**University of Alabama at Birmingham**

**Protocol**

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

**Part 3**

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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. This protocol was incorporated into the NHLBI sickle cell disease evidence-based guidelines. The guidelines state that children should be screened annually from the age of 2 until they are 16 years of age. The DISPLACE consortium originally included 28 Consortium institutions (CI) around the United States. Only sixteen of the original 28 CI sites, those with the lowest TCD screening rates who were also adherent to data management in part 1 will be participating in this portion of the protocol.

**DISPLACE Study Design**

DISPLACE Part 1 was a rigorous retrospective case medical record review study in which 5247 children with SCA at risk of stroke were enrolled into the custom-designed electronic database, WEBDCUTM. WEBDCUTM was created by The Data Coordination Unit (DCU) at the Medical University of South Carolina. WEBDCUTM is a comprehensive clinical trial management system that was established in 2005. The database is able to provide regulatory document tracking, central adjudication, query generation and electronic CRF data capture. Part 1 identified TCD screening rates at the 28 participating CI to determine which CI would be included in DISPLACE Part 3 (Part 3), the implementation study. The 16 CI with the lowest screening rates who also demonstrated excellent adherence to data management in part 1 were identified for participation in Part 3.

DISPLACE Part 2 included a multi-level qualitative assessment of barriers and enablers to TCD screening and initiation of CRCT. Part 2 was conducted by surveys and interviews with patients/families, stakeholders and providers at each of the 28 sites. Findings from Part 2 were used to design interventions for Part 3.

**DISPLACE Part 3** is multi-center implementation clinical trial designed to test novel implementation strategies with the goal of improving adherence and implementation of stroke screening (based on the NHLBI guidelines) among the CI sites with the lowest TCD (stroke screen) implementation rates.

Each part of DISPLACE has required separate IRB approval at each participating institution. Each of the three DISPLACE aims is equivalent to the respective parts of the grant (i.e. Part 1 covers Aim 1). Each participating CI will be expected to obtain IRB approval at their institution. The University of Alabama at Birmingham is the lead institution for this study.

**This protocol describes the conduct of Part 3.**

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**A. SPECIFIC AIM\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Aim 3**: Evaluate the effectiveness of a novel multi-level dissemination and implementation (D&I) strategy to increase current annual TCD screening rates and CRCT initiation rates at selectedconsortia institutions.

1. Dissemination of stakeholder informed educational material (Year 3): All consortia institutions will receive stakeholder informed, customized education about TCD (Sickle Stroke Screen) for SCD stroke prevention along with patient education materials. This will include construction of a project website and activation of social media platforms in collaboration with patient-focused groups. To enhance dissemination, local community-based organizations and patient groups will be educated to improve knowledge and purpose of stroke prevention.
2. Implementation Trial (Years 3-5): The 16 centers with the lowest TCD screening rates from Part 1 will be enrolled in a controlled, parallel, cluster-randomized trial to compare the effectiveness of two different strategies to enhance implementation of TCD screening, re-screening and CRCT initiation. Comparisons of the interventions will be assessed both within and between institutions over time to identify the most effective method(s).

**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 SCA (a high-risk form of SCD) 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 absence 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 counties ([10](#_ENREF_10)).

Parts 1 and 2 of DISPLACE gathered specific data and information regarding the current real-world implementation of TCD screening as well as highlighted barriers to appropriate/optimal TCD screening at each participating CI.

**C. PRELIMINARY DATA (from Parts 1 and 2)**

The first two parts of DISPLACE included 28 centers across the United States. In total, 5247 individuals with SCA are included in the database. TCD screening rates varied widely among institutions ranging from 30-75.2% (mean 48.4%, median 47%). Of the total in the database, only 3718 patients had a TCD during the study period (71.7%). Of those patients who had a TCD, 138 (3.7%) had an ABNORMAL TCD per STOP guidelines which is notably lower than the STOP study with a rate of abnormal TCD of 9.7% at study entry. Characteristics of patients with abnormal TCD (vs. those without) are forthcoming. These data revealed that TCD screening was clearly lower than ideal at all sites. There were 16 sites identified who submitted sufficient data for analysis and were identified as the lowest performing sites. These sites were chosen and are willing to participate in Part 3.

In addition to the data regarding screening rates, Part 2 revealed very specific barriers and facilitators to TCD screening. The most notable barrier identified was the lack of understanding of the utility and importance of TCD by patients/parents as well as by several stakeholders. Many individuals did not know what TCD meant or measured and therefore did not understand why it should be undertaken. Importantly, the name “TCD” or “Transcranial Doppler Ultrasound” also did not resonate with affected individuals or families. The other most notable, actionable barriers were the a). difficulties experienced by providers of re-scheduling patients who had missed their initial TCD screen and b). providers having accessible information about which patients had/had not received their screens. If patients presented to clinic as instructed, they were almost always able to get the screens done in a timely manner. In contrast, if patients missed several appointments, they were likely to have fallen off of provider radar or the missed TCD screening was overlooked. The current EMR systems are not set up to remind providers to ensure patients follow-up with necessary testing and screening. The systems will often remind patients/parents of appointments via phone, text or mail, but in most cases, there is no automated reminder for patients or providers that an annual screening is due or has been missed. Further, there is frequently a lack of coordination between the department where the TCD screening is conducted and the sickle cell clinic leading to challenges with rescheduling missed TCD screenings.

Facilitators to TCD screening were also examined in Part 2 of DISPLACE. Sites with a single coordinator for all TCD scheduling/reminders performed much better overall than sites who did not have a coordinator as did sites with patients covered by insurance companies that provided transportation (such as Medicaid). Patient/family education was another key facilitator; repeated and frequent information provided to families in a way that communicated what was to be done and the importance of the TCD screening was perceived to improve adherence to TCD screening appointments.

Patient and Provider Educational Intervention: As noted in Part 2, knowledge and understanding of TCD screening were among the most common barriers to implementation reported by patients/caregivers and stakeholders. Among patients/caregivers, many individuals did understand that TCD was about “risk of having stroke” or that TCD should be scheduled with specific timing. Additionally, many patients and families believed the test imaged the brain itself instead of measuring the blood flow in the blood vessels within the brain. Thus, for this study, we are will “re-brand” TCD as a “Sickle Stroke Screen”. Prior to deciding on this re-branded title, different names and logos for the screen were assessed by patients and families through qualitative assessment and structured questioning. The Sickle Stroke Screen was favored by the majority of patients and families and the logo (Figure 1) to be used for the test was also selected by patients and families.

Figure 1: Sickle Stroke Screen



Additionally, families and stakeholders felt an infographic that gave more information would be helpful along with the logo and the new “name” for the stroke screen. A similar qualitative assessment was performed with patients and families to evaluate different infographic options resulting in selection of the infographic shown in Figure 2.

Figure 2: Infographic



DISPLACE has developed a website (www.uab/sicklecell/displace) that will allow patients and providers to download Sickle Stroke Screen educational information including brochures, infographic material and current guidelines/recommendations regarding TCD screening. The brochures developed with provider and patient input are also attached to this submission. The website will be sustained after the grant as well.

**D. RESEARCH DESIGN AND METHODS**

The multi-center, implementation trial includes 16 sites chosen to participate in this trial based on results from Part 1 of the DISPLACE study. This study will use a cluster-randomized design with sites receiving either a provider-specific intervention or a patient and provider intervention (Figure 3).

Figure 3: Study design

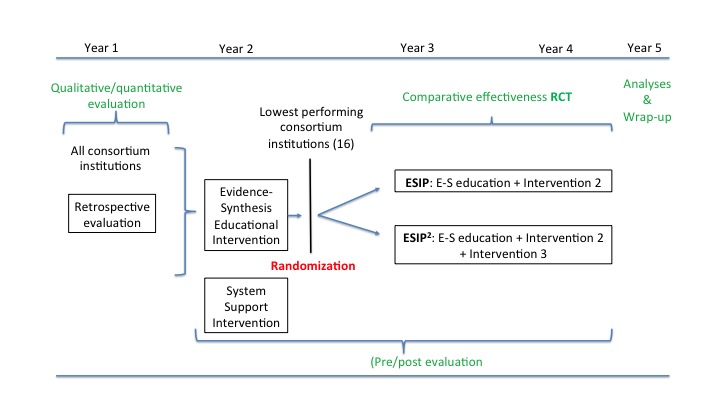


Figure 3: *Timeline for DISPLACE project including the implementation trial. Interventions labeled as ESIP (education and provider intervention) and ESIP2 (education, provider and patient intervention)*

Implementation Strategies and Interventions:

1. Patient and Provider Educational Strategy: To enhance understanding of the use and purpose of a TCD, we are making a national effort to rebrand TCD. This intervention also includes a new, patient-informed educational infographic to enhance TCD understanding. This educational strategy will be delivered to all sites.
   1. **Education Intervention**: Rebrand TCD as “Sickle Stroke Screen” (Figure 1) with a new infographic (Figure 2)
   2. This intervention is being distributed to all 28 sites in the original DISPLACE consortium and will also be disseminated via patient/provider-facing conferences and social media.
   3. This strategy will not be specifically evaluated in the cluster-designed assessment but will be evaluated through qualitative analysis as part of a separate protocol.
2. Provider reminder strategy: To improve provider recall for patients who have been lost-to-follow-up or those who have missed their originally scheduled Sickle Stroke Screen.
   1. **Provider Intervention**: *Provider Minder* is a custom designed web-based application for DISPLACE that includes a repository for test results of patient scans and an appointment booking and reminder system for health care providers. The application is fully HIPPA compliant, utilizes multi-factor authentication, and will only allow for the collection of de-identifiable information.
   2. The CI will be able to see patient-specific information, but the coordinating center will only be able to view de-identified (coded) information to ensure PHI remains private (Appendix 1)
   3. The16 CI sites will receive the *Provider Minder* intervention
3. Patient Communication Strategy: To improve communication between the CI and the patient/caregiver, half (8) of the CI sites will have a single designated coordinator with whom they will communicate about scheduling and rescheduling their Sickle Stroke Screen. Parts 1 and 2 of DISPLACE revealed that sites who utilized a single coordinator had higher stroke screening rates.
   1. **Patient Intervention**: Single Coordinator
   2. Only 50% of sites will be randomized to receive the single coordinator intervention.

c. Patient-Intervention: Hands-on Coordination in two main parts:

1. The first is that these sites have agreed to identify a single “Stroke Screen Coordinator” who will interact directly with patients to schedule, reschedule, remind and follow-up on stroke screening. The coordinator will also act as the main education point of contact for the patients and caregivers.
2. The second part of this intervention includes using the caregiver’s own mobile device. As has been shown in several studies, approximately 97% of patients and families in the US with SCD have a mobile phone. When Sickle Stroke Screens are scheduled, the coordinator will ensure these appointments are put directly into the parents’ mobile device calendar (i.e. not only in the patients’ EMR but on their own device). They will note in the patient’s chart that the appointment was placed into the mobile device for tracking purposes.

**Patient enlistment:**

This study is not using new or untested interventions. Instead, this study is seeking to improve delivery (implementation) of evidence-based care. The patients will not be the subject of the randomization. Instead, these are site level randomizations. All patients at all sites will be included (as was done in Part 1). Fifty percent of the patients are already captured in WEBDCUTM. All patient information is de-identified in WEBDCUTM and only the sites have the code-linked records (that identify which patient ID = which patient). All new patients/data will be entered into WEBDCUTM as was done in Part 1 and will be de-identified upon entry. Each patient will be assigned a Subject ID by WEBDUTM to be used upon entry into the MEDPACK *Provider Minder*.

Provider Minder will allow for each site to link their patients to their ID numbers to facilitate provider reminders; however, this information is only site level and will not be stored in the cloud (i.e. only stored on secure, site servers). Patient’s unique ID will be stored in the HIPPA-protected cloud but this will not connect to the on-site information.

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/caregiver’s information, telephone number and email address. **Only the site will have the name and contact information for each patient/caregiver.**

***Identification of Appropriate Patients (as per Part 1)***

* + - 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 01/01/2018-12/31/2019. Patients documented in the record as only being seen once will be excluded as they may have been visiting or have moved.
      3. Patients identified will include those **currently aged** 2-7. These ages are chosen based on the highest risk group to have an abnormal TCD in Part 1. Thus, children that are included will be born 2012 and onward.
      4. Those children born from 2012-2014 (who were already >/=2 years during DISPLACE Part 1 are already captured in WEBDCUTM and will not require re-entry.
      5. 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.
      6. Patients already receiving primary or secondary stroke prevention therapy with CRCT will be included in registration in WEBDCUTM but not included in *PROVIDER MINDER* as they do not require ongoing TCD/SICKLE STROKE SCREEN based on protocol.

***Data Collection in WEBDCUTM***

1. All patients will be enrolled into WEBDCUTM.
2. We estimate that each site will enroll between 30-300 patients in *Provider Minder* based on data obtained in Part 1.
3. Data entered at registration into WEBDCUTM are unchanged from Part 1. See Appendix A. This will include date of birth (DOB) only to calculate current age (DOB will not be stored in the system as a variable).
4. Additional demographic information includes gender, race/ethnicity, city/state of residence, estimated distance from sickle cell clinic and insurance type.
5. Date of last SICKLE STROKE SCREEN (TCD) will be recorded so that the system can calculate when the next screen is due.

***Data Collection in PROVIDER MINDER***

1. WEBDCUTM will be used to transfer information to Provider Minder. This will allow for the systems to continuously use the same DISPLACE Subject ID number and prevent dual entry of information.
2. The information transferred includes only DISPLACE Subject ID number, age and most recent Sickle Stroke Screen and the result (used to calculate the next Sickle Stroke Screen due).
3. Prospectively, for each new Stroke Screen (TCD), provider will enter:
   1. Did the patient come to the screening appointment?
   2. Was the Sickle Stroke Screen completed?
   3. What was the screen result (normal, conditional or high)?
      1. If normal-the app will automatically ask for the date of the next planned screen in a 10-14 month window.
      2. If conditional, the app will automatically ask for the date of the next planned screen in a 2-6 week window.
      3. If abnormal, the app will ask the provider if they plan to repeat in 2 weeks, start the patient on CRCT, or if they have another plan.
   4. If missed-provider will be asked to enter an identified reason the screen was missed.
   5. If missed-was it rescheduled? The new date will need to be entered.
   6. The app will continue to alert the provider every 3 days until the information is recorded and the test is completed or rescheduled. If a patient has moved or is terminally no longer eligible for participation, the provider will enter that information in Provider Minder.
4. 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 collected. The type of CRCT (simple, automated or manual exchange will also be noted).
5. For Abnormal and Conditional Sickle Stroke Screen, additional questions will be asked. These include:
   1. Current Concomitant Medications (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, and other anticoagulant. We will also ask that any iron chelation medication be recorded.
   2. Most recent laboratory assessments: We will request that recent labs (standard of care) from each patient including CBC, LDH and reticulocyte count and ferritin be entered in WEBDCUTM (from the labs drawn nearest the time of TCD assessment in the medical record).
   3. Other Neuro-Radiologic studies (obtained for standard of care): If patients have undergone a head CT, MRI brain, MRA brain, or MRV brain (or other neuro-imaging) between 01/01/2012-12/31/2016, we require the date and result of the exam.
   4. If the patient has had a stroke, we will ask for the date, type and location of the stroke to be recorded.

This protocol includes the collection of some elements of private health information (PHI). The dates of birth and dates of services (TCD/Sickle Stroke Screen) are necessary to calculate patient age at time of procedures. The birthdate will not be directly transmitted to the data collection site and will only be used to calculate age.

Process Measures:

In addition to the defined measures above, additional short-term and intermediate data will also be obtained.

Year 3: Additional feedback (de-identified) is requested on the educational materials used in the study. Feedback will be obtained using a QR code on the brochure which will link to a REDCap survey and will be completely anonymous. As the brochures are not limited to the DISPLACE sites in the trial, feedback can be obtained from anyone who sees the brochure but will be used to assess generalized information gained, appropriateness of information, readability of information and will also allow individuals to request additional data on the Sickle Stroke Screen (TCD) and on Sickle Cell Disease.

Year 4 and Year 5: Sites will be asked to obtain additional (**separate**) IRB approval for surveys and qualitative assessment of patients and providers as completed in Part 2. These will include both surveys and key informant interviews with patients/caregivers, health care providers and other stakeholders. These will be analyzed using appropriate quantitative methods to identify themes pertaining to organizational readiness, barriers and enablers to obtaining TCD screening, overall perceptions of the intervention(s), barriers and enablers to implementing the intervention(s) and satisfaction with the intervention(s). Themes around barriers and enablers identified in Part 3 will be compared to barriers and enablers identified in Part 2 to better understand how the interventions may have addressed previous barriers.

**E. Statistical Analysis**

Statistical analysis will be completed by the statistical team at the MUSC College of Nursing under the direction of senior biostatistician Martina Mueller, Ph.D. 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 do 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.

We will test an overall effect of the multilevel interventions on change in TCD rates using GLMM. This approach obtains individual regression slopes for level, i.e. baseline assessment, educational intervention Year 2 and randomized phase Years 3+4, modeling change in quarterly TCD rates over time. Intervention (Pre, Years 3-4) and variables to represent time and successive time periods will be included as fixed effects; center will be included as random effect to account for clustering of patients within centers. Autoregressive parameters will be included as appropriate to account for potential correlation among repeated measurements. Model fit will be assessed using log likelihood. Coefficients of primary interest are the parameter estimates for the multilevel interventions and the time period. Similar to TCD screening rates, unadjusted differences in pre/post multilevel intervention changes in CRCT initiation rates will be compared between the 2 intervention groups using two-sample t-test or non-parametric Wilcoxon Rank Sum test. Unadjusted pre/post intervention differences in mean CRCT initiation rates will be compared across the 16 participating institutions using paired t-test (or equivalently non-parametric Wilcoxon Signed Rank test).

**Outcomes**:

The primary goal of DISPLACE is to significantly improve uptake and use (adoption) of the stroke prevention guidelines (STOP Protocol) as defined in the NHLBI 2014 SCD Guidelines. These primary practice improvement outcomes will be defined as:

1. Institutional increase in annual TCD screening by at least 30% over baseline.
2. Institutional initiation of CRCT in at least 95% of patients noted to have abnormal TCD.
3. Institutional improvement in re-screening of patients with conditional TCD by at least 20% over baseline.
4. A difference in TCD screening rates of at least 17% between intervention arms to determine optimal implementation procedures.

**Secondary Outcomes:** Key informant interviews with patients/caregivers and stakeholders will be analyzed using content analysis to identify themes pertaining to barriers and enablers to obtaining TCD screening, overall perceptions of the intervention(s), barriers and enablers to implementing the intervention(s) and satisfaction with the intervention(s). Themes around barriers and enablers identified in Part 3 will be compared to barriers and enablers identified in Part 2 to better understand how the interventions may have addressed previous barriers. As per above, a separate IRB protocol will be submitted for the qualitative study.

**F. Data Management**

MEDPACK LLC will design the Provider Minder application. A detailed description of the Provider Minder storage and safety components are included in the attached contract. Provider Minder will also data transfer information to the Data Coordination Unit (DCU) at MUSC for assessment and analysis. 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 multi-center clinical trials. The DCU has coordinated over 60 multi-center 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, or 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 be entered by coordinators at each CI including radiologic results (i.e., TCD, MRI). The actual scan will not be read or interpreted by central radiologists; instead only the report will be utilized 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. Queries will be generated by the DCU team to ensure data cleanliness and integrity. Regulatory documents will be collected and monitored in WEBDCUTM for oversight of training and fulfillment of regulatory requirements by all study team members. This will include GCP and Human Subjects Protection Training.

**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 7 (during the years of assessment, 01/01/2018-12/31/2019) that require(d) TCD screening will be included in the implementation trial. These records will be captured at all consortium institutions by local data coordinators and entered into the *Provider Minder* and by data transfer to WEBDCUTM for evaluation. Waiver of consent is requested for this implementation protocol as there is no additional risk to patients. 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 95% African American, 3% Hispanic and 2% Other based on the data acquired in Part 1. Of course, 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 9 based on study determinants. 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 are anticipated to fall in the cognitively impaired range as the result of severe neurocognitive deficits or intellectual disability.

A small subset of patients/caregivers and providers will be asked to participate in the qualitative assessment. The consent process, inclusion/exclusion criteria will be defined in a separate IRB application. This interview will specifically be targeting guardians and caregivers as well as physicians and clinical personnel to better understand how the implementation strategies and interventions have affected barriers to care. These respondents will be of all nationalities and ethnicities 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. Physical data (hardcopies) 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.

**2. Potential Risks**

**Confidentiality**

The 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.

Financial Coercion: N/A

Patients will not be directly contacted about enrollment into this study to avoid confounding real-world study impact and novel drug/procedures are not being used. There are no financial benefits to being in the DISPLACE Consortium or study.

Alternatives

To our knowledge, there are no other implementation trials currently targeting improved stroke prevention in Sickle Cell Disease.

Note: The primary study does not require consent as it is a site-level study and patients/providers are not being asked to provide consent.

**3. Adequacy of protection against risks**

***a. Enrollment and Informed Consent***

**Enrollment**

No patient recruitment is required as this is an implementation study designed to enhance current practice only. As the sites have agreed to participate, it is the **site** that is being randomized, not the patient. Patients with sickle cell disease between the age of 2 and 7 and the sickle cell anemia genotypes that require TCD screening will be included in the data capture system to enhance stroke screening. 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 CTMS.** Patient names will be used at the site level only. All patients will be given confidential IDs for data entry purposes. Data linkage information will be kept only at each individual CI.

***b. Protection against Risk***

Reducing Confidentiality Risk

We will implement several procedures to ensure that risk of loss of confidentiality is minimized as noted in the protocol. These include the use of an anonymous identifier on all patient information.

Each site will be required to keep 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 individuals with SCA, particularly those who might have been lost to follow-up or had not received this necessary screen. 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.

**H. REFERENCES/LITERATURE CITATIONS**

1. DeBaun MR, Casella JF. Transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med. 2014;371(19):1841-2.

2. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, Wethers DL, Pegelow CH, Gill FM. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998;91(1):288-94.

3. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, Abboud M, Gallagher D, Kutlar A, Nichols FT, Bonds DR, Brambilla D. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998;339(1):5-11.

4. Hulbert ML, McKinstry RC, Lacey JL, Moran CJ, Panepinto JA, Thompson AA, Sarnaik SA, Woods GM, Casella JF, Inusa B, Howard J, Kirkham FJ, Anie KA, Mullin JE, Ichord R, Noetzel M, Yan Y, Rodeghier M, Debaun MR. Silent cerebral infarcts occur despite regular blood transfusion therapy after first strokes in children with sickle cell disease. Blood. 2011;117(3):772-9.

5. Smith LA, Oyeku SO, Homer C, Zuckerman B. Sickle cell disease: a question of equity and quality. Pediatrics. 2006;117(5):1763-70.

6. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639-44.

7. Brousseau DC, Owens PL, Mosso AL, Panepinto JA, Steiner CA. Acute care utilization and rehospitalizations for sickle cell disease. JAMA. 2010;303(13):1288-94.

8. Nietert PJ, Abboud MR, Zoller JS, Silverstein MD. Costs, charges, and reimbursements for persons with sickle cell disease. J Pediatr Hematol Oncol. 1999;21(5):389-96.

9. Telfair J, Haque A, Etienne M, Tang S, Strasser S. Rural/urban differences in access to and utilization of services among people in Alabama with sickle cell disease. Public Health Rep. 2003;118(1):27-36.

10. Davis H, Gergen PJ, Moore RM, Jr. Geographic differences in mortality of young children with sickle cell disease in the United States. Public Health Rep. 1997;112(1):52-8.

11. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psych Res. 1975;12(3):189-98.

12. Varni JW, Seid M, Kurtin PS. Reliability and validity of the Pedistric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care. 2001;39(8):800-12.

13. Panepinto JA, Pajewski NM, Foerster LM, Hoffmann RG. The performance of the PedsQL Generic Core Scales in children with sickle cell disease. J Pediatr Haematol Oncol. 2008;30(9):666-73.

14. McClellan CB, Schatz J, Sanchez C, Roberts CW. Validity of the Pediatric Quality Of Life Inventory for youth with sickle cell disease. J Pediatr Psychol. 2008;33(10):1153-62.

15. Limbers CA, Newman DA, Varni JW. Factorial invariance of child self-report across age subgroups: A confirmatory factor analysis of ages 5 to 16 years utilizing the PedsQL 4.0 Generic Core Scales. Value in Health. 2008;11(4):659-68.

16. Varni JW, Limbers CA, Newman DA, Seid M. Longitudinal factorial invariance of the PedsQL 4.0 Generic Core Scales Child Self-Report Version: One year prospective evidence from the California State Children's Health Insurance Program (SCHIP). Qual Life Res. 2008;17:1153-62.

17. Panepinto JA, Torres S, Bendo CB, McCavit TL, Dinu B, Sherman-Bien S, Bemrich-Stolz C, Varni JW. PedsQL sickle cell disease module: feasibility, reliability, and validity. Pediatr Blood Cancer. 2013;60(8):1338-44.

18. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, Amtmann D, Bode R, Buysse D, Choi S, Cook K, Devellis R, DeWalt D, Fries JF, Gershon R, Hahn EA, Lai JS, Pilkonis P, Revicki D, Rose M, Weinfurt K, Hays R. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol. 2010;63(11):1179-94.

19. Rothrock NE, Hays RD, Spritzer K, Yount SE, Riley W, Cella D. Relative to the general US population, chronic diseases are associated with poorer health-related quality of life as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS). J Clin Epidemiol. 2010;63(11):1195-204.

20. DeWalt DA, Gross HE, Gipson DS, Selewski DT, DeWitt EM, Dampier CD, Hinds PS, Huang IC, Thissen D, Varni JW. PROMIS pediatric self-report scales distinguish subgroups of children within and across six common pediatric chronic health conditions. Qual Life Res. 2015.

21. Saffer BY, Lanting SC, Koehle MS, Klonsky ED, Iverson GL. Assessing cognitive impairment using PROMIS((R)) applied cognition-abilities scales in a medical outpatient sample. Psychiatry Res. 2015;226(1):169-72.

22. Varni JW, Thissen D, Stucky BD, Liu Y, Gorder H, Irwin DE, DeWitt EM, Lai JS, Amtmann D, DeWalt DA. PROMIS(R) Parent Proxy Report Scales: an item response theory analysis of the parent proxy report item banks. Qual Life Res. 2012;21(7):1223-40.