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Management of Severe Acute Malnutrition in SCD, in Northern Nigeria
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Management of severe acute malnutrition in children with sickle cell disease greater than 5 years of age living in northern Nigeria

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1. PROJECT SUMMARY

The overall goal of this feasibility trial is to determine the acceptability of a randomized controlled trial to ascertain the optimal strategy for the treatment of severe malnutrition in children with sickle cell disease (SCD) older than 5 years of age. No international standard or evidence-based guidelines exist for the treatment of severe malnutrition (defined as BMI Z-score below –3) in children with SCD. With an expanding pediatric population of more than 75 million in Nigeria, coupled with decreasing childhood infectious disease-related mortality, the next emerging threats to preventable childhood deaths are non-communicable diseases. Data from our ongoing NIH-funded randomized controlled primary stroke prevention trial in Nigeria (NCT02560935), in which we evaluated children with SCD between 5 and 12 years of age, demonstrated that 29% (230/803) of the cohort met criteria for severe malnutrition. Approximately 92% of the cohort in northern Nigeria identified as having severe malnutrition was below the 5th percentile for weight of children with SCD living in the US, Canada, or Europe. These data indicate older children with SCD living in northern Nigeria are undernourished when compared to children living with SCD in high-resource settings. A potentially unique attribute to treating malnutrition in children with SCD is the use of FDA approved anti-metabolite, hydroxyurea, to prevent vaso-occlusive pain events in children. The beneficial effects of hydroxyurea include, but are not limited to, decreased inflammation and increased hemoglobin levels. Preliminary evidence in our cohort of older children with sickle cell anemia (SCA) in northern Nigeria reveals that moderate fixed-dose hydroxyurea (20 mg/kg/day) significantly increases BMI in children with severe malnutrition. We propose a randomized controlled feasibility trial in older children (5 to 12 years of age) with SCA living in northern Nigeria. In preparation for a definitive phase III trial to determine if a nutritional supplement (Plumpy'nut) and moderate fixed-dose hydroxyurea therapy is superior to a nutritional supplement alone, we will randomly allocate 150 children between 5 and 12 years of age with SCA and severe uncomplicated malnutrition to each of the two arms. In **aim 1**, we will assess the feasibility (rate of recruitment, retention, and adherence) of a randomized controlled trial (RCT) in children with SCA and severe malnutrition to a 12-week intervention period. For **aim 2**, we will establish the safety protocol to monitor for unknown rates of complications associated with treating malnutrition in children with SCD. To decrease the likelihood of sharing limited food resources in a poor family and to determine the specificity of malnutrition for children with SCD in northern Nigeria, we will screen and treat up to 100 malnourished non-SCD siblings of the trial participants. After completion of this feasibility trial, we will use the acquired knowledge to design a phase III trial to definitively determine the optimal treatment strategy for severe malnutrition in older children with SCD living in Africa, potentially affecting thousands of children in this region.

2. BACKGROUND

Significance: High burden of sickle cell disease (SCD) and severe malnutrition in Sub-Saharan Africa Approximately 80% of all children born with SCD live in Africa.[1] The most populous country in Africa, Nigeria, has approximately 150,000 born each year with sickle cell anemia (SCA), 50% of the newborns with SCD in the world, as compared to about 1,800 births with SCA in the USA [2] The highest prevalence of global childhood malnutrition is estimated to occur in low- and middle-income countries, with a prevalence of approximately 8% in sub-Saharan Africa. Case-fatality rates among hospitalized children with severe malnutrition can be as high as 20-60%,[3,4] and children with severe malnutrition have 9.4-fold higher odds of dying compared to non-malnourished children.[5] Malnutrition in children is also associated with significant long-term morbidities including poor cognitive development, impaired behavioral development, heightened anxiety levels, depression, and low self-esteem.[6-11] Severe malnutrition is associated with high mortality in children under 5 years of age; however, data on morbidity and mortality specifically in children with SCD and children above 5 years of age are lacking.

Malnutrition is associated with adverse events in SCD Reduced growth and delayed maturation have been previously described in children with SCD[12,13] due to multifactorial causes, including poor dietary intake (which decreases as the individual gets older),[14] hyper-metabolism and increased nutrient demand,[15,16] increased hemolysis causing a compensatory increase in reticulocyte production to maintain tissue oxygenation,[17] and poverty. Individuals with SCD are more prone to infections with encapsulated organisms due to auto-splenectomy, which occurs as a result of repeated splenic infarction.[18] Several interventional studies demonstrated that zinc and micronutrient supplementation (vitamins A, B and magnesium) given to children with SCD leads to improvement in growth, decreased emergency room visits, decreased acute vaso-occlusive pain episodes, and reduced rates of infection.[14-16] Amino acids, particularly L-arginine and its precursor L-glutamine, are critical for growing children and are a key component for immunological, inflammatory, intestinal permeability and healing responses.[19-21] An *in-vitro* study demonstrated increased usage of glutamine by sickled erythrocytes for nucleic acid (antioxidant) production.[22] In July 2017, the U.S. Food and Drug Administration (FDA) approved Endari (L-glutamine oral powder) for the treatment of SCD in adults and children > 5 years of age.[23]

Hydroxyurea therapy is associated with increased weight gain in children with SCD A recent review of hydroxyurea in children with SCD enumerates that fetal hemoglobin (HbF) induction that results in (1) decreased sickle polymerization; (2) decreased inflammation based on lower neutrophil and reticulocyte counts from ribonucleotide reductase inhibition and marrow cytotoxicity; (3) decreased adhesiveness and improved rheology of circulating neutrophils and reticulocytes; (4) reduced hemolysis through improved erythrocyte hydration, macrocytosis, and reduced intracellular sickling; and (5) nitric oxide (NO) release with potential local vasodilatation and improved vascular response.[24] Multiple studies have demonstrated that hydroxyurea therapy, an anti-metabolite chemotherapeutic agent, approved for secondary prevention of acute vaso-occlusive pain, is associated with increased BMI and linear growth in children with SCD

when compared to children with SCD not treated with hydroxyurea.[25-27] Given that hydroxyurea therapy is associated with decreased inflammation, increased hemoglobin, and increased weight gain when compared to children not on hydroxyurea, we postulate our global hypothesis is biologically plausible for treatment of uncomplicated severe malnutrition.

Outpatient community-based therapeutic care of severe malnutrition in children is safe Several studies have demonstrated the safety of outpatient treatment of uncomplicated severe malnutrition in children below 5 years of age in low-resource settings, using ready-to-use-therapeutic food (RUTF).[28] Outpatient community-based therapeutic care reduces mortality and cross-infection rates, as well as costs, and increases access to treatment and recovery rates.[29-31] Several clinical trials in severely malnourished children demonstrated successful recovery in outpatient settings with RUTF, reaching 100% weight-for-height.[30,32] However, none of these trials have specifically included children with SCD and all of the malnutrition intervention studies have been in children under 5 years of age. Thus, we do not know the prevalence of refeeding syndrome in this population. Due to limitations of malnutrition, and the lack of recognition of the high prevalence of malnutrition in children > 5 years of age, only children with severe malnutrition less than 5 years of age are screened and treated for malnutrition in Kano, Nigeria.

Preliminary Data: The prevalence of severe malnutrition in children with SCA in northern Nigeria is high when compared to children with SCA in high-income countries. A total of 803 and 1,127 children with SCA in the Nigerian and SIT cohort, children with SCA from the USA, Canada and Europe screened for a silent strokes (n=1,127)[33], were included in the analysis, respectively. The median age in the Nigerian and the SIT cohorts was 8.2 and 8.5 years (range 4.9-13.8 and 5.0-13.8), respectively, and approximately half were male

Table I : Baseline Characteristics and Nutritional Status of Pediatric Cohorts with SCA in Nigeria compared to High-Income Countries

Variable	Nigerian Cohort (n=803)	SIT Cohort (n=1,127)	P value#
Age, median (range) (years)	8.2 (4.9-13.8)	8.5 (5.0-13.8)	0.001§
Sex, male, %	49.4	51.4	0.402
Weight, median (kg)	19.0	25.9	<0.001§
Height, median(cm)	119.7	126.8	<0.001§
BMI, mean	13.7	16.4	<0.001
Hemoglobin, mean	7.6	8.2	<0.001
White Blood Count, mean	14.7	12.6	<0.001
Nutritional status- WHO-Growth Standard			
Weight Z-score, mean (SD)	-2.5	-0.2	<0.001
Height Z-score, mean (SD)	-1.6	-0.5	<0.001
BMI Z-score, mean (SD)	-2.3	-0.1	<0.001
Underweight**, %	63.1	33 4.4	<0.001
Stunting**, %	37.6	8.7	<0.001
Wasting**, %	50.7	3.2	<0.001
Severe stunting and severe malnutrition			
Severe stunting**, %	14.1	1.3	<0.001
Severe malnutrition**, %	28.6	0.3	<0.001

SCD, sickle cell disease; WHO, World Health Organization; BMI, body mass index; Hb, hemoglobin; WBCs, white blood cells. **Underweight; Weight-for-age Z-score < -2, Stunting; height-for-age z-score < -2; Wasting: weight-for-height/BMI-for-age z-score < -2, Severe stunting; height-for-age z-score < -3, Severe malnutrition/wasting: BMI Z < -3. # Chi-square test for categorical variables and independent sample t-test for continuous variables, unless otherwise noted. P-value < 0.05 was set for statistical significance. §Mann-Whitney U test

(49.4% and 51.4%) (Table1). The Nigerian cohort had significantly higher rates of underweight, stunted and wasted children than the SIT cohort: All anthropometric variables and laboratory values in the Nigerian cohort were significantly lower when compared to the SIT cohort in high-income countries; mean BMI was 13.7 versus 16.9 kg/m^2 ($p<0.001$); children in the Nigerian cohort exhibited overall significantly poorer nutritional status ($p<0.001$) and were shorter ($p<0.001$). Prevalence of severe stunting and wasting in children with SCA in Nigeria is high: A total of 28.6% (230/803) in the Nigerian cohort met criteria for severe wasting and 14.1% (113/803) for severe stunting, which was significantly higher when compared to the age- and gender-matched pediatric cohort in high-income countries (0.3% (3/1,127) and 7.5% (84/1,127) respectively, ($p<0.001$). In our primary stroke prevention trial in Nigeria, children with severe malnutrition receiving hydroxyurea therapy had a statistically significant increase in their BMI when compared to those receiving hydroxyurea that were not malnourished (a comparative increase in BMI of 2.2, $p=0.006$; there is a similar comparative increase in BMI for age z score of 1.9, $P=0.001$). Taken together these studies demonstrate the previously undescribed challenge of severe malnutrition in older children with SCA.

Innovation: For the tens of thousands of older children with SCD with severe malnutrition living in Nigeria and other locations in Africa, the optimal and safe strategy for treatment is a critical unanswered question. Despite the high prevalence of severe malnutrition in Nigeria and elsewhere, no specific malnutrition program is designed to screen and treat children with SCD. In fact, the problem is not even recognized as a treatable entity by any international malnutrition guideline, including the WHO guidelines. In Kano, Nigeria, all malnutrition philanthropic efforts and government support programs are designed specifically for children less than 5 years of age. Thus, even when older children with SCD are identified, there is no systematic approach to manage their severe malnutrition. To our knowledge, **this would be the first severe malnutrition trial specific for children with SCD in Africa or elsewhere**. Regardless of the results, this feasibility trial will provide vital evidence and experience necessary for a Phase III trial for severe malnutrition in SCD in Africa.

3. SPECIFIC AIMS

The overall goal of this feasibility trial is to determine the acceptability of a randomized controlled trial (RCT) for the treatment of severe malnutrition in children with sickle cell disease (SCD) 5 years and greater. With an expanding pediatric population in Nigeria that currently exceeds 75 million, coupled with a decreasing childhood infectious disease-related mortality, the next emerging threats to preventable childhood deaths are non-communicable diseases. As a result of our ongoing primary stroke prevention trial (NCT02560935, 5R01NS094041-03) using hydroxyurea therapy in northern Nigeria, we unexpectedly identified **severe malnutrition in children greater than 5 years of age**, a previously unrecognized medical problem in older children. We demonstrated that 29% (230/803) of the cohort met criteria for severe malnutrition (BMI Z-score <-3), and 14.1% (113/803) were severely stunted (height-for-age Z-score <-3).[34] Approximately 92% of the cohort of children with malnutrition was below the 5th percentile for weight of children with SCD living in the USA, Canada, or Europe.[35] These data indicate that older children with SCD living in northern Nigeria are undernourished when compared to children with SCD in high-resource settings. Unfortunately, no international standard has been developed for the management of severe malnutrition in older children (greater than 5 years of age) irrespective of their disease status, and no standard of care has been established for the treatment of severe malnutrition in children with SCD at any age. A potentially unique attribute to treating malnutrition in children with SCD is the use of the FDA-approved anti-metabolite, hydroxyurea, to prevent vaso-occlusive pain events in children. Preliminary evidence in our cohort of older children with sickle cell anemia (SCA) in northern Nigeria reveals that moderate fixed-dose hydroxyurea (20 mg/kg/day) significantly increases BMI in children with severe malnutrition with no specific nutritional supplement. We propose a randomized controlled feasibility trial in older children with SCA living in northern Nigeria. **In preparation for a definitive phase III trial to determine if nutritional supplement (Plumpy'nut) and moderate fixed-dose hydroxyurea therapy is superior to nutritional supplement alone, we will randomly allocate 150 older children with SCA to each of the two arms.** To collect the necessary data for designing the phase III trial, we will complete the following aims:

Aim 1: To assess the feasibility (rate of recruitment, retention, and adherence) of a RCT in a 12-week intervention period. For this aim, the primary outcome will be acceptable recruitment, retention, and adherence rates (to monthly medical appointments and nutritional and hydroxyurea therapy). Among a pool of 700 potentially eligible children with SCD seen weekly at two clinical sites in the same neighborhood in northern Nigeria, we will recruit and randomize a total of 150 children with uncomplicated severe malnutrition. In the first week after starting therapy of Plumpy'nut (one sachet daily, 500 kilocalories, for children 5 to 9 and two sachets daily for children 9 to 12 years of age), we will reevaluate the patient in clinic; subsequently all participants will be evaluated monthly and called weekly.

Aim 2: To establish the safety protocol for monitoring unknown rates of complications associated with treating malnutrition in children with SCD. For this aim, the primary outcome will be to determine the ability of a newly developed safety protocol to detect

refeeding syndrome and other potential complications associated with treating uncomplicated severe malnutrition in children with SCD on nutritional supplementation with and without simultaneous treatment with hydroxyurea. We will enroll 150 children with severe malnutrition and 100 siblings from the same family with severe malnutrition and assess the safety monitoring approach that may be specific to children with SCD. Due to polygamy, most families, in northern Nigeria, have a large number of siblings making recruitment feasible.

This feasibility trial will allow a more informed design of a future randomized controlled phase III trial to treat uncomplicated severe malnutrition in older children with SCD living in Africa, more specifically, Nigeria. Ultimately, if we find evidence to support our **global hypothesis,** that hydroxyurea therapy combined with nutritional supplement is superior than nutritional supplement alone, we will be well-positioned to implement an SCD-specific treatment for older children with SCD with severe malnutrition in the country with the greatest burden of SCD in the world and in a region where severe malnutrition is common, found in at least 25% of older children with SCD. With an estimated 150,000 children born with SCD in Nigeria each year, our strategy could be used for over 30,000 children in Nigeria per birth cohort with SCD and could be applicable to other children in Africa with SCD.

4. APPROACH

Overview: The immediate goal of this feasibility trial is to obtain prerequisite data to guide the development of a definitive, NIH-funded randomized controlled phase III trial to determine the optimal strategy for treating severe acute malnutrition in older children with SCD. We will use the well-established approaches implemented for our currently funded 3 clinical trial stroke prevention trials in children with SCD.[36]

Design: A 12-week, open label, randomized controlled feasibility trial in children with SCD between 5 and 12 years of age to treat uncomplicated severe malnutrition.

- **Aim 1:** To assess the feasibility (rate of recruitment, retention, and adherence) of randomized controlled trial in a 12-week intervention period.

- **Aim 2:** To establish the safety protocol for monitoring unknown rates of complications associated with treating malnutrition in children with SCD.

4.1 STUDY METHODS

For these two aims, we will conduct the screening and the recruitment at the SCD outpatient clinic at AKTH and MMSH, 3 miles away. The Hasiya Bayero will serve as a referral site. During the screening phase, baseline demographic and clinical data will be obtained, as well as a physical exam (including edema checks, weight and height measurements). The average turnaround time for the laboratory investigations is 24 to 48 hours. We will also recruit and enroll up to 100 malnourished siblings without SCD, but in the same age range for the comparison group. However, where this is not possible, non-siblings who meet the inclusion criteria for the study will be recruited for comparison purposes. Children with **complicated** acute severe malnutrition (including, but not limited to, poor appetite, altered mental status, fever, other signs of infection, bilateral edema of the extremities or respiratory distress) will be **excluded** and referred for inpatient treatment. All possible complications will be strictly monitored. For those research participants who develop complications (pneumonia/acute chest syndrome, re-feeding syndrome, or sepsis, etc.), it is expected that the site Pediatrician will activate the standard care protocol, and such participants will be followed until resolution or stabilization at no cost to the parents. Such participants will continue with the trial after stabilization. During the first visit, baseline demographic and clinical data will be obtained, as well as a physical exam (including edema checks and anthropometric measurements). The anthropometric measurements will include weight, height, mid-upper arm circumference (MUAC), skinfold thickness, and knee height. Stool microscopy will also be performed during the initial visit to rule out infectious etiology. However, Helminth in stool will not be considered an exclusion criterion for the study. Stool will also be collected at week 12 (visit 4) of the study, during the evaluation of recovery of severe acute malnutrition for future microbiome analysis. The microbiome analysis will be utilized to describe possible differences between participants who did and did not recover from severe acute malnutrition during the trial. Participants will be

evaluated at monthly outpatient visits, which will include a physical examination, edema check and anthropometric measurements. The participants will be asked to come to the clinic for evaluation if the following medical complications were to occur: hypothermic or hyperthermic state (<35.5 or ≥38.0 degrees Celsius), cough, diarrhea and/or vomiting, signs of dehydration (dry mucus membranes, low urine output, cold hands and feet, sunken eyes). According to standard of care practices, all children with severe malnutrition will be treated with the following: a 7-day course of antibiotics (amoxicillin),[37] and deworming treatment (albendazole). As per standard care, all children with SCD are routinely prescribed Folic acid, antimalarial prophylaxis (Proguanil) and also oral penicillin up to 10 years of age. A four-week supply of Plumpy'nut (RUTF specifically designed to treat acute malnutrition without complications) will be given to augment their pre-existing diet. Parents will receive ongoing face-to-face SCD-specific education about nutrition and hygiene. In response to an allergic reaction to the Plumpy'nut product, the participant will be removed from the study and will not be considered evaluable. The participant will be referred to standard of care procedures and an AE form pertaining to the event will be filled out and submitted.

To assess adherence, our research team will make weekly phone calls in between the monthly clinic visits and ask about number of empty sachets and adherence to hydroxyurea (missed doses in last week). During the monthly clinic visits, the family will be asked to bring back the empty Plumpy'nut sachets (92 g). One or two sachets a day of Plumpy'nut will provide a nutritional supplement to home foods (one sachet for children 5 to 9, and two sachets for children 9 to 12 years of age). A 24-hour dietary history using a USDA multi-pass interview method will be obtained during the weekly phone calls and at the monthly clinic visits, and a Nigerian-specific food and nutrient coding database will be used to estimate daily overall caloric intake.[38] For emphasis, the participants enrolled in the study will have a study visit in the middle of the first week after enrolment. This will be followed by weekly phone call by the study personnel to ask for any unanticipated problems (i.e. questions on safety and adverse events), and to reemphasize adherence to study medication. To improve the adherence of the study participant consuming all prescribed calories, there will be community visits for a certain number of enrollees who consents to community visits as part of the study. The community visit will include a research team member traveling to the study participant's community. They will meet with the local community to discuss the importance of the study participant consuming the prescribed nutrition supplement. The participants will also come for monthly study visits for physical examination, anthropometric measurements and laboratory evaluation.

- **Inclusion criteria for children with SCD:** 1) laboratory diagnosis of SCA (HbSS or HbSB^0 thalassemia); 2) informed consent from parent or legal guardian; 3) severe malnutrition defined as a BMI Z-score below –3; 4) age between 5 and 12 years (assessment can take place up until the 13th birthday), reside within a 2 hour driving distance from the medical center to facilitate weekly phone call in between the monthly clinic visits.
- **Exclusion criteria**: 1) children with complicated severe acute malnutrition; 2) children with electrolyte disturbances (serum Na, K, Ca, PO_4) at baseline; 3) children on

disease-modifying therapy (hydroxyurea or regular blood transfusion therapy); and 4) children enrolled in other studies; 5) children with diabetes and other chronic illnesses; and 6) children with known HIV infection; 7) children with known allergy to dairy or peanuts.

- **Inclusion and exclusion criteria for siblings without SCD, but malnourished.** Entry criteria will be identical to participants in the trial, except they will not have SCD and must be between 5 and 12 years of age. Any child in the family identified as having severe acute malnutrition, but less than 5 years of age, and not eligible for the trial, will be referred to the hospital nutritional clinic for counseling and standard care management.

- **Methods for children with SCD with uncomplicated severe malnutrition:** All children between ages 5 to 12 years of age with SCD will be screened for malnutrition during outpatient clinic visits along with their siblings that also attend the clinic appointment. Basic demographic information, SCD phenotype, and anthropometric measurements (weight, height and MUAC, skinfold thickness, and knee height) will be collected. To identify risk factors for malnutrition, additional demographic data will be collected at monthly outpatient clinic visits, including but not limited to parental education level, marital status, annual family-income, number of rooms and people living in the house. We will also ask the caregivers or parents of all participants to complete the previously validated U.S. Household Food Security Survey and children with SCD and malnutrition aged 12 years the Self-Administered Food Security Survey Module for Youth Ages 12 and Older, because there are no validated food security surveys in specific to Africa. Additionally, we will pilot basic food insecurity questions for all subjects 5-12y with a time interval of last week/7days. These will be structured interview questions as a pilot. Food insecurity surveys will be performed at study enrollment (visit 0) and the last study visit (visit 4). We will ask the mothers to complete the Public Health Questionnaire-9 (PHQ-9) to assess maternal mental health. The mothers will be referred to their primary care physicians if their PHQ-9 score is suggestive of depression (score ≥9) and will be re-assessed during the following study visit.

- **Methods for siblings of children without SCD, but with uncomplicated severe malnutrition:** A comparison group including up to 100 siblings without SCD, between 5 and 12 years of age, will be screened for malnutrition. The siblings will be recruited upon study enrollment of the participant with SCD (visit 0). All sibling participants will be treated according to the same protocol as their sibling with SCD. If the site investigator believes that other siblings are likely to require nutritional supplements, but they are not malnourished, then at the discretion of the site investigator they may provide additional sachets for the siblings in the household. These sachets will be funded outside of the clinical trial.

- **Methods to assess safety:** Per WHO guidelines, severe malnutrition without medical complications can now be effectively managed in the community, with RTUF.[39] However, given the superimposed physiologic changes associated with SCD and

susceptibility to bacteremia and malaria, the risks of refeeding syndrome and other known complications of SCD during nutritional supplementation are unclear. For this purpose, comparable to what we have done for our two RCTs for stroke prevention in Nigeria using hydroxyurea therapy, the Executive Committee will review laboratory values at the various predefined intervals (Table 1), with pre-defined local abnormal values for children with SCD. We will obtain serum Na, K, Ca, PO_4 at baseline to screen out those with significant electrolyte derangements and repeat those measures at the midpoint of week 1 and refer those with significant abnormalities for inpatient treatment management. Electrolyte derangement during study will be considered a complication of the treatment. Those individuals will be managed by the site pediatrician until full recovery at no cost to the parents. Supplementation of amino acids (<0.42mmol/L) will be based on local management practices, outside of this research protocol.[40] Per WHO guidelines, a weight increase of 5g/kg/day (35/g/kg/week) will be defined as adequate growth per week. If at monthly visits, participant does not achieve this growth rate, the family will be interviewed to assess challenges with caloric intake and potential another sachet will be provided.

- **Nutritional supplement-PlumpyNut**: is a ready to use therapeutic food that is used in the outpatient treatment of severe acute malnutrition. It is a fortified peanut butter-like paste that contains essential macro and micronutrients sufficient to result in rapid weight gain.[1]
    - **Composition**: Vegetable fat, ground nut/peanut butter, skimmed milk powder, lactoserum, maltodextrin sugar, mineral and vitamin complex. It comes in a 92g per sachet form equivalent to 500 kcal/sachet.[1]
    - **Benefits:**
        - It provides calories and essential nutrients that restore and maintain body weight and health in severely malnourished children more effectively than F100.[2]
        - It does not require refrigeration nor water for preparation. This makes it convenient for use in low-resource settings
        - It can be administered at home without the need for hospitalization or medical supervision
        - It has a 2-year shelf-life making it convenient for low-resource settings

- **Hydroxyurea** is an antimetabolite chemotherapy agent, also NAFDAC approved for the use of preventing acute vaso-occlusive pain and other complications in SCD.

Table 2 Study Protocol Timeline					
Treatments/tests	**Week 0 Visits 1**	**Week 0 Within 7 days (goal of 3 to 5) days after Rx Visit 2**	**Week 4 Visit 4**	**Week 8 Visit 5-12**	**Week 12 Visit 13**
Informed consent for study enrollment	X				
Demographic/clinical baseline data	X				
Physical exam; weight, height, MUAC, oedema check	X	X	X	X	X
Recall food questionnaire	X	X	X	X	X
U.S. Household and Youth Food Security Survey and Youth Food Security Questionnaire	X				X
PHQ-9 Questionnaire (mothers)	X	X	X	X	X
Stool microscopy	X				X
CBC and serum pre-albumin	X	X	X	X	X
Phosphate, Calcium, Magnesium, Potassium	X	X			
Test dose ready-to-use Soy Plus to establish no acute allergy	X				
4 week supply of Plumpy'nut	X	X	X	X	X
Participants with severe uncomplicated malnutrition: - 7-day course of amoxicillin and Albendazole 400mg	X				
Parental education on nutrition	X	X			

4.2 STUDY PROCEDURES

- Personnel – Informed consent will be obtained by the site PI or their designees (pediatrician or research coordinator who has the strongest relationship with the patient during the return clinic visit). Screening: During routine weekly clinic SCD visits at AKTH and daily SCD clinic visits at MMSH, the study pediatricians will discuss the study with the parents of eligible children with SCD between ages 5 to 12 years old. As part of standard of care, physical examination including anthropometric measurements (weight and height) will be completed. Once the child is identified as having severe malnutrition (BMI Z-score below –3) they will be referred to the nutritional clinic for management per local standard of care protocol. Children with severe malnutrition who qualify and agree to participate will be invited to sign consent and assent for study recruitment to this study.

- Randomization procedures**:** The unit of randomization is the individual**.** All study participants with SCD will be randomized to either of the two arms of the treatment groups in a ratio of 1:1. The project statistician, Mark Rodeghier, PhD, will implement a permuted block allocation scheme, likely based on block sizes of 2 and 4, stratified by gender, within clinical site. Randomization will be accessed at each site through Research Electronic Data Capture (REDCap). The randomization module in REDCap allows us to load a randomization table that will allow the research coordinator at each site to click a 'randomize' button. There will be no randomization for the study participants without SCD, as all of these participants will receive only Plumpy'nut.

- Recruitment and Retention Plan: At the two participating sites, they will draw from a pool of potential participants of at least 600 children with SCA over 5 years of age. Based on current assessment in 900 children with SCA screened for our primary stroke prevention trial (NCT02560935, 5R01NS094041-03) we expect approximately 29% of participants will be severely malnourished. Thus, we plan to enroll all study participants within 3 months from initiation of the study or sooner if the recruitment rate is similar to our primary stroke prevention feasibility trial of ~90%.[41] To ensure that we start enrolling participants shortly after the receipt of funding, both clinical sites and the Data and Clinical Coordinating Center have IRB approval for an earlier version of the study and will submit an amendment to adjust for the most recent changes. To enhance retention, we developed strategies to reduce loss to follow-up, including clear written instruction for management of severe malnutrition, offset the cost of patient transportation during monthly follow-up visits, and weekly phone calls. We will collect phone numbers of both or either of the parents or alternatively a close relative or a neighbor. Further, we will request the names, addresses, and phone numbers of two family members or friends who would know how to get in touch with the participant in the event of a missed appointment (this information will be kept at each site and will not be entered into the central database).

- Study follow-up visits: In addition to the safety check at mid-week of week 1, all participants with severe uncomplicated severe malnutrition will undergo monthly study and weekly phone calls to ensure monthly adherence to protocol and weekly weight gain. In the first week of the trial the patient will be re-evaluated in clinic to monitor for refeeding syndrome. Siblings will be encouraged to visit during trial enrollment visit for assessment of their nutritional status, and if severely malnourished, will be asked to enroll if $\geq$ 5 years of age or referred to the malnutrition clinic if < 5 years of age. If the site investigators believe that the family will share the sachets for the participant enrolled in the trial, they will also be provided with additional sachets per the discretion of the local site investigator. We will also determine adherence to Plumpy'nut therapy with weekly phone call and by the family bringing back the empty sachets at monthly study visits. We will assess the adherence to hydroxyurea, by all of the following - weekly phone calls for missed doses, pill count return at each visit, fetal hemoglobin at baseline and upon exit, MCV change from baseline and with each CBC, and absolute neutrophil count from baseline and each CBC.[41] We will record all cases of hospitalizations. In cases of treatment failure (e.g. when the participants do not gain weight 12-weeks after enrollment or lose weight); participants will be re-consented for hydroxyurea therapy and Plumpy Nut (ready-to-use-therapeutic food). These participants will be followed for an additional 12 weeks and re-evaluated. If a participant is enrolled in treatment failure, then at week 24, their fetal hemoglobin will be evaluated.

- Nutrition and Vocational Training: Unlike severe malnutrition treatment in acute caloric deprivation or increased energy expenditure, children with sickle cell anemia in Kano, Nigeria, will continue to experience insults to their nutritional status from a biological and socioeconomic standpoint after trial cessation. Therefore, in addition to malnutrition treatment within the trial, we propose a multifaceted program[42] focused

on empowerment through nutrition education with demonstration of readily available local foods and vocational education. These programs will aim to increase the agency of the primary caregiver to improve the nutritional status of the participant.

Nutrition programming. The trial already contains nutritional education for the caregivers. However, to increase the sustainability of the weight gain of short-term nutrition intervention (Plumpy'Nut), it is apparent that a more intensive nutrition education tailored to the economic environment of the households. The participant's mother and a designated partner will receive education about using local foods and vocatio. The designated partner is an individual who has a primary role in the participant's nutrition, either purchasing, preparation, or allocation of the foodstuffs. The mother and designated partner will attend the nutrition workshops held biweekly for a total of 3 workshops over 6 weeks. The workshops will contain the following education:

- Education regarding the specific nutritional needs of a child with sickle cell anemia
- Individual economic education regarding the cost of purchasing foods that could fill nutrient gaps[43,44] (affordable nutrient-dense foods)
- Provision of one week of nutrient-dense food for the family to increase visibility and demonstrate the feasibility of economic nutritious food choices
- Interactive cooking preparation and demonstration with subsequent serving size demonstration appropriate for the participant
    - The low bioavailability of some essential micronutrients can be substantially enhanced with appropriate processing and food combinations.[45]

Additionally, there will be a one month check-in to assess anthropometric changes after the nutritional and vocational education.

Vocational education. We will also incorporate vocational education and general life skills coaching. Technical skills training and support will also be provided biweekly for a total of 3 workshops over 6 weeks. The training will increase the caregiver's occupational or entrepreneurial skills to increase the caregiver's agency. Ultimately, the goal is to increase employment and earnings. The programming will integrate both hard skills and life skills training, as the combination is thought to be more effective.[46] General life skills support will be discussed at every clinic study visit even after the formal vocation programming finishes.

Stipend. Due to the increased demand for study participants and their caregivers and designated partners, we propose increasing the stipend for each visit. Additionally, the designated partner will receive a stipend at each nutrition workshop.

Follow-up. We will record the weight and height measurements of study participants who have exited the trial through standard of care measurements at follow-up visits in their respective sickle cell clinics.

- **Treatment Failure: Indication for PlumpyNut and Hydroxyurea Therapy (SCD participants only):** enrolled participant that has fulfilled all the inclusion criteria but still has a BMI Z score of less than -3 or is losing weight after 12 weeks of Plumpy'nut would still be eligible for the 4-5 sachets of RUTF (Plumpy'nut). The main difference is that this would translate to "standard RUTF," where the RUTF is provided in sufficient quantity to meet all of the nutritional requirements of a child recovering from severe acute malnutrition. However, our intervention is investigating the use of RUTF provided to children with SAM as a supplement to the usual family diet.

    - **PlumpyNut sachets / day:** In view of the fact that no standard protocol for the use of Plumpy nuts in children > 5years exists, we intend to dispense 4 to 5 sachets of plumpy nuts / participant / day
        - **Our justification for the prescription includes:** We shall adopt the UNICEF/WHO guidelines (outpatient management of SAM) of achieving at least 150 to 200 kcal/kg/day for children weighing more than 12 kg. This is the maximum limit obtainable according to the UNICEF reference table (for outpatient management of SAM) as shown in the table below. This can be achieved by ingesting 4 to 5 sachets / day.[47]
        - Most studies conducted on HIV adult patients with SAM on nutritional rehabilitation used 4 sachets of plumpy nuts/patient/day. Notable examples are in Ethiopia (2014) 3 Kenya (2011).[48]
    - **Monitoring/Follow up visits**: This will entail a total of 12-weeks follow-up visits with the first visit within 1 week of initiation of Plumpy'nut (optimally within 3-5 days) then subsequently 3 monthly visits. During each visit, a clinical history and examination will be taken. Edema check, MUAC, weight, height, temperature, respiratory rate, pulse oximetry, and blood pressure will be assessed and documented. Parents/legal guardians of all participants enrolled will be provided with infrared thermometers with different color coding, easy to use even for parents with low literacy level. The caregiver will be educated on temperature control and signs of dehydration. In addition, the caregivers will be given a thermometer with strict guidelines on how to assess the temperature at home. These are as discussed in the MOP under monitoring of patients on Plumpy'nut.
    - **Hydroxyurea Therapy**: We will constitute hydroxyurea to children with SCD only, routine folic acid and palludrine. Enrolled participants will receive amoxicillin and albendazole only once at the study initiation prior to commencement of Plumpy'nut.
    - **Weekly Phone calls**: Will be done weekly in between the bi-weekly clinic visits. Care givers will be asked about adherence and the number of consumed sachets. A 24-hour dietary recall will be done. They will be asked to bring the empty sachets when coming for their follow-up visits.

TABLE: REFERENCE TABLE FOR PRESCRIPTION OF RUTF(based on 92g packets)[1]

Weight in (kg)	Sachets/day(200 kcal/kg/day)	75% of prescribed amount (150 kcal/kg/day)
3.5 – 3.9	1 1/2	1 1/4
4.0 -4.9	2	1 1/2

5.0 – 6.9	2 1/2	2 1/4
7.0 -8.4	3	2 1/2
8.5-9.4	3 1/2	2 3/4
9.5 -10.4	4	3 1/4
10.5-11.9	4 1/2	3 1/2
≥12	5	4

- **Steps to limit and monitor adverse events (AE) or serious adverse events (SAE):** Monitoring for unanticipated adverse effect will be performed by querying participants at each follow-up visits about the occurrence of complications since the participant's last follow-up contact. Data will be collected by local research staff on AEs, and on any abnormal findings (history, physical exam, laboratory, or imaging) of a participant in the study. AEs will be recorded at study visits every week using a structured form for detecting signs of complicated severe acute malnutrition and classified based on seriousness, expectedness, and relatedness by physicians not otherwise involved in this study. Unexpected AEs are adverse reactions that are not consistent (nature or severity) with the available information on outpatient treatment of malnourished children with or without SCD with Plumpy'nut. A pharmacovigilance structure will also be instituted at participating sites to monitor and identify adverse effects.

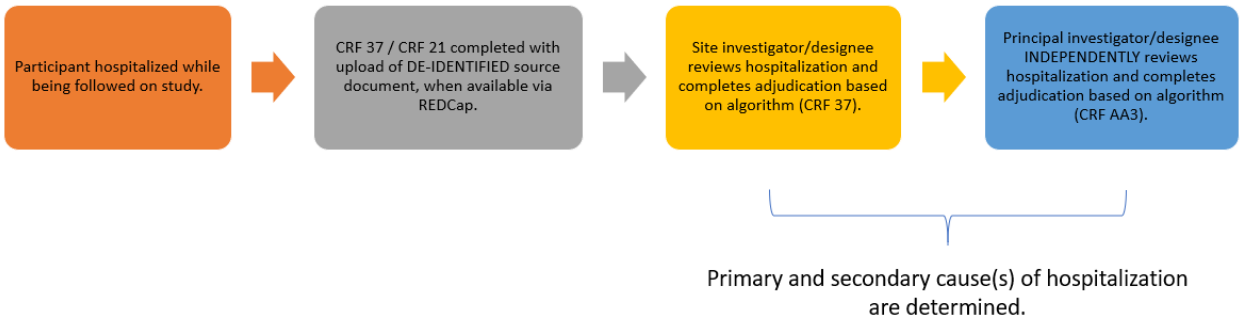
A serious adverse event (SAE) is an event that:

a. Results in near death or death;
b. Life-threatening (participant at risk of death at the time of the event);
c. Requires or prolongs hospitalization more than 7 days;
d. Causes persistent or significant disability;
e. Results in a congenital anomaly;
f. Other medical events (in the opinion of the investigator) that may put the participant at risk or require intervention to prevent a SAE.

SAEs will be scored using the Common Toxicity Criteria for Adverse Events (CTCAE) 3.0 of the National Cancer Institute and the standard nomenclature for defining the causal relation between the AE and study drug (unrelated, probably not related/remote, possibly related, probably related, and definitely related). All SAE including death require prompt reporting by email communication or telephone to the Principal Investigator as well as BMS Worldwide Safety worldwide.safety@bsm.com) within 24 hours of becoming aware of the event, and to the IRB of record within the required timeframe. If pneumonia/acute chest syndrome, refeeding syndrome or sepsis is suspected, research personnel should activate the standard care protocol at site without the consent of the Coordinating Center and Statistical Coordinating Center. All SAEs should be followed until resolution or stabilization. All SAE reports of death in the first 6 months of the study will be reported to the DSMB within two weeks of occurrence. The SAE report will include a description of

the event provided by the site, indication of tests, and details of hospitalization, as available. All SAEs should be followed until resolution or stabilization.

Adjudication Process by Site Investigator and Principal Investigator



Adjudication Process for Primary Cause of Hospitalization:

- **IF** the patient presents with neurological deficits confirmed to be a stroke or transient ischemic attack and acute chest syndrome, pain, fever, or other symptoms; **THEN** the primary cause of the hospitalization is **STROKE/TRANSIENT ISCHEMIC ATTACK**.

- **IF** the patient presents with acute chest syndrome, pain, fever, other symptoms, and no indication of neurological deficits for stroke or transient ischemic attack; **THEN** the primary cause of the hospitalization is **ACUTE CHEST SYNDROME**.

- **IF** the patient presents with pain, fever, other symptoms, and no acute chest syndrome or indication of neurological deficits for stroke or transient ischemic attack; **THEN** the primary cause of the hospitalization is **PAIN**.

- **IF** the patient presents with fever and other symptoms, and no pain, acute chest syndrome, or indication of neurological deficits for stroke or transient ischemic attack; **THEN** the primary cause of the hospitalization is **FEVER**.

- **IF** the patient presents with fever and other symptoms, and no pain, acute chest syndrome, or indication of neurological deficits for stroke or transient ischemic attack; **THEN** the primary cause of the hospitalization is **FEVER**.

- IF the patient presents with other symptoms, and no fever, pain, acute chest syndrome, or indication of neurological deficits for stroke or transient ischemic attack; **THEN** the primary cause of the hospitalization is **OTHER**. The primary reason should be provided after adjudication along with all applicable secondary reasons for hospitalization.

When the primary cause of hospitalization adjudicated by site investigator/designee and principal investigator is CONCORDANT, no further action is needed. The final adjudication is the primary cause agreed upon by both parties.

When the primary cause of hospitalization adjudicated by site investigator/designee and principal investigator is DISCORDANT, a joint review occurred to discuss the file collaboratively to determine the final primary cause based on the algorithm.

The secondary cause(s) of hospitalization will be reviewed; however, the final adjudication is at the discretion of the site investigator/designee completing the adjudication. For the duration of the study, participant hospitalizations are documented with CRF 39: Interim Hospitalization and CRF 21: Adverse Event, as applicable. When available, a de-identified source document will be uploaded for review. The adjudication of all parties are documented via REDCap in CRF AA3: Principal Investigator Adjudication of SPRING Hospitalizations.

Definitions:

1) **Pain:** a SCA-associated pain episode requiring admission to the hospital and treatment with opioids. Emergency department visits were not included in this definition due to the variation in outpatient pain management practices and to capture only acute severe pain events.[49] Headaches treated with opioids were also not included in this
   definition due to the difference in proposed pathophysiology of headaches as opposed to
   acute vaso-occlusive pain.[50]
2) **Fever:** Temperature greater than or equal to 110.4°F or 38°C.
3) **Acute chest syndrome (ACS):** presence of at least 2 of the following criteria, including positive chest signs: temperature greater than 38°C, increased respiratory rate of greater than the 90th percentile for age[51] or >20 breaths per minute, positive chest pain or pulmonary auscultatory findings, increased oxygen requirement (SpO2drop >3% from a documented steady-state value on room air), and a new radio-density on chestroentgenogram.[52] In the absence of abdominal shielding, a chest X-ray will be done as available. A diagnosis of pneumonia will be considered an ACS episode. All cases of acute vaso-occlusive pain and ACS episodes will be adjudicated with the site pediatrician, hematologists and principal investigator on the research team to ensure a uniform definition.[53]
4) **Malaria:** Based on World Health Organization and local study site guidelines, a fever (greater than or equal to 110.4°F or 38°C) and positive light microscopy, rapid diagnostic test that can detect *P. falciparum* completed (depending on test availability).

The adjudication will be completed using the algorithm and entered in REDCap for all participants with hospitalizations with the above indices. The adjudication process will

include the study principal investigator(s), site pediatrician, hematologist, data coordinator and any study personnel, as needed.

SAMPLE SIZE AND STATISTICAL ANALYSIS PLAN

Sample Size and Power for Aim 1:

We will use the data from the R21 feasibility study to better define recruitment efficiency, retention rate, and adherence rates to protocol. We will also assess weight gain in the two arms of the trial. Sample size calculations were not performed because our immediate goal of this study is to assess the feasibility an RCT of this nature in northern Nigeria. Due to budget constraints, we will recruit a total of 150 children with severe malnutrition and up to 100 siblings without SCD with severe malnutrition that are identified during enrollment of participants with SCD.

Data analysis plan, data integrity, management and dissemination:

To assess feasibility of a RCT, the primary outcome for aim 1 will be: proportion of eligible individuals that agree to be included, referred to as recruitment rate, the retention rate for the trial and the adherence rates to both the protocol and to therapy (Plumpy'nut and hydroxyurea). The demographic characteristics of all children will be summarized as mean and standard deviations for continuous variables; for categorical variables, counts and percentages will be used. Prevalence will be summarized by proportions. Anthropometric indices (BMI-for-age (BMIZ), weight-for-age (WAZ) and height-for-age (HAZ) Z-scores) will be calculated using WHO 2007 R Macro Package to assess growth and development of the children.[54]

Weight gain will be determined by calculating the change from baseline and compared to children with uncomplicated severe malnutrition without SCD. Comparisons will be made using the Student's t-test for continuous parameters and a chi-square test, or Fisher's exact test, for categorical parameters. Adherence rate will be assessed by proportion of the number of empty food sachets returned during the monthly visits. If adherence rate is <90% and the dropout rate is >20%, then the original protocol will be re-examined and alternative strategies to enhance retention and adherence will be considered. To study what characteristics are associated with weight gain for all participants (children with and without SCD), we will use two regression models. The models will include the following covariates, age, gender, average weekly caloric intake, and hemoglobin levels. First, we will use a linear regression model to study the change in weight from baseline (dependent covariate); second, we will use a logistic regression model to study whether weight increased by at least 15%, or not, from baseline (dependent covariate). Additional models will investigate the characteristics that affect the morbidity (hospitalization for pain or any other reason) and mortality rates, controlling for change in weight and caloric intake. The relative-risk ratios for the outcomes will also be computed, and Kaplan–Meier plots of time to recovery of at least 15%. Significance will be set at $P<0.05$ for all analyses. We will determine the number of individuals that complete the study protocol, referred to as the retention rate. The primary outcome for aim 2 will be our ability to identify serious adverse events (SAE), defined as death, ICU admission, or life-threatening infection in a timely manner and monitor such events. We will assess the percentage of children with SAEs during the study period (expressed as a point estimate ± 95% CIs), and also the rate of events (events/person year). Secondary outcomes will be the percentage ± 95% CIs for all adverse events during study period in the SCD group and that of their non-SCD

siblings. Non-parametric statistics (such as the Mann-Whitney test) will be used to compare the number of hospitalizations between the two groups; Kaplan-Meier analysis or Cox regression will be used to compare the time to an adverse event. If we observe 2 or more SAEs in either arm, the trial will be suspended and reviewed with the Data Safety Monitoring Board as to whether the trial should be halted. Two SAEs suggest that a 1-sided 95% Wilson CI (unadjusted for multiple looks at the data) for the proportion of SAEs exceeds 1%. If the true rate of adverse events is 1%, the probability of suspending the trial is <2%. If the true SAE rate is 10%, the probability of suspending the trial is >60%. We will determine the incidence rate for all cause hospitalizations for participants with SCD and severe malnutrition compared to children with SCD and no malnutrition. Reasons for hospitalizations during the study period for all participants will be recorded.

Missing data: Inspection of the missing data patterns will be performed with an R package, SensMice, to perform a sensitivity analysis to evaluate the possible mechanism of data missing (missing at random vs. missing not-at-random).[55,56] As we have in our previous work, to minimize missing data, we will institute online training for the data coordinator prior to the start of the study; and assess weekly missing data in REDCap with weekly feedback to site coordinators regarding missing data.

5. STUDY COORDINATION

- **Study Withdrawal**

Participants may decide to discontinue participation at any time during the study. If a patient voluntarily requests withdrawal from the trial, we request that the site investigator elicit the reasoning for the withdrawal, and provide documentation in the clinic record and complete the respective case report form. The site must invest time in trying to meet the needs of the patient and their caregivers in order to make the patient's participation a success. The patient's caregiver should provide the withdrawal in writing for the clinic record. All voluntary withdrawals must be communicated to the Clinical Coordinating Center located at Vanderbilt University Medical Center by completion of the case report form in REDCap, and should be recorded in the participant's study binder onsite.

- **Data Collection and Management**

Research information, including consent forms and questionnaires will be collected once the participant agrees to participant and has completed the consent for the study. The study coordinator will collect data and maintain all consents, study assessments, and study data forms in a secure fashion in research charts located in a locked file room or locked file cabinet. Only the study personnel will have access to the research charts and database, to identify any information on participants that are in the consented for the study.

Each participant will be identified with a unique identifying number in REDCap. Through chart review of standard care procedures, the clinical information will include, but will not be limited to baseline measurements of CBC and hemoglobin analysis.

The data gathered will be entered into the REDCap data system,[57] with each ID having a unique identifier for each participant. REDCap is a secure, web-based application for building and managing online databases. All data will be de-identified and samples will only have a unique identifier that will link the unique identifier with the patient's name.

REDCap is a free, secure, web-based application designed to support data capture for research studies. The system was developed by a multi-institutional consortium initiated at Vanderbilt University. Data collection is customized for each study or clinical trial by the research team with guidance from Harvard Catalyst EDC Support Staff. REDCap is designed to comply with Health Insurance Portability and Accountability (HIPPA) regulations. REDCap provides user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails, and the ability to set up a calendar to schedule and track critical study events such as blood-draws, participant visits, etc. Also, designated users can assign different levels of access for each member of the research team.

REDCap and REDCap Survey (RS), as hosted by Vanderbilt, are available only to investigators from Vanderbilt University, but can be used by investigators at other institutions as long as they are part of a project/group from Vanderbilt that is utilizing REDCap or RS. REDCap and RS as software applications can be used at other institutions, when installed by and hosted at those institutions, if they are willing to sign a tech transfer agreement and join the REDCap Consortium.

- **Utilization of Study Data**

The results of the research study may be published, but participants' names or identities will not be revealed. Records will remain confidential. In order that confidentiality can be maintained, the principal investigators will keep records in locked cabinets and results of tests will be coded to prevent association with volunteers' names. Participant records will be available to the study staff and to each site's IRB.

The research personnel will have access to the medical records of all consented and screened patients for the duration of 5 years. This includes access to their medical records (i.e. clinic visits, laboratory testing, dietary questionnaires, etc.)

Data Safety Monitoring Board

Members of the Data Safety Monitoring Board (DSMB) will be appointed by the Director of the National Institute of Child Health and Human Development (NICHD) and report to the Director and to the NICHD Project Officer or the PIs. The members are selected to reflect a mix of appropriate clinical expertise in sickle cell disease and knowledge of the design, monitoring, analysis and ethical issues of clinical research to protect the participants' safety during a scientifically rigorous study. The DSMB will monitor study quality, safety of participants, and efficacy.

The DSMB will monitor the study performance by reviewing:

- participant recruitment
- flow of forms
- quality control of the data
- adequacy of medical monitoring
- adverse effect reporting
- adherence to protocol
- appropriateness of protocol changes with regard to scientific integrity

The DSMB will monitor the safety of participants by reviewing:

- risk of harm inherent in participating in the study
- adverse events (type, incidence, and severity)

- effect of protocol changes on risk

The DSMB will monitor the efficacy of the study by reviewing:

- data
- planned and/or unplanned interim analyses
- stopping rules, their implementation, and resulting decisions
- results and conclusions

The CC and DSMB will provide information to this Committee as requested. The DSMB will review study data reports, including primary end point analysis, every six months either in a meeting or on a conference call. The DSMB will also decide on the criteria for trial termination.

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