**Medical University of South Carolina**

**Protocol**

**Dissemination and Implementation of Stroke Prevention Looking at the Care Environment (DISPLACE)**

**Part 1**

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**DISPLACE (**Dissemination and Implementation of Stroke Prevention: Looking At the Care Environment) is a multi-center, national NHLBI-funded grant to evaluate the real world implementation of the STOP protocol in which transcranial Doppler (TCD), a measure of cerebral blood vessel velocity, is used to screen for stroke risk in children ages 2-16 with sickle cell anemia (SCA) ( ). Based on the STOP protocol, children identified as high risk of stroke by TCD are initiated on chronic red cell transfusion therapy (CRCT) for stroke prevention. Children with normal TCD are screened annually from the age of 2 until they are 16 years of age.

**This will be a THREE-part study beginning with Part 1 - a retrospective case record review followed by Part 2 - a multi-level qualitative assessment of barriers and enablers to TCD screening and initiation of chronic red blood cell transfusions and later adding Part 3 - a multi-center implementation clinical trial. Each part of DISPLACE will require separate IRB approval. There are three aims of the grant and each aim is equivalent to the respective parts of the grant (i.e. Part 1 covers 1 aim). Each of the 28 consortium institutions (CIs) will be expected to obtain IRB approval at their institution. The Medical University of South Carolina is the lead institution for this study.**

The protocol explained in this document is only for Part 1 of the DISPLACE study.

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**A. SPECIFIC AIMS\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Aim 1: Using case records from 2010 to 2016; we aim to determine the rate of annual TCD screening and initiation of Chronic Red Blood Cell Transfusion therapy (CRCT) per STOP protocol among all patients associated with consortium institutions.**

* 1. Identify proportion of patients associated with each treatment center within the consortium institution with a diagnosis of sickle cell anemia (SCA).
     + 1. Patients will be identified at each center using ICD-9/ICD-10 codes.
       2. To be included, patients must have been seen (documented in the medical record) a minimum of TWO times in either the inpatient or outpatient setting at the institution between 2010-2016
       3. Patients identified will include patients born from 1996-2014.
     1. Identify proportion of patients in #1 who have undergone a transcranial Doppler annually (12 months +/- 2 months) as indicated by the NHLBI 2014 SCD guidelines.
        1. These patients will also be identified at each center using ICD-9/ICD-10 and TCD procedural codes
        2. We will obtain the number and dates of TCD screens PER patient PER year from 01/01/ 2010-12/31/2016.
        3. Proportion of known at-risk SCD patients initiated on CRCT: The number and characteristics of patients started (or not started) on CRCT after identification of high risk by TCD
        4. Proportion of known patients with SCD who were identified as having a conditional TCD: The number and characteristics of patients identified as having a high conditional TCD whose TCD was repeated within the subsequent 2 months (+/- 1 month).
        5. Proportion of known patients with SCD who had an abnormal TCD and were started on Hydroxyurea.
     2. Lost to Follow Up Rate: The number of patients not being seen currently as a fraction of the total, the age at which patients become lost-to follow up and the overall fraction of patients for whom vital and stroke status are unknown
     3. Demographics: Additional information will be obtained from all charts including current condition of living patients, last documented payer source, last known zipcode of home address, last physician note and cause of death (if deceased) as well as last identified contact information. Other implementation factors such as access to transportation, proximity of caregiver, social support, etc. will also be assessed

**B. BACKGROUND AND SIGNIFICANCE\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

Sickle cell disease (SCD) is a group of inherited blood disorders associated with acute and chronic anemia, intermittent vaso-occlusion and multi-organ dysfunction. Sickle cell anemia (SCA) is a subset of this patient group that includes individuals with HbSS and HbSB0 disease. Stroke is a devastating complication of SCA that places patients at increased risk for mortality and potentially life-changing consequences, including neurocognitive and motor deficits ([1](#_ENREF_1)). The risk of having a first stroke in patients with sickle cell anemia (a high risk form of SCA) by age 20 is estimated at 11%. By age 45, the estimated chance of stroke is 24%. Ischemic strokes are more prevalent among children whereas hemorrhagic strokes are more prevalent among adults with SCA ([2](#_ENREF_2)). Silent stroke, which occurs in the absent of overt stroke symptoms, is an additional consequence of SCA associated with neurocognitive deficits and increased risk for overt stroke. Silent stroke may affect as many as 33% of children with SCA ([1](#_ENREF_1)).

Chronic red cell transfusion (CRCT) is considered the first line of treatment for patients with SCA at high risk for stroke as measured by transcranial Doppler (TCD), a screening tool used to detect high blood velocities associated with stroke risk. Specifically, TCD was determined to be an effective screening tool for identifying children between 2 and 16 years of age with sickle cell anemia who are at risk of stroke. CRCT has been shown to reduce the risk of having a first stroke by 90% in patients with abnormal TCD studies ([3](#_ENREF_3)). CRCT has also demonstrated other important treatment effects for patients, including reducing the progression of silent strokes and blood vessel stenosis (i.e., cerebral vasculopathy), both of which are risk factors for overt stroke ([4](#_ENREF_4)).

While TCD screening and initiation of CRCT has been demonstrated to be a potentially life-saving therapy, not all patients with SCA are currently receiving standard of care treatment. The extent of implementation issues for TCD and CRCT is poorly understood and it is likely that a combination of patient, family, and health care system variables are involved ([5](#_ENREF_5)). In terms of patient-level factors, previous research suggests that age may be an important factor in terms of receiving standard medical care. Research also suggests that important socioeconomic variables, including proximity to comprehensive sickle cell care and urban versus rural status, are important for understanding issues of access to care ([8](#_ENREF_8), [9](#_ENREF_9)). Finally, research suggests that health care-related factors are involved in terms of access to standard medical care and adherence to medical guidelines. For example, previous research suggests that adherence with standard medical guidelines for SCA (e.g., prophylactic penicillin) and mortality rates for patients with SCA vary widely by geographical region, with some research suggesting health disparities even at the level of state counties ([10](#_ENREF_10)).

No prior studies have specifically examined the extent of implementation issues for TCD or CRCT, specifically, nor have studies determined the specific barriers faced by patients and their families in terms of implementing this screening and treatment protocol. The current proposal was designed to describe the current status of TCD and CRCT care for patients at high risk for stroke and to identify remediable factors that are involved in poor adherence. The long-term objective of the study is to design implementation strategies that ensure all patients with SCA identified as high risk for stroke have access to potentially life-saving care.

**C. PRELIMINARY STUDIES\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

We gathered preliminary retrospective data on patients with sickle cell disease who had been started on transfusion therapy at MUSC for a primary neurologic indication (either previous abnormal TCD, overt stroke, or multiple silent strokes).  The data set included 144 patients with SCD with a mean age of 23.4 years and over 96% with HbSS subtype. Of those, only 47.2% currently remain on transfusion therapy.  A total of 22.2% are not treated with chronic transfusion therapy (but have continued their care at MUSC) and the remaining 30.6% have been completely lost to follow-up but are not likely receiving any current treatment. Patients who are currently on chronic transfusion therapy are statistically significantly younger than patients receiving transfusions. Also of significance, 91% of patients currently on transfusion therapy have a specialty (sickle cell) provider (p<0.0001) while those not on therapy have not been followed by a specialist.  Additionally, 75% of those on transfusion therapy are on Medicaid compared to patients not on transfusion therapy (p=0.027; table 1). No statistically significant difference was observed between the groups in regards to geographical area. These preliminary data demonstrate that while we know transfusion therapy is effective for both primary and secondary stroke prevention, it is not being continued in the older patient population who do not continue to follow up with SCD specialists further confirming the need to better understand the barriers to these practices and identify methods for enhanced dissemination and implementation.

**D. RESEARCH DESIGN AND METHODS**

This proposal will assess the current status of care and implementation of TCD screening and CRCT initiation. This part of the study will utilize a retrospective chart review to assess 1) identification of patients who have been seen at each institution from 01/01/2010-12/31/2016 that require a TCD, 2) determining current patient status (if they have had an annual TCD when due, the result of the TCDs, the action taken for abnormal TCDs), if the patient is lost to the designated system of care, if the patient is not eligible for a TCD for some reason 3) medical chart review. As the entirety of Part I of this study is retrospective, it will not require a consent as a waiver will be requested for this portion of the study).

***Identification of Patients***

* + - 1. Patients with sickle cell anemia (SCA) will be identified at each institution through ICD-9/ICD-10 codes and local patient databases
      2. To be included, patients must have been seen by the designated institution (documented in the medical record) a minimum of TWO times in either the inpatient or outpatient setting at the institution between the years of 01/01/2010-12/31/2016. Patients only seen x1 in the record will be excluded as they may have been visiting or have moved.
      3. Patients identified will include patients born from 1996-2014.
      4. Patients will have their disease phenotype confirmed by history of HPLC, Hemoglobin electrophoresis, IEF or other confirmatory diagnostic procedure already available in the medical record.
      5. “High risk for stroke” and “High conditional” will be defined as a patient with a history of abnormal TCD studies based on STOP protocol
      6. In addition to the administrative data assessment and medical chart review, we will ask each site to assess TCD compliance using only ICD-9/10 codes TCD procedure codes. This type of evaluation will use an administrative data (“big data”) approach to obtaining this quality assessment information in order to compare the rates of TCD/patient/year obtained using each method of evaluation.

***Determining Current Patient Status***

1. Each patient who requires a TCD will be between the ages of 2 and 15.99 at the time of review, have documented sickle cell anemia (confirmed by hemoglobin electrophoresis, IEF, genotype or HPLC in the medical record) and will be evaluated to determine whether or not they are current patients at their local treatment center who are lost to follow-up. This stage will also involve determination of whether patients are alive or deceased.
2. "Lost to follow-up” will be defined as more than 24 months without care at local treatment center or by those designated providers
3. Patients in the 2-15.99 age range during the target time period should undergo an annual TCD per screening guidelines. For this study, we will allow the time period to equal 12+/-1 months per screening. Thus, patients who are 2-15.99 from 2010-2016 should have had 7 TCD scans during the time period. However, 6 scans per patient will be considered 100% compliant per patient for this study assessment.

***Data Collection***

1. We estimate that the chart review will include 5300 records; 300 MUSC and 5000 within the consortium institution
2. TCD results from each TCD done and the date of the study
3. Transfusion: If the patient has been started on CRCT (chronic red cell transfusion therapy), the date of the initiation of CRCT will be noted. If the patient has stopped CRCT, the date they withdrew from CRCT will be collect. The type of CRCT (simple, automated or manual exchange will also be noted)
4. Vital signs recorded from the outpatient or inpatient visit closest to the TCD will be collected (annually) to include: heart rate, blood pressure, oxygen saturation. We will also record patients’ height and weight.
5. Concomitant medication (conmeds): For the purpose of streamlining data entry, we will only ask for the entry of specific conmeds. For each year of evaluation, we will request to know if the patient is on Hydroxyurea (and what dose), aspirin or other platelet inhibitor, other anticoagulant. We will also ask that any iron chelation medication be recorded.
6. Additional laboratory assessments: We require each patient to have a CBC and reticulocyte count and ferritin entered in the case report form (from the labs drawn nearest the time of TCD assessment in the medical record)
7. Neuro-Radiologic studies: If patients have undergone a head CT, MRI brain, MRA brain, or MRV brain (or other neuro-imaging) between 01/01/2010-12/31/2016, we require the date and result of the exam.
8. If the patient has had a stroke, we will ask for the date and location of the stroke to be recorded.
9. Other: If patients have undergone an echocardiogram from 01/01/2010-12/31/2016, we request the date of that echocardiogram be recorded.
10. Demographics: We will ask for the date of birth, the zip-code of the patient and insurance type.
11. Each patient will be assigned an ID upon entry into the WebDCUTM. The local site will keep a code-linked record to the patient’s name for follow-up. In addition to the patient’s name, we recommend each site’s documentation contain the patient’s caregiver information, telephone number and email address if available so that the data is already stored for Parts 2 and 3 in which that contact information will be needed. Only the site will have the name and contact information for each patient.

Patients Lost to Follow-up

1. For patients lost to follow-up, all last known data will be entered.
2. As per above, the site will also collect from the patient’s medical records to aid in contacting the patient, including the following: last known telephone number and address for the patient and his/her caregivers and last known payers (insurance type and group numbers).

This protocol includes the collection of some elements of private health information (PHI). The dates of birth and dates of services are necessary to make assessments of patient age at time of procedures. The patient’s last known zip code is needed to assess distance as a factor in implementation of care. Sites have been instructed to assess if a data-use agreement (DUA) is required by their IRB to transfer this information.

**E. Statistical Analysis**

Statistical analysis will be completed by Martina Mueller, Ph.D. (biostatistician at MUSC) in collaboration with the MUSC Data Coordination Unit (DCU). Analyses will be conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Demographic variables, clinical characteristics, and rates of TCD screening will be evaluated. Comparisons between those who have had TCD screenings done appropriately and those who have not will be explored using pooled t-test and Chi-square tests or Fisher’s Exact tests. Chi-square tests and logistic regression will be used to explore potential predictors of TCD screening, TCD assessment, CRCT initiation, outcomes and mortality.

**F. Data Management**

The Data Coordination Unit (DCU), established in May 2004, housed within the Department of Public Health Sciences (DPHS) at the Medical University of South Carolina, will oversee the data management for DISPLACE. The DCU specializes in the design, implementation, management, analysis and reporting of multicenter clinical trials. The Unit has coordinated over 60 multicenter clinical trials, most of which are NIH-funded. Cumulatively, these trials have involved over 1200 healthcare institutions in North America as well as international institutions throughout South America, Europe, Australia and Asia. All trial management activities are conducted using the DCU’s internally developed Clinical Trials Management System (CTMS) referred to as the WebDCU™ system. WebDCU™ offers a full collection of web-enabled modules for central randomization, protocol and site management, study monitoring, safety reporting, data entry and validation, and report generation. The system provides a secure, web-based collaborative environment for all study partners and provides all the required tools for site coordination and data management in one integrated, efficient and user-friendly system. Secure data entry occurs at the clinical sites via an online user-friendly data-entry interface. The DCU will provide training and technical support to all CI users of WebDCU™ including study team members and coordinators. Trainings will be conducted at in-person meetings, via webinar, via video and will be tailored to the user.

The WebDCUTM data safety is protected by the industry standard multiple-tier system architecture design which ensures data integrity by: (1) the logic tier between the user interface and the database; (2) central relational database structure that eliminates data redundancy and discrepancy within the database; (3) full audit trails for every data edit; (4) daily differential backup; (5) weekly full backup; and (6) server operation environment safety protection provided by the MUSC Data Center which is a Tier/Level 3 facility covering virus, power supply, and natural disaster plan. All data will entered by coordinators at each CI including radiologic results (i.e., TCD, MRI). The scans will not be over read as this is an evaluation of real-world assessments. Results will be collected directly from the institutional coordinators (not re-evaluated or verified by a central radiologist). Sites with delay in data entry or other issues will undergo corrective action.

**G. PROTECTION OF HUMAN SUBJECTS\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**1.**  **RISKS TO THE SUBJECTS**

***a. Human Subjects Involvement and Characteristics***

**Medical Record Review:**

All patients with SCA between the age of 2 and 16 (during the years of assessment, 01/01/2010-12/31/2016) that require(d) TCD screening will be included in the medical record review along with those patients identified as having abnormal TCD who should start CRCT. These records will be captured at all consortium institutions by local data coordinators and entered into the Web DCU (database) for evaluation. All chart review will be conducted at each institution and waiver of consent is requested for this retrospective review. Patient names will not be included in the data capture system. All patients will be given confidential IDs for data entry purposes.

**Characteristics of Participants**

The patient population is estimated to be close to 100% African American, though patients of any race or ethnicity are eligible to participate. It is anticipated that the majority of patients will currently be under the age of 24 based on study determinants (they will have been ages 2-16 during the years 01/01/2010-12/312016). The population is estimated to be heterogeneous in terms of education and socioeconomic status; however, it is likely that over 50% of patients will fall below the federal poverty level. A small subset of patients is anticipated to fall in the cognitively impaired range as the result of severe neurocognitive deficits or intellectual disability. For the majority of participants, the guardian/care giver of the participants (children) will be responding to the survey questions for the patients. Additional interview and survey questions will specifically be targeting guardians and caregivers as well as physicians and clinical personnel to best understand the barriers to care. These respondents will all be of all nationality and ethnicity and no identifiable information will be collected.

**Data Linkage and Storage**

All of the local data collected are specific to the present project. All data will be marked with an anonymous identifier created automatically for each patient. Only the local PIs and research coordinators will have access to patient names. Data will be stored in a locked filing cabinet located in the PIs office. Data detailed above will be entered into the WebDCUTM as per above. Any documents containing patient names or institutional medical record numbers (e.g., consent forms) and a master list of participant IDs will be stored in a separate, locked cabinet from the data collected. Audio recordings will be stripped of patient identifiers and stored on password-protected MUSC network storage for at least 6 years.

**2. Potential Risks**

**Confidentiality**

The retrospective data collections are estimated to have minimal risks to patients. One potential risk to patients is loss of confidentiality of the information provided. We will implement several procedures to ensure that this risk is minimized, including the use of an anonymous identifier on all patient files, keeping any forms with patient identities (e.g., consent forms) in a separate location from the files, and ensuring that all documents are stored in a secure location. Thus, we anticipate that the actual risk due to loss of confidentiality is quite small.

**Coercion**

There is no possibility of coercion in part 1 of this study as it is all retrospective data collection..

Financial Coercion

Alternatives

To our knowledge, there are no other studies assessing the status of and barriers to care for TCD and initiation of CRCT in patients with SCD. However, patients do not have an option to be included as this is a retrospective study. As a study team, we have an obligation to report results of this study to patients.

**3. Adequacy of protection against risks**

***a. Recruitment and Informed Consent***

**Recruitment**

Chart Review

No patient recruitment is required for chart review. Patients with sickle cell disease between the age of 2 and 16 and the sickle cell anemia genotypes that require TCD screening will be included in the medical record review. These records will be captured at all consortium institutions by local data coordinators, entered into the WebDCUTM (database) for evaluation and will also include those patients identified as having abnormal TCD who should start CRCT. All chart review will be conducted at each institution and waiver of consent is requested for this retrospective review. Patient names will not be included in the data capture system. All patients will be given confidential IDs for data entry purposes.

Patients Lost to Follow-up

For patients who have been lost to follow-up (more than 24 months without care at target center), information will be collected from the patient’s medical records to aid in contacting the patient, including the following: last known telephone number and address for the patient and his/her caregivers and last known payers (insurance type and group numbers). Using the patient’s name and insurance information, we will look up the patient’s last known contact information and record this only at local institutions for part 2 of the study.

***b. Protection against Risk***

Reducing Confidentiality Risk

We will implement several procedures to ensure that risk of loss of confidentiality is minimized, including the use of an anonymous identifier on all patient files, keeping any forms with patient identities (e.g., consent forms) in a separate location from the files, and ensuring that all documents are stored in a secure location at only the local site.

**4. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS**

The proposed research is anticipated to have potential direct benefits to the participants, particularly including those lost to follow-up. Specifically, patients who have been lost to follow-up will (in part 2) have the option of receiving information on local, specialty providers, regardless of their participation in the study. These patients may experience direct benefits from being contacted, including re-initiating potentially life-saving care. Additional potential benefits include enhanced education for involved providers and their patients.

**5. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED**

The information obtained from the study is anticipated to be broadly beneficial for the overall population of patients with SCD by informing improved implementation practices for care and prevention. In particular, the use of questionnaires and qualitative interviews with patients is anticipated to allow patients to express their opinions of TCD and CRCT as well as barriers to TCD and CRCT, which is information that would otherwise be difficult to obtain. The potential to improve access to TCD/CRCT for all patients at high stroke risk is a significant benefit to patients with SCD in consideration of the minimal risks involved.

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