outweigh its risks. Although hydroxyurea has been associated with increased levels of fetal hemoglobin (Hb F) in patients with sickle cell anemia, and anecdotal descriptions of reduction in the frequency of vaso-occlusive (painful) crises have been reported by patients comparing their experiences before and after starting therapy with hydroxyurea, there has been no quantitation of the size of this effect, no parallel comparison to placebo to estimate the size of this effect, and no check of this effect against the waxing and waning natural history of vaso-occlusive (painful) crises in sickle cell anemia. The true effect of hydroxyurea must be shown to be large (> 50% reduction in frequency of vaso-occlusive crises) to decide the uncertainty in favor of benefits of therapy because the risks and discomforts are considerable. The risks include bone marrow suppression and its consequences --- infection, hemorrhage, cancer, anemia --- mutagenicity and teratogenicity (observed in animals but not in humans), liver or kidney dysfunction, and a variety of lesser disturbances such as hair loss and rash. The discomforts of hydroxyurea therapy include close medical supervision and frequent phlebotomy to monitor for bone marrow toxicity. The balance (equipoise) of uncertainty as to the risks and benefits of hydroxyurea therapy in sickle cell anemia will be remedied in large part by

information to be obtained from the Multicenter Study of Hydroxyurea in Sickle Cell Anemia.

Since the safety and efficacy of hydroxyurea for children with sickle cell anemia has not been the subject of previous research, the MSH is designed for adult patients.

To make the measurement of 50% or greater reductions in observed crisis rates feasible, a minimum of three vaso-occlusive (painful) crises per year are required for each participant. Patients will be excluded for contraindications to hydroxyurea or unwillingness to practice birth control during the study.

During orientation the nature of the study, the procedures to be followed, and the level of commitment to the MSH required for study participation will be explained to the patient. The orientation period will also provide an opportunity to address each potential participant's concerns and questions regarding the MSH.

3.2 INCLUSION CRITERIA

Patients must meet the following inclusion criteria:

1. A hemoglobin pattern consistent with diagnosis of sickle cell anemia by gel electrophoresis (on cellulose acetate and agar), done by the Core Laboratory.
2. At least 3 vaso-occlusive (painful) crises in 12 months prior to enrollment (see section 7.2).
3. Successful completion of a 2-week run-in period comprising two visits with baseline blood sample collections, completion of a fourteen-day diary, and daily ingestion of a folic acid tablet.

3.3 EXCLUSION CRITERIA

Patients are excluded from the study if:

1. They are unwilling to use contraception unless tubal ligation, hysterectomy or vasectomy has been performed (in the patient or partner(s)).
2. They are receiving prescriptions for more than 30 oxycodone capsules (or equivalent-see section 6.2) at a time from clinic personnel.
3. Creatinine is >1.7 mg/dL;
4. Transfusions have been received within 2 months of enrollment, or the patient is on a chronic transfusion program; or the patient is likely to begin chronic transfusion therapy in the next two years;
5. Active liver disease is present, as defined by alanine aminotransferase (ALT) or aspartate aminotransferase (AST)>300 units or abnormal and increasing on serial samples;
6. There is a contraindication for potentially immunosuppressive therapy (HIV antibody testing is required for eligibility and a positive test will result in patient ineligibility);
7. Serum B12, ferritin or folate is abnormally low (patients are acceptable after treatment of deficiency states);
8. Hydroxyurea therapy has been or is currently being administered;
9. The patient is pregnant (tested for in all women before randomization) or breast-feeding;
10. S/β^0 thalassemia is known to be present;
11. The patient is receiving theophylline, androgen, estrogen, progestin (except for birth control), calcium channel blockers, danazol, or any other drug suspected to have an anti-sickling effect;

12. The patient has a history of cerebrovascular accident (stroke) and has been on a chronic transfusion program;
13. The patient has a history of congestive heart failure and has been on a chronic transfusion program;
14. There has been failure to obtain informed consent.
15. Hemoglobin-A greater than 15%.

3.4 PATIENT ORIENTATION

Patients will be informed that this is an experimental study in which half the patients entered will receive placebo; that the MSH goal is to decrease the rate of crises, and that the crisis rates will be compared between patients taking placebo and patients taking hydroxyurea; that the drug is not a "cure", and if it is effective, will be effective only while it is taken; that beneficial effects may or may not be observed for a period of months; and that they should not join the study unless they are prepared to continue treatment for at least 2 (and up to 3) years. The procedures of eligibility, the run-in period, enrollment, follow-up and close-out will be explained to each prospective patient before eligibility assessment begins.

3.4.1 Explanation of Run-in Period

It will be explained to each patient that at least three study contacts will be required prior to actual start of randomly assigned study treatments. The study contacts will be separated by two weeks (as will all regularly scheduled study contacts) and require the collection of blood specimens to establish the patient's blood counts prior to the start of study treatments. In addition to checking the patient's blood counts, the patient's ability to take prescribed tablets and to return for a blood specimen collection every two weeks will be noted. The patient and study investigators will have a chance

to discuss whether the patient should undertake a commitment to the research project based on their experience fitting the run-in period activities into the patient's usual schedule of activities.

3.4.2 Informed Consent

Written informed consent must be obtained from each patient, and no Clinical Center will begin enrolling patients before its consent form is on file at the Data Coordinating Center. The exact language used on a Clinical Center's consent form may vary from institution to institution, but the text must be comprehensible to persons with a 7th grade reading level, and no form will be considered as having been given final approval until it has been reviewed at the Central Office. A draft, model consent form is included in Exhibit 3-1. Items relevant to the presentation of each consent form are listed below:

1. The purpose of the study is to determine whether hydroxyurea administration can decrease the frequency of crises. The effect of hydroxyurea is to increase Hb F ("baby hemoglobin") synthesis; Hb F prevents red cells from sickling if enough of it is present. There is a 50-50 chance of getting drug or placebo ("look-alikes").
2. The extent of patient involvement is one out-patient visit every 2 weeks for up to 3 years. The patient should not join unless he/she is prepared to continue for that period of time. About 2 teaspoons of blood (10 ml) will be taken on each visit; over the course of the entire study, about 100 tablespoons (1500 ml maximum) of blood will be drawn. Each clinic visit will take about half an hour, and twice a year a member of the clinic staff will administer a questionnaire concerning the quality of the patient's life.

3.The potential benefit is that crisis frequency may be reduced. It may take some months for a beneficial effect to be noticed, if a beneficial effect exists. The inherent variability in frequency of vaso-occlusive (painful) crises may increase or decrease attack rates independent of any treatment effect.

4.The potential risk is primarily bone marrow depression, with attendant risks of bleeding, infection, and increased symptoms of anemia. Bleeding and infection have not been encountered in the preliminary study of hydroxyurea in sickle cell anemia; increased symptoms of anemia have been rapidly reversible. Other risks which have been described, but not encountered in our preliminary studies, include GI disturbances, dermatological abnormalities (including skin rash and (as a remote possibility), hair loss), and liver or kidney dysfunction. In our preliminary studies with sickle cell anemia patients, many of them gained weight (a few more than 20 pounds). There may be other risks, but the drug is not new, and they should be very unlikely to occur. Hydroxyurea might be harmful to people with AIDS, and all patients will be tested before they enter the study. If the test is positive, they cannot enroll in the MSH; they will be offered counseling.

5.Hydroxyurea might increase the risk of developing cancer. The risk is small, but the patient should be aware of the possibility.

6.There is also a risk of teratogenesis and mutagenesis. Patients planning a pregnancy (men or women) should not join the study, and they must agree to use contraceptive measures

unless the patient or partner has had vasectomy, tubal ligation or hysterectomy. All women entering the study must have a negative pregnancy test, and such tests will be repeated during the study if menstrual periods become irregular. If pregnancy should occur in a female patient, she will be counseled, but she cannot continue taking study treatments while pregnant. Men who father babies during the study must understand the possibility of fetal abnormality, and they and their partners will receive the same counseling given women in the study who become pregnant.

7. Each patient must take a daily tablet of folic acid.
8. Compliance is very important if the study is to be a success; blood samples will be tested from time to time to see if the capsules are being taken.
9. Patients will be asked to fill out a simple diary each day; they will be paid $5/wk for doing so. They will also be reimbursed $40/month for travel and telephone costs. There will be no charge for hydroxyurea or folic acid.
10. Each patient must report to the MSH investigators each vaso-occlusive (painful) crisis he/she has, and Central Office staff will call each patient monthly to ask about his/her health.
11. If patients become ill, because of sickle cell anemia or some other illness, the study has made no promise to pay for medical care. It also has made no provision to pay for analgesics.
12. By signing the consent, the patient gives the MSH investigators permission to get records from any medical facility attended during the study. The study records will be kept

confidential; patients will not be identified by name; but, data may be shared with the National Heart, Lung, and Blood Institute, the manufacturer of hydroxyurea, or the U.S. Food and Drug Administration (FDA). The FDA can audit medical records at the clinical center.

13. The alternative to participating in the study is for the patient's medical care to continue as before. Patients may withdraw from the study at any time, without prejudice.

14. By signing the consent, the patient acknowledges that he/she understands what he/she has been told, and that all of his/her questions regarding the study have been answered.

15. In accord with local institutional requirements, means for seeking more information about patient protection and redress from injury due to the study, must be spelled out.

16. This protocol has been approved by the local Institutional Review Board (IRB).

EXHIBIT 3-1

MULTICENTER STUDY OF HYDROXYUREA IN SICKLE CELL ANEMIA

(Consent Form)

1. Nature and Purpose of the Study

You have sickle cell anemia and you suffer from attacks of pain. The purpose of this study is to see if a medicine called "hydroxyurea" can reduce the number of your painful attacks. Over 250 patients with sickle cell anemia are expected to join this study.

The time between your own painful attacks may be short or long. The reason some patients go for a long time with no attacks and then have many of them is not known. Because painful attacks vary so much, it can be hard to tell if a new medicine really works. To find out if hydroxyurea can make patients have fewer attacks, we have to test it along with an inactive "look-alike" capsule.

Hydroxyurea is used to treat other sicknesses. It can change some of the hemoglobin in your red blood cells from sickle cell to fetal (baby) hemoglobin, which was in them before you were born. This baby hemoglobin does not sickle and may help prevent your red cells from sickling which causes pain.

2. What to Expect

If you agree to join this study you will be asked to take capsules every day. Half of the patients will get capsules of hydroxyurea and the other half will get a capsule with the inactive "look-alike". This will be decided by chance, like a lottery. Neither you nor your doctor will know which of the two kinds of capsules you are taking. However, the study office will keep a record of what you are taking, should it become necessary for your doctors to know this. You will be asked to

take your capsules every day for 2-3 years or as long as you are in the study. You will also receive folic acid vitamin pills. You should not join the study unless you are ready to continue for 2-3 years.

As long as you are in the study, you will need to be seen every two weeks. Each visit will take about half an hour. At each visit a blood sample from a vein will be drawn with a needle and a test tube to be sure that your treatment is safe, and to decide on any changes in the dosage of your medicine. These samples will also be used to see if you are taking your medicine. Each sample will use only about two teaspoons of blood (about one pint per year).

We will ask you to keep a record, every day, of whether you have had any pain. At each visit we will go over your medicine and your pain records. We will ask if you have had to visit a hospital or clinic because of pain. Someone from the study office in Maryland will call you at home once a month to ask how you have been feeling. Pain medicine will be prescribed for you if you need it. Twice a year we will fill out a form about how much you can do and how well you feel.

Dr. _____ and the study staff will ask about your health in the past. You will be asked to sign forms so that we can get records from your private doctor or hospitals where you have been treated.

Hydroxyurea could be harmful to someone with the AIDS virus so you will be tested before you join the study. Only you will be told of the result. If the AIDS virus test is positive you will not be able to join this study, but we will give you advice on how to get good medical care for this infection.

3. Risks of Taking Hydroxyurea

Sometimes hydroxyurea can cause a sick stomach and vomiting, skin rash, hair loss, liver or kidney disease, infection, or bleeding. These bad effects have not been seen so far in studies of sickle cell patients. As far as is known these bad effects of hydroxyurea happen to fewer than one in a hundred patients and usually clear quickly when the drug is stopped.

There is a small risk that you may gain a lot of weight.

Because hydroxyurea can reduce your blood count we will check it every two weeks. If your blood counts are too low, or if other side effects occur, or when study plans call for a break in treatment, your study treatment will be stopped until study plans call for you to start your treatment again.

Hydroxyurea might increase the risk of some cancers. Although this risk is not certain to exist and at the most is small, you should be aware of this possibility.

Hydroxyurea could damage an unborn baby. If you are planning a pregnancy you should not join this study. All patients (or their partners) must use birth control. You may only join this study if you and your partner agree to use birth control (pills, rubbers, or diaphragm, for example), or have had an operation to prevent pregnancy (tubes tied, womb removed, or vasectomy). If you are not already using birth control, we will help provide it. All women who enter this study will be tested for pregnancy. If a pregnancy occurs while you are in this study you will be offered the most complete advice available. You cannot continue to take hydroxyurea while pregnant.

If any man treated in the study fathers a child he will have to think about the possibility of bad effects on the baby even though it is he and not the woman who is taking the study medicine. Men in the

study and their pregnant partners will need advice of the same sort as any woman who enters the study and becomes pregnant. We do not know if it will be safe to have a pregnancy after treatment is stopped.

As with studies of all new treatments, there may be other risks to using hydroxyurea that are not now known. If any new bad effects are observed, patients in the study will be told as soon as possible and action taken to protect their safety.

4.Benefits

You may have pain less often if you take hydroxyurea. If a good effect is seen, it may take several months to develop. Any important medical information about you or about the results of this study will be available to the doctors who take care of you.

5.Privacy

In this study only your own clinic and the central, assistant coordinator will know your name. They will make note of your initials, age, sex, weight, and height. Only that identification will be stored in the study computer. You will not be identified personally in any report from this study. Your personal medical reports will be kept private. At the end of the study a computer tape of the study results will be made for future use. It will not include any information that could identify you directly. Information may be given to the National Institutes of Health or the Food and Drug Administration, but your name will not be used in such files.

6.Other choices

If you join this study, it is your own choice. You may refuse to take part in it or you may leave it at any time. If you do not join, or leave, doing so will not harm your present or future care at the

hospital or clinic. Instead of taking part in this study you may go to your doctor for your usual treatment of sickle cell anemia.

7. Costs paid for by the study

You will not be charged for any of the study visits, treatments or procedures. The cost of the hydroxyurea, folic acid, and blood tests for this study will be covered by the study.

8. Costs not paid for by the study

If you need medicine other than hydroxyurea or folic acid the study will not pay for it. If you must visit your private doctor or emergency room, or must stay in the hospital, those costs will not be covered by this study.

9. Payments to you

You will be paid $5.00 per week for filling out the pain record each day. You will also be paid $40.00 a month for travel and telephone costs. You will receive this money (a total of $60.00 each month if all pain records are complete) from the clinic once a month during one of your study clinic visits. If you do not attend study clinic visits or become unable to take part in the study then you will no longer be paid that money.

10. Rights

You will be given a copy of this consent form to keep. If at any time you have questions or concerns about the study you may call either _____, the study staff, or _____, a person whose job is to watch over the well being of patients in medical research projects. Should you have any bad effect of treatment during the study, care will be provided to you. The cost of treating such bad

effects is not covered in the study, and no money has been set aside to pay for these bad effects.

11.Questions

This study has been explained to you by Dr. _____ and your questions were answered. If you have any other questions about this study you may call Dr. _____ at _____.

CHAPTER 4

RANDOMIZATION AND ENROLLMENT OF PATIENTS

4.1 ELIGIBILITY ASSESSMENT

Clinical center staff may begin enrolling patients in the MSH once a minimum of five patients have completed eligibility requirements, and are ready to be enrolled.

Potential patients are identified by the Clinical Center directors. Patients will complete patient orientation (see Section 3.4), provide informed consent, and complete the run-in period. All eligibility forms must be received at the Data Coordinating Center where they will be entered into electronic data files and the eligibility will be assessed based on data submitted.

Patients who meet all eligibility criteria in a Clinical Center enrolling MSH patients will be able to enroll in the study. Patients who are not eligible may be re-evaluated as long as the enrollment period is still open. The exclusion criteria which could change and allow re-evaluation for eligibility include age (if less than 18 years old), unwillingness to use birth control, receiving more than 30 oxycodone capsules at a time, transfusion within 2 months of enrollment, active liver disease, low serum B12, ferritin or folate, pregnancy or breastfeeding, treatment with theophylline, androgens (including danazol), estrogens, progestins (except birth control pills), calcium channel blockers or any other drug suspected of having anti-sickling effect, at least 3 vaso-occlusive (painful) crises in twelve months before enrollment, and successful completion of the run-in period including diaries. The run-in period (see Section 3.4.1) must be successfully completed within six weeks of meeting all other eligibility criteria.

4.2 RANDOMIZATION AND TREATMENT ALLOCATION

Data Coordinating Center staff will prepare a unique randomization schedule for each MSH Clinical Center. Each randomization schedule will be unknown to the study physicians outside of the Data Coordinating Center and Central Office. Individual treatment assignments will be available to Data Coordinating Center and Central Office staff only on a "need-to-know" basis. Clinical Center investigators forced by urgent circumstances to unblind an individual patient's treatment, will be required to follow procedures and provide documentation as set out in Section 5.6.1. The randomization schedule will assign randomly ordered treatments to patients enrolling at a clinic in sequence. Each treatment assignment will be either for hydroxyurea or placebo. A standard procedure for stratified (by Clinical Center), blocked randomization will be used.

4.2.1 Treatment Allocation

The Data Coordinating Center will identify eligible patients on a daily basis throughout the enrollment period. As soon as five eligible patients, identified in a Clinical Center, have completed the run-in period and provided written informed consent, Data Coordinating Center staff will send to the Treatments Distribution Center a treatment assignment (hydroxyurea or placebo) and directions to issue a study treatment to the Clinical Center. For each eligible patient Data Coordinating Center staff will issue to the Clinical Center a confirmation of enrollment into the study, including the MSH Patient Identification Number and Namecode. Clinical Center staff will return to the Data Coordinating Center a form confirming the date the patient returns for enrollment in the study and starts study treatment.

CHAPTER 5

TREATMENT

5.1 INTRODUCTION

For patients enrolled in the MSH and assigned to hydroxyurea treatment, hydroxyurea dosage will be increased at regular intervals until toxicity is encountered, and then reduced to the maximum tolerated dose (MTD). Patients will be maintained on the MTD for at least a year. Capsules should be taken in the morning (after brushing teeth, with morning coffee, etc.) but they can be taken at other times if such a choice seems more likely to assure their regular ingestion. All patients will receive folic acid, 1 mg/day.

The Data Coordinating Center will send to the Treatments Distribution Center printouts of all blood counts received, with a listing of recent blood counts, study medication prescription history, adverse reactions, and a recommendation for the next prescription, by noon of the second day after blood counts are received in the Data Coordinating Center (see Appendix III). The Treatments Distribution Center coordinator will verify that prescriptions are correct. All verified prescriptions will be filled and sent. Clinics will acknowledge receipt of medication batches by means of a form sent to the Data Coordinating Center.

5.2 DOSE TITRATION

The starting dose of hydroxyurea will be 15 mg/kg (once a day, orally). If neither toxicity nor pre-toxic blood counts occur the dose will be increased by 5 mg/kg every 12 weeks until a maximum of 35 mg/kg is prescribed. If toxicity occurs, treatment will be stopped until

blood counts return to non-toxic values, and treatment will then resume at a dose 2.5 mg/kg lower than the previous dose starting a new 12-week cycle. If that dose does not cause toxicity and the patient is not pre-toxic at 12 weeks, an attempt will be made to increase the dose by 2.5 mg/kg; if toxicity occurs the dose will be lowered further.

If a patient is pre-toxic at the end of a 12-week cycle, the dose is not increased, but is maintained for another 12 weeks. If the patient is pre-toxic at the end of two consecutive 12-week cycles, that dose will be the patient's MTD.

If toxicity develops twice at a given dose, the patient's MTD will be the first lower dose that does not cause toxicity for two consecutive 12-week cycles.

The goal will be to maintain patients on the maximum non-toxic dose (also the MTD) for at least 12 months. No patient will be maintained on a dose higher than 35 mg/kg/day. If patients develop blood counts in the toxic range while on an established MTD, treatment will stop until the patient is non-toxic and then treatment will resume with the previously established MTD. An outline of the dose titration algorithm is indicated in Exhibit 5-1.

Data Coordinating Center staff will devise schedules so that placebo doses are changed and stopped in a manner similar to changes and stops among patients assigned to treatment with hydroxyurea. Placebo prescriptions will be changed through the Treatments Distribution Center as are hydroxyurea doses. Dose titrations for all patients (whether assigned to hydroxyurea or placebo) will be made only at clinic visits with appropriate blood specimens collected.

5.3 TREATMENT PREPARATION

Hydroxyurea will be encapsulated into differently colored 200 and 500 mg capsules at The Johns Hopkins Hospital. Placebo (Starch 1500) will be packed in identically appearing capsules. The capsules will all be the same size, and will contain a white powder, the 200 mg capsules containing Starch 1500 as a filler. Within 4 days of a clinic visit (see Appendix III) Data Coordinating Center staff will generate a prescription recommendation for the patient, and send it to the Treatments Distribution Center with a synopsis of recent blood counts. Treatments Distribution Center staff will check prescription recommendations. The Treatments Distribution Center will count out 17-day supplies of each type of capsule, bottle them in child-proof containers, and label them with the patient's namecode, study ID number and instructions (including the "Investigational Drug" warning, "Multicenter Study of Hydroxyurea in Sickle Cell Anemia", a prescription number, instructions on how to take the capsules, and the "emergency call" telephone number of the Treatments Distribution Center). Study treatments will be shipped in 12-week batches, (consisting of six 17-day treatment supplies) assuming no dose reductions are necessary, and in sufficient time to assure that the clinics will receive the bottles before the patient's next scheduled visit. Typically, patients will receive 1-2 bottles of capsules on each visit. Inventory records for drug and placebo will be kept by Study Treatments Distribution Center staff.

5.4 DEFINITIONS OF TOXICITY AND PRE-TOXICITY

The only toxicity observed in preliminary studies has been bone marrow depression. Hydroxyurea has rarely been reported to be the

cause of fever, skin rash, nausea, vomiting or hair loss. Such manifestations will be investigated locally and will be reported to the Food and Drug Administration (FDA) as adverse reactions if other etiologies are not apparent.

Pre-toxic bone marrow depression is defined as absolute neutrophil counts less than 2,500/mm^3, absolute reticulocytes less than 95,000/mm^3 (if the hemoglobin concentration is below 9 gm/dL), platelet counts less than 95,000/mm^3, or a fall in hemoglobin concentration from $\geq$ 7.0 g/dL (pre-enrollment) to 5.1 - 5.3 if reticulocytes < 320,000. Toxic bone marrow depression is defined as absolute neutrophil counts less than 2,000/mm^3, absolute reticulocytes less than 80,000/mm^3 (if the hemoglobin concentration is below 9 gm/dL), platelet counts less than 80,000/mm^3, or a fall in hemoglobin concentration from $\geq$ 7.0 g/dL (pre-enrollment) to 4.5 - 5.0 if reticulocytes < 320,000, or hemoglobin concentration <4.5 gm/dL.

The following occurrences will also be monitored: serum creatinine increase from < 0.5 to $\geq$ 1.5 or from 0.6 - 0.8 to $\geq$ 1.7 or a doubling or more from $\geq$ 0.9; an increase in alanine aminotransferase (ALT) from < 100 to $\geq$ 150 or a doubling or more from $\geq$ 100; unexplained gastrointestinal disturbance, or unexplained rash or hair loss (confirmed by a dermatologist).

5.5 MONITORING FOR TOXICITY

Most patients will be seen at the Clinical Centers and will have blood sampled every two weeks. A few will be seen in peripheral clinics which are visited by the clinic director every 4 weeks, but will have their blood sampled at 2 week intervals. Blood specimens may be collected on any weekday except Friday, but patients must always

keep their scheduled appointments in the same week of their two-week cycles. If a patient misses his/her clinic day, and there is another clinic day (and blood shipment) that week, the patient can complete his/her clinic visit (and blood shipment) on the other clinic day. Blood samples and unstained blood films from all patients will be shipped to the Core Laboratory so that they arrive within 24 hours. Samples can be sent Monday-Thursday. Clinics will store an extra 3 ml of blood in a tube with (EDTA) in the refrigerator for 48 hours, in case the tube shipped to Baltimore breaks in transit. One tube of blood will be obtained for a blood count (including white blood cell count, platelet count, reticulocyte count (%) and differential white blood cell count) will be collected for fetal hemoglobin studies. Clinic coordinators will prepare blood films using an automated device (Miniprep^{R}, Geometric Data Corp.) and ship them with the blood in waterproof slide containers. Blood counts and/or chemistries will be performed, reports generated, and results transmitted to the Data Coordinating Center within 24 hours of receipt.

The Central Office coordinator will scan the in-coming reports for "toxic" results. If there are such she will notify the Treatments Distribution Center and Data Coordinating Center of the need for a stop order. After TDC staff confirm a stop order, the Central Office will notify a) the Central Office assistant coordinator, who will call the patient and tell him/her to stop treatment, and b) the participating clinic by telecopy (FAX). The clinic and patient will only be told to "stop treatment", without use of the word "toxicity".

The Data Coordinating Center will provide the Central Office coordinator with weekly lists of placebo patients whose treatments are to be stopped, in just the same manner as patients with toxicity

identified. Data Coordinating Center staff will receive and edit incoming Core Laboratory reports, and compare them to previous reports for the patient. Data Coordinating Center staff will notify the TDC and study coordinator of any discrepancies between the Data Coordinating Center computer reviews of Core Laboratory reports and the stop orders initiated by the Central Office coordinator.

Patients will be notified of stop orders within 72 hours of a clinic visit. All remaining capsules of the study drug must be returned on the next clinic visit. When treatment is stopped, the Data Coordinating Center will send a recommendation to the Treatments Distribution Center for treatment at a reduced dose. The Treatments Distribution Center will prepare a 12 week supply of the new dose for shipment to the clinic.

5.6 BLINDING

In the Clinical Centers, the patients, directors, coordinators, and other study staff will be blinded to treatment assignments. In the Central Office, the assistant coordinator as well as the Crisis Review Committee members will be blinded to study treatment assignments. Staff of the Central Office, Core Laboratory, Treatments Distribution Center and Data Coordinating Center will have access to individual patient treatment assignment and current dose on a "need-to-know" basis. The Treatments Distribution Center, and Data Coordinating Center will maintain records of each patient's drug assignment and current dose.

Plans have been made to prevent toxicity monitoring from resulting in unblinding of patient treatments. Despite these precautions, if the Clinic Director thinks he/she inadvertently has become unblinded,

patient contact must be carefully managed to avoid any comments to the patient or coordinator regarding unblinding. The person who has major patient contact, usually the coordinator, must be rigidly excluded from any contact with lab data.

The Clinical Center directors will assert at the outset the intention to avoid seeking information that may unblind them with regard to individual patient's treatment assignments, especially laboratory results. Clinic coordinators will conduct patient follow-up visits and process and maintain files of study documents. Although not preferred, clinic directors may be primary care providers for MSH patients, and will be aware of the need to maintain blinding under normal circumstances and maintaining the patient on study drug including during hospitalization. Discussions among Clinical Center staff or with patients regarding possible patient treatment assignment are inappropriate. As long as official unblinding has not been done and the patient notified, the clinical coordinator must avoid seeking any information that may unblind him/her.

5.6.1 Emergency Unblinding

Every patient will be given an identification card describing his participation in the study, listing emergency study telephone numbers (e.g., the Central Office and/or Treatments Distribution Center telephone number, and the clinic director's telephone number). The Treatments Distribution Center "emergency call" telephone will be answered by a member of the Central Office at all times. If MSH patients become ill, treating physicians will be urged to call the clinic director before altering the patient's study regimen.

In an emergency, if the 24-hour telephone number is called, arrangements will be made so that the patient's medication can be disclosed to the clinic director after consultation between the clinic director and a Central Office physician (one of whom will always be available). Reasons for unblinding are limited and are based on clinical grounds. Unblinding must be initiated by the clinic director. Reasons for unblinding include pregnancy, accidental ingestion of study medications by another person, development of infection or bleeding which could be due to reduced white blood cell or platelet counts and in which management might be changed if the nature of the study drug were known. Examples include thrombocytopenia (use of prednisone vs use of platelet transfusion) and neutropenia (choice of antibiotics).

If a patient's therapy is unblinded, the Treatments Distribution Center must send a report to the Central Office and Data Coordinating Center. In general, treatment will stop and follow-up will continue. The nature of the patient's medication will be withheld from the clinic coordinator.

5.6.2 Treatment Interruptions

There may be instances of treatment interruption either related to medical conditions (e.g. acute, intercurrent illnesses such as an infection when it may be advisable to interrupt study therapy without unblinding) or for other reasons (e.g., study treatments lost in a robbery). Interruptions for medical conditions should be allowed only with the advice of the clinic director and not at the discretion of local medical doctors. The clinic director is responsible for notifying the Data Coordinating Center of treatment interruptions.

These notifications are important because they may in turn have an influence on dose titration.

5.7 ASSESSMENT OF COMPLIANCE

At approximate three month intervals each patient's plasma samples will be assayed for hydroxyurea at the Core Laboratory. Neither patients nor clinic staff will know when blood specimens will be assayed for hydroxyurea.

Capsule counts will be done at each regular follow-up visit. If capsule counts are not consistent with regular compliance, the nature of any difficulties will be discussed with the patient. The importance of compliance will be emphasized for all patients.

Even if patients are repeatedly considered to be non-compliant, they will continue to be followed and will continue to receive their travel/telephone allowances.

5.7.1 Missed Visits and Drop-outs

Each regularly scheduled clinic visit missed by a patient will be reported to the Data Coordinating Center. Patients who do not wish to continue attending clinic visits in the MSH will continue to be telephoned by the assistant coordinator to ascertain crises, identifiable events and vital status.

5.8 DURATION OF STUDY TREATMENT

The goal of the study will be to maintain all patients on protocol for at least two years after study entry. Although the time to establish an MTD may vary, this length of follow-up should permit at least one year of follow-up on the MTD for each patient. The first patients enrolled may be followed in the study for as long as three years. Study treatments will continue with the assigned medication until the common close-out date for all patients. See Appendix IV for study timetable.

EXHIBIT 5-1

MULTICENTER STUDY OF HYDROXYUREA IN SICKLE CELL ANEMIA

DOSE TITRATION ALGORITHM

Goal To find the maximum tolerated dose (MTD), defined as the highest dose maintained for two consecutive 12-week periods without observed blood count toxicity; and to maintain the patient at the MTD thereafter.

Escalation phase

1.Start at 15 mg/kg.

2.Increase by 5 mg/kg every 12 weeks unless pre-toxic or toxic, or the dose is 35 mg/kg or the patient has achieved his/her MTD. Once toxicity occurs, any dosage increases will be 2.5 mg/kg thereafter.

3.If pre-toxic at a 12-week point, continue with same dose for another 12 weeks. If pre-toxic at the end of next 12 weeks, declare MTD at that dose.

4.For patients who are not toxic after two consecutive 12-week periods of treatment with 35 mg/kg, 35 mg/kg is the MTD.

5. If toxicity develops:

a.A stop order is issued for the balance of the current 2-week cycle, and a dose lower by 2.5 mg/kg is prepared for the next 12 weeks.

b.As long as the patient does not become toxic over the 12 weeks on the lower dose or is not pre-toxic at the 12-week mark, increase the dose by 2.5 mg/kg. This may be repeated as long as tolerated.

c.If a patient becomes toxic at any given dose twice, no further increases will be made. The first lower dose that does not produce toxicity for two consecutive 12-week periods is the MTD.

Maintenance phase

1.If patient becomes toxic after the MTD is established, a stop order is issued and continues for the balance of the two week cycle; the same dose is resumed thereafter.

CHAPTER 6

CONCOMITANT CARE

6.1 INTRODUCTION

The basic principles of concomitant care for patients enrolled in the MSH are the recommendations in the Management and Therapy of Sickle Cell Diseases. Charache S, Lubin B, and Reid CD, eds. United States Public Health Service, National Institutes of Health, Publications No. 85-2117, September 1985. Concomitant care should be selected to be appropriate whether the patient is receiving hydroxyurea or placebo; treating physicians and house officers may find it easier to plan concomitant therapies as if the patient were receiving hydroxyurea. Cooperation of treating physicians and house officers should be solicited as much as possible to enhance adherence to study protocol. Patients will be issued study identification cards requesting treating physicians and house officers to contact the patient's MSH clinic director with questions concerning patient involvement in the MSH.

6.2 HOSPITAL ADMISSIONS

During hospital admissions for any cause, the patient's care must be directed to address the patient's main, acute medical condition. If a patient is admitted to hospital, study drug is to be continued unless a stop order has been issued or the patient is unable to swallow. If a patient forgets to bring medication with him when admitted, a family member or friend should bring it to the hospital as soon as possible. Exact arrangements used to dispense a study drug to an inpatient may differ between clinics; such arrangements must be explored before recruitment begins, and the Central Office is available for assistance

in such administrative matters. For clinics which may have patients admitted to one of several hospitals, such arrangements should be made, in advance, for all likely possibilities. There will be multiple opportunities for unblinding when patients are admitted; clinic directors, coordinators and other investigative staff must anticipate such encounters, and try to avoid them.

6.3 ANALGESICS

Patients will not receive more than 30 tablets of oxycodone (or equivalent) at any outpatient visit. Oral doses of other narcotic agonist analgesics equivalent to 5 mg oxycodone (one Percodan tablet) are:

Morphine 10 mg	Leuorphanol 0.7 mg
Hydromorphone 1.2 mg	Meperidine 50 mg
Codeine 30 mg	Propoxyphene 25 mg

6.4 BIRTH CONTROL AND PREGNANCY DURING THE STUDY

Before randomization, all patients (men and women) will be advised by a trained counselor as to possible risks to a fetus conceived or carried during hydroxyurea therapy. Contraceptive advice will be given, and condoms made available if needed. Gynecological referrals will be made if desired (for fitting of diaphragms, pelvic examinations, etc). Female patients will be asked about their last menstrual period at each clinic visit. A serum pregnancy (HCG) test will be performed if amenorrhea or menstrual irregularity develops. Patients becoming pregnant during the study will be taken off further treatment (regardless of whether or not they were receiving hydroxyurea). Such patients treatment assignment will be unblinded, and if they were receiving hydroxyurea they will be counseled regarding

the risks of teratogenicity. Patients taken off drug because of pregnancy will not resume treatment after delivery or termination of the pregnancy but follow-up will continue.

6.5 TRANSFUSION DURING THE STUDY

Primary care physicians will be discouraged from transfusing patients. Chronic transfusion therapy should be avoided as much as possible for patients enrolled in the study (patients who are likely to begin chronic transfusion therapy within two years of study entry should not be enrolled in the Study -- see Section 3.3). Acceptable reasons for transfusion include: hemoglobin <5 g/dL (if usually 7 g/dL or more); angina or congestive heart failure; pneumonia with arterial pO_2 <70 mm Hg on oxygen; general anesthesia (if transfusion considered necessary); stroke or intracranial hemorrhage; and acute hemorrhage. These criteria do not mandate that transfusions be given in the mentioned conditions. Transfusions should not be used to treat painful crises or ankle ulcers. If a patient is transfused, study treatments continue, but the transfusion volume and date(s) will be recorded on study forms.

6.6 USE OF OXYGEN

Increase in inspired oxygen content above 0.20 is discouraged unless the arterial oxygen saturation is below 90% as estimated by pulse oximetry or direct arterial blood gas (ABG) measurement. Calculated oxygen saturation (based on P_aO_2, pH and temperature) is unreliable in sickle cell anemia, due to altered whole blood oxygen affinity, and such calculated oxygen saturations should be ignored. Oximetry should be used to maintain arterial oxygen saturation between

90% and 98%, or P_aO_2 between 80 and 100 mm Hg, and never less than 70 mm Hg.

6.7 BONE MARROW TRANSPLANTATION

Bone marrow transplantation is not an acceptable concomitant therapy for MSH patients who have not already experienced a study end point (e.g., chronic transfusion therapy or stroke).

CHAPTER 7

STUDY END POINTS

7.1 INTRODUCTION

The primary objective of the Multicenter Study of Hydroxyurea is to determine the safety and effectiveness of hydroxyurea in the prevention of vaso-occlusive (painful) crises occurring among patients with sickle cell anemia. The primary analysis in this study will compare the occurrence of vaso-occlusive (painful) crises during the first two years of follow-up after study entry in patients randomly assigned to treatment with hydroxyurea versus those assigned to placebo.

The analysis of the primary study outcome will be conducted on an "intention to treat" basis, with two-sided statistical tests comparing the outcome between groups of patients defined at study entry by the random assignment to the hydroxyurea and placebo groups. A detailed analysis plan is presented in Appendix VI.

7.2 DEFINITIONS: CRISIS AND PRIMARY END POINT

For purposes of defining the primary study outcome, a vaso-occlusive (painful) crisis will be considered a visit to a health care facility lasting more than four hours for treatment of an acute painful event (including priapism) which requires treatment with either (1) parenteral narcotics; or, (2) an equi-analgesic dose of oral narcotics, if the episode is treated at a facility in which parenteral narcotics are not routinely used to treat crises; or, (3) parenteral non-steroidal anti-inflammatory drugs (NSAIDs). If a second painful episode requiring treatment with parenteral narcotics or NSAIDs, or an equi-analgesic dose of oral narcotics begins within 24 hours of a crisis, both episodes will be considered to be part of a single crisis,

and not two separate events. Episodes of "pneumonia" and "chest syndrome" (defined as new chest infiltrates associated with fever) will be considered crises; episodes of hepatic sequestration (defined as a sudden increase in liver size associated with right upper quadrant pain, increased abnormality of liver function tests not due to biliary tract disease, and a drop in hemoglobin concentration of 2 g/dL or more) will also be considered crises; surgical procedures and pain due to acute exacerbations of chronic conditions (e.g., ankle ulcer, hip necrosis, or osteomyelitis) will not be considered crises.

An episode classified as a vaso-occlusive (painful) crisis will be considered an in-patient crisis if the patient is officially admitted to a hospital or if the patient is not officially admitted to a hospital, but stays at a medical facility for more than 24 hours.

7.3 PRIMARY END POINT CLASSIFICATION

Episodes which are suspected of being crises will be initially identified during the patient's medical review at regular follow-up visits and from review of the patient's daily diary. Clinical Center staff will abstract key data onto a study form and append further documentation of the episode. The form, together with copies of pertinent records from the medical facility involved, will be sent to the Coordinating Center within one month of the clinic visit. Once a month, the assistant coordinator in the study Central Office will contact patients by telephone to determine whether they have had any episodes that should be reviewed as possible crises within the last month. The assistant coordinator will report any possible crises to the Data Coordinating Center, where these reports will be compared to those filed by the Clinical Centers. Clinical Center staff will be notified to resolve any discrepancies.

Data Coordinating Center staff will assemble documentation for any painful episode requiring medical treatment for review by members of the Crisis Review Committee, who will determine whether the episode was a vaso-occlusive (painful) crisis according to the study definition. Each episode will be independently reviewed by two members of the Crisis Review Committee. If the two reviewers disagree on whether an event is a crisis, then documentation for the event will be sent to a third reviewer, and the event will be classified according to the decision of two out of three reviewers.

7.4 STATISTICAL ANALYSIS OF THE PRIMARY END POINT

Vaso-occlusive (painful) crises occurring during the first two years after a patient is enrolled will be counted in the primary analysis of study outcome. For each patient, the total number of crises observed and the total amount of time that the patient has been followed for crises during the first two years after study entry will be calculated. A crisis rate will be calculated for each patient by dividing the number of crises observed by the length of time the patient is followed. If a patient's follow-up ends before two years, the crisis rate is calculated by dividing the number of crises observed by the time from study entry to the end of follow-up for that patient. It is anticipated that during the first two years of follow-up a small percentage of patients may die, have a stroke, or develop an indication other than a stroke (e.g. pulmonary failure) for treatment by chronic transfusion therapy. Patient outcomes at two years will be ranked as follows: 1) patients who die will be ranked worst; 2) patients who have a stroke or must be treated with chronic transfusion therapy will receive the next worst ranks, 3) other patients will be ranked according to their individual crises rates. The ranks for patients

assigned to hydroxyurea will be compared to the ranks for patients assigned to placebo using the Van der Waerden (normal scores) test.[1] Further discussion of the primary outcome analysis and sequential monitoring plans is contained in Appendix VI, and power calculations for the primary outcome analysis are given in Appendix V.

7.5 SECONDARY END POINTS

Secondary end points related to the occurrence of vaso-occlusive crises will include:

1. Crises which occur between two years after study entry and the end of follow-up for each patient.
2. In-patient crises.
3. The duration of hospitalization for each in-patient crisis.

Records will also be kept of the occurrence of events which are clearly-defined, sickle-related and not painful crises, including:

a. Death;

b. Stroke;

c. Development of any indication resulting in treatment with chronic transfusion therapy, such as stroke or pulmonary failure;

d. New osteomyelitis, proved by culture, with consistent abnormalities on x-ray and/or bone scan;

e. Development of a new ankle ulcer or recurrence of a previously healed ankle ulcer;

f. Infections;

g. Aseptic necrosis of bone.

Because carcinogenicity related to therapy with hydroxyurea has not been documented, records will also be kept of the occurrence of any cancers.

7.6 OTHER MONITORED RESPONSE VARIABLES

7.6.1 Clinical adverse effects

Gastrointestinal disturbance, skin rash, and hair loss without other explanation have been reported as rare side effects of hydroxyurea, although these effects have not been seen with doses given to sickle cell patients in the just-completed study by the Hydroxyurea Study Group. The occurrence of these or other side effects will be reported to the Central Office and to the Data Coordinating Center, and if indicated Data Coordinating Center staff and the Study Chairman as IND holder will prepare appropriate reports for the FDA.

7.6.2 Laboratory measurements

Laboratory measurements will be performed to monitor for evidence of drug toxicity (defined in Section 5.3), to document changes in fetal hemoglobin (HbF) production and other hematological responses to treatment with hydroxyurea, and to monitor compliance with assigned study medication.

7.6.2.1 Measurements Used to Monitor Toxicity

Blood counts will be performed every two weeks in the Core Laboratory to obtain the following measures:

a. Absolute neutrophil count (bands plus mature neutrophils);

b. Absolute reticulocyte count;

c. Platelet count;

d. Hemoglobin concentration;

The following determinations are to be performed monthly, by the Core Laboratory.

a.Serum creatinine;

b. Blood urea nitrogen;

c. Serum alanine aminotransferase (ALT);

d. Serum aspartate aminotransferase (AST);

e.Direct and total bilirubin.

7.6.2.2 Measurements Used to Document Hematologic Response to Hydroxyurea

The following measures are to be used to document hematologic responses to hydroxyurea. Two measurements are to be made in the run-in period before patients are randomized. After randomization, repeated measurements will be performed every 4 weeks during patient follow-up.

a.Percent fetal hemoglobin (HbF) in hemolysates.

b. Percent F-cells.

In addition to these measures, the following measurements will be performed every three months:

a. Median corpuscular hemoglobin concentration (MCHC).

b. Percent dense cells.

7.6.2.3Monitoring for Compliance

The presence of hydroxyurea in plasma will be assayed four times a year to monitor compliance with the assigned study medication.

7.6.3 Pain and Quality of Life

The following measures of quality of life will be collected:

1.Daily patient diary of intensity of pain recorded on a scale from zero to ten.

2.Medical Outcomes Study Form SF-36 (twice a year).

3.Profile of Mood States (twice a year).

7.7 REFERENCES

1.Conover WJ. Practical Nonparametric Statistics, Second Edition, New York, John Wiley & Sons, Inc., 1980; 316-323.

CHAPTER 8

FOLLOW-UP PROCEDURES

8.1 INTRODUCTION

Patients will be scheduled for follow-up visits every two weeks. A small number of patients living in outlying areas will have complete follow-up visits scheduled every four weeks, but blood specimens will be collected from them at two weeks (as for all patients in the MSH) to monitor blood counts for patient safety. At the time of each scheduled visit, a medical review is conducted including ascertainment of death, possible crises and adverse effects. Specimens for laboratory determination are collected as scheduled. Study medication is reviewed.

At semi-annual follow-up visits, study forms evaluating medical review and quality of life will be administered. Collection of blood specimens will be performed at all regularly scheduled MSH clinic visits.

Secondary ascertainment of medical contacts is conducted monthly by the Central Office assistant coordinator. Crisis Review Committee members will classify crises, identifiable events and deaths.

8.2 FOLLOW-UP VISITS

At the regular follow-up visit, a medical review will be conducted including weight, ascertainment of possible crises and adverse effects, transfusions, other major procedures, current therapies and deficiencies, pregnancy in patient or partner, collection of the previous study medication, capsule count, and collection of the diary pages. Menstrual irregula

Blood will be drawn and prepared for shipment to the Core Laboratory. The patient's current address and telephone number are ascertained and reported on study forms to the Central Office assistant

coordinator. The prescribed study medication for the following two weeks is dispensed, and the diary pages for the following two weeks are given to the patient.

8.2.1 Ascertainment of Crises, Identifiable Events and Adverse Effects

At the regular follow-up visit, the patient will be questioned about any medical contacts, and the diary sheets will be reviewed for indication of medical contacts which will be recorded on a clinic visit form. Each medical contact will be documented to ascertain the nature of the contact, including indication(s) and treatment(s). Contacts involving primary medical care will be followed up by the clinic coordinator for collection of documentation such as emergency room reports, hospitalization records and office visit records. These will be forwarded to the Data Coordinating Center where they will be compiled and distributed to the Crisis Review Committee for classification.

Once monthly, the Central Office assistant coordinator, who will be blinded to study treatment assignments, will contact each patient by telephone at pre-arranged times and question him/her about any medical contacts. If a patient is not reached after five attempts, no further call will be made that calendar month.

Data collected from the telephone calls will be recorded on MSH forms and will be submitted to the Data Coordinating Center. Data Coordinating Center staff will be responsible for discovering discrepancies between those reports, medical contacts reported on patient diaries, and forms filed by Clinical Center staff. Data Coordinating Center staff will be responsible for assembling documentation of possible deaths, crises, and adverse effects and sending those documents to the Crisis Review Committee.

The medical contact forms and documentation will identify events of death, stroke, chest syndrome, hepatic sequestration, new osteomyelitis, development or recurrence of ankle ulcer(s), hematuria, transfusion, and other possible events. If any study patient dies, vigorous efforts will be made to obtain complete post-mortem information. Final discharge summaries, and narratives of the final event will be reported on study forms and sent to the Data Coordinating Center.

All medical contacts indicating possible adverse effects, whether treated on an out-patient or in-patient basis, will be reviewed by the Operations Committee. Adverse treatment effects will be reported to the Food and Drug Administration.

8.2.2 Orders to Stop Study Medication

Based on the two-week cycle of blood specimen analysis for toxicity monitoring and the simulation of drug stoppages in the placebo group, the Study Treatments Distribution Center may issue a directive to stop study medication. The Central Office assistant coordinator will contact the patient by telephone to direct him/her to discontinue taking the daily medication. The Central Office Coordinator will notify clinics by telecopy of stop directives. The stop directive will be reported on study forms which will be submitted to the Data Coordinating Center.

8.2.3 Laboratory Data Collection

Blood specimens for priority laboratory determination will be collected at each two-week visit and will be prepared, packaged and sent by overnight courier to the Core Laboratory for next-day arrival. Priority laboratory determinations are listed in Appendix II. They will be processed by the Core Laboratory within 24 hours of receipt.

The data will be transmitted to the Data Coordinating Center within the next 24 hours. The data will be edited, the toxicity/titration program will be run and the next recommended dosage will be transmitted to the Study Treatments Distribution Center within the next 24 hours. See also Appendix III and Sections 5.3 and 5.4.

Blood specimens for non-priority determinations will be collected monthly or quarterly. These determinations are listed in Appendix II. They will be prepared, packed and shipped by overnight courier in batches. They will be processed at the Core Laboratory. The data will be transferred to the Data Coordinating Center where they will be edited.

8.2.4 Pregnancy

If a positive serum human chorionic gonadotropin (HCG) test is reported in a female patient, study treatments will be stopped by the clinic and the Central Office notified immediately. Suspected pregnancies are to be referred for confirmation which is to be obtained as rapidly as possible. If the pregnancy is confirmed, it will be reported on MSH study forms to the Data Coordinating Center, including documentation of pre-natal care and outcome. Study medication will be unblinded and stopped, and the patient will be referred for counseling. The case will be reviewed by the Operations Committee. The patient will continue to be followed by the Central Office assistant coordinator for ascertainment of medical contacts.

8.3 PATIENT MANAGEMENT DURING MEDICAL CONTACTS

Each patient will be given an identification card to be carried at all times and to be presented at any medical contact, stating that he/she is enrolled in the MSH, that his/her medication must be continued if at all possible, that indications for transfusion (section

6.5) should be followed, that the MSH will require records of medical contacts, and that the MSH Central Office is to be contacted in case of the need to know the study treatment assignment.

Medical staff at MSH Clinical Centers should be aware of study requirements for the management of patients presenting with sickle cell crisis, and the requirements of documenting all medical contacts. The patient should be maintained on study medication if hospitalized. Transfusions are to be avoided unless medically indicated. MSH Clinical Center directors will avoid seeking information which may unblind them with respect to the MSH treatment assignment. Usual treatment for management of sickle cell vaso-occlusive (painful) crises, as well as management of other conditions, should be administered.

8.4 SECONDARY ASSESSMENTS

8.4.1 Psychosocial Evaluation

Data from the Profile of Mood States and the Medical Outcomes Study Form SF-36 will be used in secondary analyses. Questionnaires will be administered prior to enrollment and every six months during the study and at the close-out visit.

8.4.2 Pain

A daily record of severity of pain will be kept by each patient on a weekly calendar, for which he/she will be recompensed at $5/week. An adaptation of the Memorial Pain Assessment Card will be used as a model for the records of pain intensity, relief and psychological distress. These diaries will be reviewed by the clinic coordinator at the regular two-week visits for additional ascertainment of possible medical contacts. The information regarding the occurrence and severity of pain will be used in secondary analyses.

8.5CLOSE-OUT VISIT

If the study proceeds to the planned, common termination point, patients will complete a final regular follow-up visit (the close-out visit) at which time study medication will be discontinued. Although the primary study analysis is limited to crises observed within two years of study entry, secondary analyses will include later occurring crises, and patients will continue study treatments until the planned, common termination. The close-out visits should be completed for all enrolled patients within a relatively short period of time. Every effort will be made to schedule patients for the close-out visit, including patients for whom study medication has been discontinued. Vital status will be ascertained on all patients lost to follow-up including at least one search via the National Death Index.

8.6 DEBRIEFING CONTACT

After final data have been collected and final reports prepared and submitted for publication, patients will be scheduled for a debriefing contact. They will be informed of the primary results of the study and the recommendations of the MSH investigators. They will be informed of their individual study treatment assignment.

CHAPTER 9

PARTICIPATING UNITS

9.1 INTRODUCTION

The Multicenter Study of Hydroxyurea in Sickle Cell Anemia will be composed of about 17 Clinical Centers each contributing five or more eligible patients, and four central units. The Clinical Center staff will be trained in accordance in the procedures set out in the study Manual of Operations. The objective is to standardize all study procedures carried out in the Clinical Centers and at the operational central units.

Study monitoring will be carried out by the Data and Safety Monitoring Board (DSMB), Steering Committee and Executive Committee. Monitoring will include adherence to protocol, achievement of recruitment goals, patient safety and efficacy of treatment.

The Crisis Review Committee will review reports of possible crises to ascertain the primary study end points. The Scientific Affairs Committee will review proposals for secondary analysis and ancillary studies.

An organizational chart for the MSH is presented in Exhibit 9-1.

9.2 PARTICIPATING UNITS

9.2.1 Central Office

The Central Office staff will comprise the Principal Investigator/Study Chairman, the study coordinator, the assistant coordinator, the director of the Core Laboratory, and the director and the coordinator of the Treatments Distribution Center. The Central Office has fiscal and administrative responsibility for the cooperative agree-

ment which governs the Clinical Centers, the Core Laboratory, the Treatments Distribution Center, and the Crisis Review Committee.

The Central Office will maintain close ties with the Data Coordinating Center and the standing committees. Central Office staff will provide substantial technical and scientific guidance in developing the Protocol and Manual of Operations, study forms, clinical center procedures, quality control systems, study treatment titration and distribution procedures, and laboratory specimens preparation and processing. The Central Office will implement disciplinary actions as directed by the Operations Committee resulting from major or minor protocol violations. The Central Office will also collaborate in formulating agendae and contents of reports for Data and Safety Monitoring Board and Steering Committee meetings.

9.2.2 Clinical Centers

The collaborating centers, which are funded by subcontracts through a Consortium Agreement, will each have a clinic director and a coordinator. In some, a second physician has been designated as an primary care physician, to help maintain the blinding of the clinic director as well as the coordinator. Clinical centers may be added with the concurrence of the DSMB and NHLBI. Exhibit 9-2 lists the Clinical Centers identified at the start-up of the study. Clinical Centers may not begin to enroll patients until at least five patients have met eligibility requirements and are ready to be enrolled (see Section 4.1). If a Clinical Center has not enrolled five patients by the end of the sixth month of the enrollment period (expected to be 3/31/92), the subcontract with that center will be terminated, it will receive no further payments, and it will be dropped from the study.

Should a center be dropped, voluntarily or involuntarily, it can be replaced by an alternate. Additional centers can also be added to the consortium agreement if necessary to meet recruitment goals. Such replacement or new centers must meet the requirements of the NHLBI, the FDA, and the certification process. After those requirements are met, the Study Chairman, the Data Coordinating Center director and the NHLBI Sickle Cell Branch staff will make the arrangements necessary to add new collaborating centers to the study organization.

New centers will not receive "start-up" funds; financial arrangements of their subcontracts will be the same as those of other centers in all other regards. If a center is dropped, and subsequently meets enrollment requirements, it can rejoin the consortium if funding permits. In similar fashion, if a participating center wishes to exceed its recruitment goals, it can do so within the limits of funding.

A final recruitment report specifying the number of patients enrolled by each certified Clinical Center will be distributed after the end of enrollment.

9.2.3 Core Laboratory

The Core Laboratory has responsibility for receiving blood samples from the Clinical Centers and performing hematological analyses as required for monitoring effects of hydroxyurea on blood counts, which in turn will be used to titrate study drug dosages. Priority analyses are those performed on the blood samples drawn at the two-week visits (see Appendix II), and used for toxicity monitoring. In addition, the Core Laboratory will perform other hematological analyses (listed in Appendix II).

9.2.4 Treatments Distribution Center

The study treatments (hydroxyurea and placebo) for the MSH will be composed and distributed by the Treatments Distribution Center. Treatments Distribution Center staff will review the recommended prescription sent by the Data Coordinating Center which are based on current information from the clinic visit and laboratory determinations. Physicians from the Central Office will be available 24 hours a day for emergency unblinding of assigned study medication. They will maintain records of all patient prescriptions and dosages (and the specific combination) dispensed for each patient visit.

9.2.5 National Heart, Lung, and Blood Institute

The National Heart, Lung and Blood Institute (NHLBI) staff -- Sickle Cell Disease Branch (Division of Blood Disease and Resources) and Biostatistics Research Branch (Division of Epidemiology and Clinical Applications) -- will assist study investigators and key study personnel through all phases of the study,and a member of the Sickle Cell Disease Branch (Division of Blood Disease and Resources) will serve as a voting member on the Steering Committee, and other study committees as appropriate. The purpose of NHLBI membership on the Steering Committee is to assist throughout the phases of protocol development, recruitment, follow-up, data analysis and interpretation.

The NHLBI staff will provide technical assistance in the monitoring of issues concerning recruitment, treatment, follow-up, quality control, and adherence to protocol to assist the study investigators in assessing potential problems affecting the study and potential changes in the protocol. They will provide advice in the management of the consortium agreement which funds the study, and assistance in developing solutions to major problems such as

insufficient participant enrollment. A Data and Safety Monitoring Board will be appointed by the NHLBI to provide overall monitoring of the study.

9.2.6 Data Coordinating Center

The Data Coordinating Center staff will comprise the Principal Investigator/Data Coordinating Center Director, Study Manager/Deputy Director, statistician, computer programmer(s) and coordinator(s). Data Coordinating Center staff for the MSH will provide expertise in the areas of study design, quality control, data processing and data analysis. The Data Coordinating Center will provide biostatistical and epidemiological advice for the overall conduct of MSH; collaborate with the MSH investigators in all phases of the study including planning, participant recruitment and follow-up, development and maintenance of a data management system for MSH, preparing required statistical analyses; generate Core Laboratory work lists, report forms, blood specimen transmittal lists, and progress reports; and, assist in the preparation of manuscripts for publication. Data Coordinating Center staff will undertake the primary responsibility for the collection, processing, storage and analysis of the study data, as well as cooperating with the Central Office to ascertain that the provisions of the Protocol are carried out by each participating center.

9.3 STUDY ADMINISTRATION

9.3.1 Study Chairman

The Study Chairman is the Principal Investigator of the Central Office, serves as Chairman of the Steering Committee and Co-Chairman of the Operations Committee. The Study Chairman is responsible for overall conduct of the study and adherence to the study time table (see Appendix IV).

9.3.2 Operations Committee

The Operations Committee will comprise the Principal Investigator of the Central Office (Committee Co-Chairman), his deputy, the Director of the Core Laboratory (Deputy Committee Chairman), the Director of the Study Treatments Distribution Center, the Principal Investigator (Committee Co-Chairman), Deputy Director and Statistician of the Data Coordinating Center, and an ex-officio member from the NHLBI. The Operations Committee will meet frequently (every two weeks) to oversee interaction among study units, implement changes in procedures, recommend disciplinary actions when necessary, and recommend changes to the protocol for review by the Steering Committee and the Data and Safety Monitoring Board.

9.3.3 Steering Committee

The Study Chairman will preside over the Steering Committee which will consist of the directors from each Clinical Center and the four central units. They will meet every 8 months, in Baltimore, to review progress of the trial.

9.3.4 Data and Safety Monitoring Board

The Data and Safety Monitoring Board will be appointed by the NHLBI. Board voting members will include experts in sickle cell anemia, the clinical uses of hydroxyurea, biostatistics and bioethics who are not connected with the study, and ex officio (non-voting) members -- the directors of the four central units -- and representatives of the NHLBI who will attend meetings to present information and receive recommendations. The Board will review the initial study Protocol and approve all changes made to it during the course of the study, review Data and Safety Monitoring Reports, and

make recommendations on major Protocol changes and/or early release of study results. The Operations Committee will report any unexpected or unusual findings to the Board which may be convened ad hoc for a special review of the MSH any time circumstances so warrant. The Board will meet at least yearly, to review the annual MSH report. It will review safety as the trial progresses, will evaluate treatment efficacy at four pre-specified interim time points for possible early termination of the study, and will approve dropping of any clinics because of insufficient numbers of patients or non-adherence to the protocol, and inclusion of new centers.

9.3.5 Crisis Review Committee

Forms and records received from the clinics will be reviewed on a regular basis by a committee consisting of experienced hematologists who are familiar with the spectrum of illness in sickle cell anemia and who have no other connection with this study.

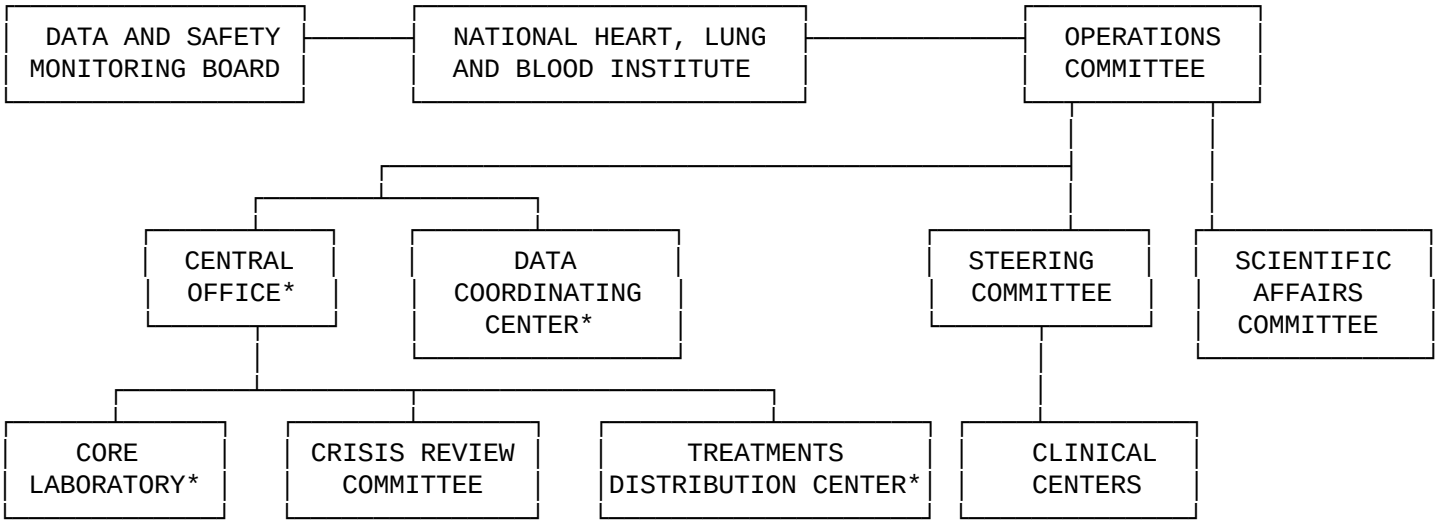
9.3.6 Scientific Affairs Committee

The Scientific Affairs Committee comprises a Chairman named by the Operations Committee, two rotating members from the Central Office, two rotating member from the Data Coordinating Center and three rotating members from the Steering Committee. This committee is responsible for overseeing the writing of main papers as directed by the Board and as approved by the NHLBI. In addition, the committee receives and reviews all scientific proposals for use of study data, including ancillary studies. Their considerations in evaluating proposals will include scientific merit, feasibility and resource availability, including statistical, computing and technical support. No ancillary study will be approved which interferes with the conduct of the overall study.

Exhibit 9-1

MULTICENTER STUDY OF HYDROXYUREA IN SICKLE CELL ANEMIA

ORGANIZATIONAL CHART



*Central units.

Exhibit 9-2
PARTICIPATING CLINICAL CENTERS

CLINICAL CENTERS	Approximate Projected Number of Patients
Jefferson Medical College (Philadelphia, Pennsylvania)	15
Howard University (Washington, D.C.)	17
Emory University (Atlanta, Georgia)	14
University of California (San Francisco, California)	8
University of Medicine and Dentistry of New Jersey (Newark, New Jersey)	9
St. Louis University (St. Louis, Missouri)	5
University of Illinois (Chicago, Illinois)	64
Medical College of Georgia (Atlanta, Georgia)	39
University of North Carolina (Chapel Hill, North Carolina)	17
University of Miami (Miami, Florida)	15
Duke University (Durham, North Carolina)	16
St. Luke's - Roosevelt Hospital (New York, New York)	24
Case-Western Reserve University (Cleveland, Ohio)	7
University of Mississippi (Jackson, Mississippi)	10
Medical College of Virginia (Richmond, Virginia)	20
Children's Hospital of Oakland (Oakland, California)	6
The Hospital for Sick Children (Toronto, Canada)	10
TOTAL	296

CHAPTER 10

CONDUCT OF THE STUDY

10.1 INTRODUCTION

The study time-line is presented in Appendix IV. During the start-up period of approximately six months, the Protocol and Manual of Operations are developed, the central units put their procedures into place, and Clinical Centers identify possible patients and prospectively observe pre-recruitment crisis frequencies for use as baseline data. Towards the end of the start-up period, the Data and Safety Monitoring Board meets to approve the Protocol and the Steering Committee meets in conjunction with clinic staff members and Central Unit (Central Office, Core Laboratory and Data Coordinating Center) personnel at the training session. Clinical Center personnel begin certification. Certification of Clinical Center staff may continue until the end of the enrollment period. The enrollment period begins when one or more Clinical Centers are certified to enroll patients, and continues for 12 months (through the 18th month from the beginning of the planning phase) or until recruitment goals are met.

Follow-up continues for at least three years after the beginning of enrollment and proceeds until the last patient enrolled has completed two years of follow-up. Central Office, Core Laboratory, Treatments Distribution Center, Clinical Center, Data Coordinating Center and National Heart, Lung, and Blood Institute staff will collaborate throughout all phases of the study.

10.2 TRAINING AND CERTIFICATION

The goal of training and certification is to standardize all procedures relating to the conduct of the study.

Clinical Center directors and coordinators must attend at least one training session and successfully complete the certification process, which will include satisfactory completion of practice procedures and data collection with patients. Study procedures include: scheduling and preparing for patient visits; phlebotomy, specimen preparation, packaging and shipment; conduct of orientation, eligibility, enrollment and follow-up visits; completion of all study forms and procedures directed therein, including medical reviews and examinations, interviewing patients, retrieving last study medication bottles, capsule counts, collecting and abstracting patient diaries, dispensing study medications; referral of patients for counseling and/or other follow-up; requesting and abstracting documentation from primary care facilities for possible events; and responding to edit messages from the Data Coordinating Center. Clinical Center certification will require the identification of an appropriate source of genetic counselling information for patients with sickle cell anemia, and documentation that at least one study staff member is available to provide advice on contraception and teratogenesis.

Training is conducted and certification is issued by the Data Coordinating Center staff after review with the Central Office staff.

10.3 DATA EDITING AND MANAGEMENT

10.3.1 Introduction

The Data Coordinating Center will serve MSH as the repository of all forms, documents and minutes. Thus, Clinical Centers will send to the Data Coordinating Center the original of each MSH form completed and retain a copy for Clinical Center files. All MSH data collection forms and copies of transmittal lists for blood specimens shipped in the course of MSH data collection will be sent to the Data Coordinating

Center. Data Coordinating Center staff will monitor the arrival of forms and transmittal lists to identify form delinquencies based on appointment schedules and anticipated study forms. Data Coordinating Center staff will monitor Core Laboratory specimen receipt dates for specimen delinquencies based on appointment schedules, anticipated specimens, and reports of specimens received in the Core Laboratory.

10.3.2 Receipt and Inventory

Data Coordinating Center staff will receive, log in and prepare all forms for data entry. Clinical Centers should send specimens directly to the Core Laboratory with copies of transmittal lists to the Data Coordinating Center. Only forms accompany transmittal lists sent to the Data Coordinating Center. Mail from the Clinical Centers will be opened immediately and forms will be stamped with the date of receipt. Transmittal lists are compared with forms received and data transmitted from the Core Laboratory. Any discrepancies between crucial patient identifiers (e.g., name code, ID number or date of study entry/follow-up visit) that Data Coordinating Center staff find on forms received will be brought to Clinical Center attention immediately by a telephone call.

10.3.3 Expected Receipt of Forms

The expected dates for receipt at the Data Coordinating Center of the MSH patients' forms will be: one week after each visit for Qualifying Visit Forms; one week after their study entry visit for Enrollment Forms; two days after issue for the copy of the Treatments Distribution Center Prescription Forms; two days after clinic visit for Core Laboratory Report Forms and Missing Specimen Lists; two weeks for Follow-Up Visit Forms or Missed Visit Forms and for the Quality of Life

Forms; two weeks for Crisis Report Forms; and one week for the monthly Telephone Follow-Up Forms. Forms or specimens not sent to the Data Coordinating Center or Core Laboratory within two weeks of the expected date will be denoted as delinquent.

10.4 QUALITY CONTROL PROCEDURES

10.4.1 Monitoring the Clinical Centers

Data Coordinating Center staff will produce recruitment reports weekly during the recruitment phase from the data entered from forms submitted for each entered patient. A sufficiently low recruitment performance will be responded to by a site visit from Central Office, Data Coordinating Center, and NHLBI staff. Failure to improve performance after such a site visit may result in an end to support for recruitment in a Clinical Center.

On a two-week basis, the Operations Committee meets to review recruitment goals and protocol violations reported for each Clinical Center. Clinics will be notified of minor violations (see Section 11.2) with suggestions for remedial action. Major violations (see Section 11.2) will result in a site visit by the Principal Investigators of the Central Office and Data Coordinating Center and an NHLBI staff member. At each scheduled Steering Committee meeting (see Exhibit 10.1), a report of progress toward accomplishment of study goals will be presented, both for the MSH as a whole and for individual Clinical Centers. These reports may include certification status, number of eligible patients identified, number of patients enrolled of those identified, completeness of scheduled visit data collection, completeness of specimen collection, completeness of crisis reporting, adherence to study protocol and results of actions taken to improve compliance.

10.4.2 Site Visits

Prior to suspension of payments, or separation of a Clinical Center from the study, the Principal Investigators of the Central Office and Data Coordinating Center may visit the Clinical Center and provide a site-visit report to the Data Safety and Monitoring Board (DSMB) for recommendation on final action. The Clinical Centers with the greatest difficulty in meeting proposed goals for recruitment may also be site visited, and recommendations for improvement, with a report to the DSMB. Clinical Centers which are not having problems with performance may also be visited once during the study, to assure quality of data produced. For regularly scheduled site visits as well as site visits for special causes, Data Coordinating Center staff will generate computer printouts of form data for comparison to Clinical Center form copies and to actual patient charts.

10.4.3 Monitoring the Core Laboratory

The Core Laboratory will be monitored for timely submission of data to the Data Coordinating Center based on receipt of copies of shipment list copies from the Clinical Centers. Data Coordinating Center staff will set aside selected study identification numbers and create name codes for use with these reserved identification numbers on labels for the submission of replicate specimens for a program of external quality control monitoring. Summaries of Core Laboratory activities and data will be provided in performance reports including counts of specimens received, data delivered to the Data Coordinating Center and coefficients of variation on blind replicates. The Core Laboratory director must submit reports on its performance and internal quality assurance monitoring for DSMB review.

10.4.4 Data Coordinating Center

Data Coordinating Center activities in MSH will be checked internally to help enhance the quality of data and analyses. Persons (such as the Principal Investigator or Deputy Director) not involved in the preparation of the data editing programs will fill out test study data forms, making deliberate errors. These forms will be keyed and processed through the data editing system to see if all of the errors were caught by the data management system. An audit of a sample of original data forms against the data on the Data Coordinating Center computer will be used to detect problems with the data entry and with editing software prepared and provided by the Data Coordinating Center.

New analysis programs (including runs using statistical packages such as SAS and BMDP) will be tested by running against a small subfile of 10 or 20 participants and independently producing the tabulations and statistical calculations manually from the original data. This will help to assure the correct variables have been selected from the analysis file, the variables and cut-points have been defined properly, and transformations of the original variables on the analysis file have been formulated correctly.

10.5 PAYMENTS FOR CLINICAL CENTERS

Payments from the Central Office to the Clinical Centers will be based on the numbers of patients recruited. Payments will be made on a quarterly schedule. If five patients have not been enrolled within six months of the start of patient recruitment, a Clinical Center is subject to suspension. No payments will be made to suspended Clinical Centers.

CHAPTER 11

POLICY MATTERS

11.1 INTRODUCTION

Procedural guidelines are established to ensure that all clinics adhere to the protocol, to facilitate optimum use of data generated by the study, and to ensure optimal use of the resources of the Central Office and Data Coordinating Center for procedures (for quality control in the study see Section 10.4).

11.2 QUALITY ASSURANCE

Members of the Steering Committee will create a list of major and minor protocol violations. Major violations are those which endanger patients, such as repetitive failure to obtain scheduled blood counts or failure to discontinue therapy promptly when so advised. Minor violations are those which impede the progress of the study, such as not filing reports in timely fashion (form delinquencies) and excessive delays in supplying materials for the Crisis Review Committee.

After the first major violation, a clinic will be asked to submit a proposal outlining how recurrence will be prevented. After a second major violation, clinics will not be allowed to recruit more patients, but will be able to follow those already recruited. After 3 violations the clinic will no longer be supplied with study drug or funds. The Data and Safety Monitoring Board will be made aware of all major violations, and must approve dropping the Clinic after a third violation.

The Data Coordinating Center will document minor violations in performance reports, as well as notifying the clinics of them. Repeated minor violations which are not corrected will result in

suspension of payments to the clinic, which will resume when minor violations are corrected.

Prior to suspension of payments, or separation of a clinic from the study, Drs. Charache and Terrin will visit the clinic and provide a site-visit report to the Data and Safety Monitoring Board (DSMB) for recommendation on final action. The clinics with the greatest difficulty in meeting their proposed goals for recruitment will also be site visited, and recommendations for improvement made to them, with a report to the DSMB. Centers which are not having problems with performance will also be visited once during the study, to assure quality of data produced.

11.3 TYPES OF MSH RESEARCH

The Steering Committee will exercise responsibility for all end point, data bank, and ancillary studies, and for all publications and presentations evolving from the MSH research, through the Scientific Affairs Committee.

Investigators at all MSH sites, including the Data Coordinating Center and the NHLBI Program Office, have equal status with regard to developing protocols, participating in such studies as are approved and collaborating in the development and publication of research papers based on MSH material.

The procedures in this section for end point, data bank, and ancillary studies, and for publication of MSH research results are similar to those used in other cooperative clinical trials. These procedures are intended to protect the interests of all participants in the trial, namely, to assure that study data conform to the requirements of study design, are accurately presented, authorship is

appropriately acknowledged, and the text of all publications is well written.

MSH research and the resulting presentations and publications may be grouped into the following study categories:

1. End point studies;
2. Data bank studies;
3. Ancillary studies.

11.3.1 End Point Studies

An end point study is a study pertaining to the fundamental goals of the project (namely, the evaluation of the efficacy of hydroxyurea in the treatment of sickle cell anemia) or which involves data, such as treatment assignment, differences in crisis rate by treatment assignment, or mortality rates, which cannot be released prior to the end of the study. These studies will summarize the findings of the MSH, based on the entire study population, and will be written at the conclusion of follow-up or data collection.

11.3.2 Data Bank Studies

A data bank study is a study which uses data routinely collected on patients when they are logged, screened or randomized into the MSH and analyzes these to answer some scientific question. Data used in this research are not directly related to the fundamental goals of the study. In general, such studies are conducted with the idea of producing a scientific paper for publication based on the results of analysis.

11.3.3 Ancillary Studies

An ancillary study is a study which uses supplementary data collected on patients who are logged, screened or randomized into the

MSH Study, over and above the data collection required by the MSH Protocol. Such studies are usually restricted to consideration of a specific test technique or involve only supplemental data collected on MSH patients.

11.4 CLINIC DIRECTOR ACCESS TO MSH DATA FILES AT THE END OF THE STUDY

At the end of the study, Data Coordinating Center staff will produce a well documented data tape containing a refined (and reduced) set of the MSH data for the purpose of analysis by the MSH investigators and eventual release to the public domain in accordance with NHLBI policy. Center directors may analyze the data on this data tape in their own centers, but prior to submission of articles for publication must submit the analyses proposed for publication to the Data Coordinating Center where they will be reviewed and computations replicated. Clinic directors who perform their own analyses are responsible for obtaining all support necessary for the data bank or ancillary study outside of regular study resources. The Data Coordinating Center will be the center of study analysis activities as long as the MSH investigators continue in their collaborative efforts.

11.5 PUBLICATION

The authors of any publications stemming from the study will be those who actually write the document, plus the group as a whole ("Doe J, Roe K, and the Multicenter Study of Hydroxyurea"), with all investigators and coordinators listed in the appendix at the end of the paper or reference made to a publication listing all investigators. Study manuscripts may only be submitted for publication for main end point studies and approved data bank and ancillary studies. All

manuscripts related to study patients must be reviewed and approved by the Scientific Affairs Committee.

11.6 CONFLICT-OF-INTEREST

MSH investigators and their immediate family will not buy, sell, or hold stock options in any of the companies providing medication under study from the time the recruitment of patients for the trial begins until funding for the study in the investigator's unit ends and the results are made public; or from the time the recruitment of patients for the trial begins until the investigator's active and personal involvement in the study or the involvement of the institution conducting the study (or both) ends.

Each investigator will agree not to serve as a paid consultant to the companies during these same periods. The guidelines will also apply to the investigator's spouse and dependents. The Data Coordinating Center will hold and update annually conflict-of-interest statements from each investigator.

Certain other activities are not viewed as constituting conflicts-of-interest but must be reported annually to the Data Coordinating Center: the participation of investigators in education activities supported by the companies (permitted only if no honorarium is paid to the investigator); the participation of investigators in other research projects supported by the companies; and, occasional scientific consulting to the companies on issues not related to the products in the trial and for which there is no financial payment or other compensation.