Using Patient-Centered Guidelines in a Technology Platform to Improve Health Care in Adults with Sickle Cell Disease

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1.0 INTRODUCTION AND HYPOTHESIS

Sickle Cell Disease (SCD) is an inherited disorder of hemoglobin that affects approximately 100,000 Americans, most of whom are from socially disadvantaged groups.[1-4] Adults with SCD have a high use of health care resources, averaging more than 197,000 emergency room visits per year with almost 60,000 hospital admissions per year, and 90% of admissions for acute pain treatment.[4,5] For the average individual with SCD, undiscounted medical expenses are estimated to be over $900,000 by 45 years of age.[6] On top of the high use of health service, approximately two thirds of adolescents and adults with SCD are receiving public health insurance.

Over the last 40 years, SCD has changed from a life-threatening disease of early childhood to a chronic disease with life-threatening vaso-occlusive episodes.[7] With advances in health care for individuals with SCD, over 98% of children now survive into adulthood[8], but still face debilitating physical and psychosocial sequelae. The resulting paradigm shift has led to a large increase in adults with SCD needing chronic and preventive care with a dearth of providers equipped to care for this population

In 2014, the National Heart, Lung, and Blood Institute (NHLBI) published guidelines for evidence-based management of SCD.[9] Mobile health (mHealth) applications (apps) for health care providers have been developed to increase the adoption of the NHLBI guidelines.[10] Our preliminary data indicate that a lack of knowledge about SCD, is a key challenge for adults with SCD. In particular, understanding the NHBLI guidelines for the management of SCD is a major obstacle as they are not written in a manner that is understandable for individuals or family members of individuals with SCD. These findings are consistent with studies in SCD and other diseases that have found that national guidelines are written at a reading level that is too high for most patients[11-14].

In addition, many individuals with SCD and their caregivers are unsure of the best approach to use health-related technology, leading to a health care technology gap. Apps for mHealth that are patient-centered and patient-driven currently do not include evidence-based clinical guidelines. Such apps could potentially promote patient engagement and effectively close this technology gap and improve SCD-specific knowledge. Given the observation that interventions designed to increase SCD-specific knowledge can decrease health care utilization, mHealth apps with SCD-specific guidelines have the potential to improve patient outcomes.[15-18]

We will develop a patient-centered mHealth app, iManage, to test the hypothesis that delivery of the NHLBI SCD-guidelines via this mHealth app will increase SCD-specific knowledge.

1.1 PRELIMINARY DATA

The Chronic Care Model, proposed in 1996, represents an evidence-based framework for delivery of safe, effective, cooperative, life-long care through a medical home.[19] Based on the Chronic Care Model, we will leverage Health IT to improve SCD-specific knowledge and to directly engage and activate the patient to improve adherence to guidelines. Engaging and activating patients has been shown to improve health care outcomes.[20]

In 2013, Koh et al. recognized that patient engagement in their own health care relies fundamentally on health literacy, or ability to obtain, process, and understand health information. Thus, they proposed augmenting the standard chronic care model with strategies to enhance health literacy and create health-literate, activated patients.[21] The Health Literate Care Model calls for health care providers to approach all patients as if they are at risk of not understanding health information, employ a range of strategies for clear communication, and confirm patients' understanding[21]. The

Health Literate Care Model is the foundation for developing our intervention. We will use technologies to clearly communicate knowledge and confirm their understanding of this information by testing their disease-specific knowledge. Improving SCD-specific knowledge by providing access to understandable patient-centered guidelines is an important first step in creating the informed, health-literate, activated, patient and family.

Significant evidence has described how educational materials can be used to increase health knowledge.[22-28] Car et al. showed that online educational programs can significantly improve patient self-efficacy and health information evaluation skills.[23] Educational materials also increase disease-specific knowledge in SCD.[29] Six and twelve months after receiving an educational intervention[30,31] that included family-based cognitive-behavioral and psycho-educational components, individuals with SCD had higher SCD-specific knowledge compared to those who had received no intervention. In part, we have based our intervention of mobile phone technology on the prior evidence that other technologies, including CD-ROMs and private computer networks can improve SCD-specific knowledge.[32,33]

Improving SCD-specific knowledge has been shown to decrease acute health care utilization. Higher disease-specific knowledge is beneficial to adults. Increases in health knowledge—achieved through a variety of interventions, including Health IT—have been associated with improved clinical outcomes, self-efficacy, and quality of life, as well as reduced health care utilization. In a review of studies, high SCD-specific knowledge correlated with significant improvement in patients' knowledge and decrease in their depression[29]. In addition, improvements in their ability to adapt and cope, develop more positive health beliefs, and perceive a higher quality of life were all observed, though differences did not reach statistical significance. Improvement in self-management was not measured in the studies in this review. In addition, improving SCD-specific knowledge has been shown to decrease acute health care utilization.[15,30,34] Adapting guidelines to be patient-centered has the potential to improve SCD-specific knowledge and decrease health care utilization. However, there is a lack of technologies that deliver patient-centered educational materials about evidence-based clinical guidelines in SCD. While multiple methods have been shown to improve SCD-specific knowledge, we propose that that using a mHealth app will improve SCD-specific knowledge and could decrease acute health care utilization.[35]

1.2 HYPOTHESES

Adapted mobile health applications can increase SCD-specific knowledge in adults with SCD.

1.3 AIMS OF THE TRIAL

Aim 1: Integrate clinical guidelines for adults with SCD into our beta version of iManage, an mHealth app. Three focus groups will include a total of fifteen adults with SCD to identify user needs and preferences for the guidelines and app. This information will be used to adapt iManage which will then be tested and iteratively refined through usability sessions with 10 adults until ease of use and usefulness are high.

Aim 2: Evaluate the feasibility and acceptability of the refined iManage in a pilot study with adults with SCD. We will recruit 50 adults from the population of adults with SCD at the Vanderbilt Meharry Sickle Cell Disease Center of Excellence and Ohio State Sickle Cell Center for a 6-month pilot study to evaluate usability, acceptance, and usage. At the end of the study, we will conduct interviews with a subset of participants to gain an in-depth understanding of usage patterns and how

to sustain engagement to promote ongoing iManage use.

Aim 3: Evaluate the efficacy of the refined iManage app on SCD-specific knowledge. We will test the hypothesis that the refined iManage will increase SCD-specific knowledge by measuring SCD-specific knowledge at the start and end of the 6-month pilot study. We will conduct exploratory analyses of secondary outcomes including patient activation, adherence to guidelines, missed days of school/work, and self-efficacy.

Specific Aim 1:
Outcomes: The primary outcome of step 1 will be themes from focus groups that will be utilized to refine the Beta version of iManage in step 2. Outcomes from step 2 will include usability data from the System Usability Score[36], as well as quantitative and qualitative data about task completion.

Specific Aim 2:
Rationale: Technological interventions can only be successful at changing outcomes if they are feasible and acceptable. Through measurement of usability, acceptance, and usage, we can discover patterns that can lead to insights about how to modify technology to have a larger impact and reach.

Outcomes: We will measure usability and acceptability of iManage through surveys at the 6 month follow up, and we will measure usage of iManage throughout the 6-month period. Usability will be measured by the widely used and validated System Usability Scale.[36] We will measure acceptability with a validated survey instrument based on the technology acceptance model introduced by Gao et al.[37] The mobile health application for the guidelines has built-in tracking of the number of times the application is launched, how many times each of the functions are used, and how many times each button has been pushed. To measure usage, we will record the numbers of each of these events for each adult. In addition to total use, we will measure usage over time including any use, initial use, periodic use, and sustained use. We will also use a satisfaction/acceptability questionnaire to help evaluate acceptability of the app.

Specific Aim 3:
Rationale: Currently, health care providers provide education about SCD at clinic visits yet, data show that technology solutions designed to improve SCD knowledge are effective.[32] We hypothesize that delivering NHLBI SCD-guidelines via an mHealth app, iManage, will increase patients' SCD-specific knowledge

Outcomes: To test our hypothesis, we will measure the change in the primary outcome of SCD-specific knowledge between the initial visit and the 6-month follow up visit. We will measure the change in the following secondary outcomes: (1) patient activation; (2) patient and provider adherence to SCD-specific guidelines; and (3) self-efficacy. Other secondary outcomes we will assess during the pilot study period are measures from a patient-centered questionnaire, including missed days from school or work and days home in pain[38-40], barriers to care, medication adherence, PROMIS measures (Computer Adaptive Tests), PHQ-9, health literacy (through REALMSF), and acute health care utilization, specifically total emergency department (ED) visits and hospitalizations. We've elected to use all cause ED visits and hospitalizations as opposed to SCD-specific health care utilization because adults with SCD believe all-cause ED visits and hospitalization is a stronger measure of their well-being than SCD related health care utilization. We will collect ED and hospitalization data by having all participants sign information release forms during consent to track acute health care utilizations at area facilities for at least six months. Adherence to SCD guidelines: Guideline adherence is a bi-directional patient-provider interaction. We will assess whether there is documentation of recommending guidelines in the electronic medical records and see how this

compares to what patients report in iManage. Missed days from school or work: Patients will report on days missed from school or work because of illness at the 6-month follow up visit. We will also inquire about other opportunities a patient has missed because of SCD (for example missed opportunities for school or work, including having to drop out of school or work or being fired from their job).[38-40] Other outcomes include SCD-specific measures of self-efficacy and patient activation, using the validated Sickle Cell Self-Efficacy Scale[41,42] and the Patient Activation Measure.[43-45] These instruments were validated in prior studies demonstrating rigor and reproducibility.[38-45]

2.0 STUDY DESIGN, PHASING AND ELIGIBILITY

2.1 Study Design:

Specific Aim 1:

Step 1: Understanding the needs and preferences for guidelines and iManage for adults with SCD. Focus groups will be conducted with assistance from the Qualitative Research Core at Vanderbilt University in the format recommended by Morgan & Kruger.[46] Focus group questions will be designed to ensure relevance and developmental appropriateness for discussion with adults. In the first half of the focus group, participants will be asked about their needs and preferences related to the guidelines (accessibility and use), and asked for feedback and suggestions for refining the iManage app. In the second half of the focus group, clinical scenarios will be presented and discussed by participants to ensure that the guidelines are actionable. These clinical scenarios will consist of real-life examples of clinic visits where guidelines could be used. The focus groups will be audio recorded using encrypted digital recorders. Interviews may also be done remotely via phone or web meeting service (such as GoToMeeting or Skype or Zoom). Audio files will then be uploaded to rev.com.

Step 2: iManage app pilot testing. We will employ a user-centered design approach to iteratively refine iManage for use by adults with SCD with assistance from the Center for Research and Innovation in Systems Safety (CRISS) at Vanderbilt or the Research Informatics Software Engineering (RISE) at Ohio State.[47] This approach to technological design has a demonstrable track record of useful and usable designs.[48,49] However, many extant medical products were designed and deployed without the benefits of user-centered design, and have led to low adoption rates, abandonment, and use errors.[50] We will conduct two iterative development rounds of formative usability evaluations with a focus on an initial re-design of the app and further refinements after completion of the second round. We will design and employ candidate scenarios that include representative tasks that may occur during clinic visits, such as whether a patient has all of their immunizations or whether they are eligible for a certain treatment such as hydroxyurea (medication), as well as scenarios where they are likely to use the app outside of a clinic visit (e.g. to use a pain action plan for a pain episode, or to manage avascular necrosis of the hip at home). These sessions will be video recorded by a camera that mounts onto a smartphone (e.g. Mr. Tappy[51]). During each scenario, participants will be asked to “talk aloud” and prompted to talk through what they are experiencing including comments about format, content, navigation, and usability. They will be asked to voice any frustrations they are experiencing and what they like about the app. At the end of the usability session, a semi-structured interview will provide additional information about their thinking when using the app, alternative or additional functionality and opportunities for improvement. The results will include: the number and type of errors, successful completions, and qualitative comments made during and post-session. The goal of these iterative evaluations is primarily focused on if and how the participants would use iManage, and suggest any additional functionality that would be tested in future iterations.

As we have obtained feedback on our and health app, we need to adapt it based on the feedback and updated guidelines. Upon completion of this update to the app, we will want to test the usability.

These will be the same as the usability sessions in the original protocol and consent, however, we may need to recruit additional participants for the usability sessions with the updated app for 1 to 2 rounds, requiring an additional 10 participants who may need to be recruited, increasing total recruitment for this study to 85. All the usability questions, recruitment, and consent will be the same as the prior questions.

Specific Aim 2 & 3:
Participants will participate in two visits, an initial visit where participants will complete the surveys shown in Table 1, where the participant will be randomized into control arm or intervention arm (1:1 ratio), and if in the intervention arm, the research team will introduce and demonstrate the iManage app. At a 6-month follow up visit, surveys will be repeated, and the research team will conduct a semi-structured interview about what they liked about the mHealth app, what they didn't like, what barriers they had to using the app, how the mHealth app could be improved, and an example of when the app helped them with care of their SCD. Interviews will take place either in person or remotely via phone or web meeting service (such as GoToMeeting). When conducting remote interviews, we will record audio using software such as GoTo Meeting or Skype. All recording files will be saved to an encrypted drive, which can only be accessed by study team members. Once a file has been removed from the secured recording media and stored on the encrypted drive, it will be deleted from the recording media.
KSP trained in human subjects research will obtain consent and administer the surveys and interview. A member of the KSP will set up and instruct the participant on how to access the mHealth app on their mobile phone, how to login to the intervention using his/her unique study identifier. The KSP will provide a 10-minute demonstration of the mHealth app, and have the participant interact with the app as independently as possible for 10 minutes to complete assisted tasks to gain knowledge and confidence to take action independently. KSP will be available to assist with questions. Participants may also get emails periodically throughout the study to ask them if they have questions about the study or the guidelines.

Technology: iManage will include interactive content and a fully searchable collection of the SCD-specific guidelines that are age- and health literacy-appropriate. iManage will be a combination of a static website with guideline information and a REDCap database hosted at Vanderbilt. Through the mobile app, we will reinforce important points of guideline content; motivate patient engagement through quizzes and reminders (which may use the Twillio feature in REDCap); and facilitate peer support, for instance by forming teams to compete against each other to attain goals. These strategies were recommended by patients in a prior study[52]. Based on aim 1, multiple updates were made to the app. In addition to the guidelines information, iManage allows participants to develop a personal profile, choose goals, report on daily symptoms, and communicate with other participants outside of the group meetings. We are attaching the terms of use document which participants will agree prior to starting the trial. No PHI will be stored on iManage or in any databases populated by iManage data. De-identified results of entered data such as daily symptoms may be shared with other participants on iManage whenever a participant uses the review results function, which shows their results and other participants de-identified results. An example of this de-identified data sharing would be seeing the average mood score of the participants as compared to themselves, which we believe should increase engagement and return of value of iManage.

2.2 Study Phases

PHASE I – Adaptation of iManage (18 months)

During this phase we will adapt the beta version of iManage and integrate clinical guidelines for adults with SCD. During this phase, we will perform three focus groups that will include a total of fifteen adults with SCD to identify user needs and preferences for the guidelines and app. This information will be used to adapt the app which will then be tested and iteratively refined through usability sessions with 10 adults until ease of use and usefulness are high.

At the end of this phase, we will have a modified iManage that will be used in the Phase II Pilot Study.

PHASE II Pilot Feasibility Randomized Controlled Trial (30 months)
Fifty participants will be enrolled or a 6-month pilot study where they will be randomized to one of two arms, standard care (control arm), or receiving iManage that will include interactive content and a fully searchable collection of the SCD-specific guidelines that are age- and health literacy-appropriate (intervention arm). An equal number of participants will be in each of the two arms (25 in each arm). They will participate in an initial visit and a 6-month follow up visit.

PHASE III - Study Close Out and Data Analysis (12 months)
During this phase, data analysis and manuscript preparation will occur.

2.3 ELIGIBILITY

2.3.1 Patient Inclusion Criteria

1. Patient must have diagnosis of SCD (Hgb SS, SC, Sβ-thal)
2. Receive care at the community health clinic
3. Ability to speak and understand written English
4. Access to a smartphone
5. Age 18-70 years

2.3.2 Patient Exclusion Criteria

1 Lack of access to smartphone
2. Inability to understand written English

3.0 EVALUATIONS

3.1 Patient Evaluations

Participants will provide written informed consent on paper or through REDCap e-consent and sign an authorization to use or disclose personal health information (PHI) form. Participants will get a $250 check or gift card if they are in the 4-hour focus groups and a $100 check or gift card if they are in the 90-minute usability session. For the pilot study, they will be compensated with a $25 gift card for their initial visit and $50 for their 6-month follow up visit. Both visits should take about 60 minutes. All checks or gift cards will be mailed or sent electronically. During the initial visit, participants will complete surveys, and if randomized to the intervention arm, the research team will introduce and demonstrate the iManage app. At a 6-month follow up visit, surveys will be repeated, and the research team will conduct a semi-structured interview about what they liked about the mHealth app, what they didn't like, what barriers they had to using the app, how the mHealth app could be improved, and an example of when the app helped them with care of their SCD. KSP trained in human subjects research will obtain consent and administer the surveys and interview. All survey instruments will be available in electronic form (through Research Electronic Data Capture, or

REDCap) and administered via iPads. Paper forms will also be available, and KSP will be available to answer questions. The interview will be audio recorded, transcribed, and de-identified for analysis.

Table 1 Time when each activity will be completed, and time to complete each activity

Activity or Measure	**Initial visit**	**6-month follow up**	**Time (mins)**
Enrollment/Consent	X		20
Demographics	X		5
Demonstration of iManage	X		20
SCD-specific knowledge	X	X	5
SCD Specific Self Efficacy Assessment[41,42]	X	X	5
Patient Reported Outcomes Measurement Information System (PROMIS) measures	X	X	10
Patient Activation Measure[43-45]	X	X	5
Adherence to guideline measurements	X	X	5
Patient-centered Outcomes Questionnaire[38-40]	X	X	5
PHQ-9	X	X	1
REALM-SF	X	X	3
Medication adherence (Visual Analogue Scale (VAS) (1 item) and modified Morisky Scale (8 items))	X	X	1
Barriers to care	X		3
iManage usage and usability Satisfaction/acceptability questionnaire (11 items)		X	10
Semi-structured interview		X	30
Compensation	$25	$50	

3.2 Outcomes:

To test our hypothesis, we will measure the change in the primary outcome of SCD-specific knowledge between the initial visit and the 6-month follow up visit (Table 1). We will measure the change in the following secondary outcomes: (1) patient activation; (2) patient and provider adherence to SCD-specific guidelines; and (3) self-efficacy. Other secondary outcomes we will assess during the pilot study period are measures from a patient-centered questionnaire, including missed days from school or work and days home in pain[38-40], barriers to care, medication adherence, PROMIS measures (Computer Adaptive Tests), PHQ-9, health literacy (through REALMSF), and acute health care utilization, specifically total emergency department (ED) visits and hospitalizations. We've elected to use all cause ED visits and hospitalizations as opposed to SCD-specific health care utilization because adults with SCD believe all-cause ED visits and hospitalization is a stronger measure of their well-being than SCD related health care utilization. We will collect ED and hospitalization data by having all participants sign information release forms during consent to track acute health care utilizations at area facilities for at least six months. Adherence to SCD guidelines: Guideline adherence is a bi-directional patient-provider interaction. We will assess whether there is documentation of recommending guidelines in the electronic medical records and see how this compares to what patients report in iManage. Missed days from school or work: Patients will report on days missed from school or work because of illness at the 6-month follow up visit. We will also inquire about other opportunities a patient has missed because of SCD (for example missed opportunities for school or work, including having to drop out of school or work or being fired from their job).[38-40] Other outcomes include SCD-specific measures of self-efficacy and patient activation, using the validated Sickle Cell Self-Efficacy Scale[41,42] and the Patient Activation Measure.[43-45] These instruments were validated in prior studies demonstrating rigor and reproducibility.[38-45]

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4.0 SAMPLE SIZE AND STATISTICAL ANALYSIS

4.1 Data Analysis

Aim 1:

Transcripts will be transferred into the DeDoose software for coding and data management. Using the focus group moderator's guide and the first focus group transcript, we will develop a hierarchical coding system to identify and describe major themes discussed by the group. Once the coding system is finalized, each transcript will be independently coded by two coders, and the results compared and reconciled. If there are disagreements, a third person will assist with reconciliation. The focus of the analysis will be to assess user needs and preferences along with ideas about the design and functionality of the app. We will use a combined inductive-deductive approach, which will be informed by knowledge of SCD, design of usable apps and social science theory. These results will be used to adapt and refine the app. *Step two* will involve extracting usability metrics from the app to measure error, completions and other indicators of how the app was used. We will transcribe and

code the comments made during usability testing along with the responses to the semi-structured interview questions. Coding and analysis will be similar to the focus groups. Usability data will be analyzed using both qualitative and quantitative methods. Frequencies and percentages will be used for categorical data; means and standard deviations for continuous measures that are normally distributed; and the median and inter-quartile range for continuous measures that are skewed or otherwise not normal.

Aim 2&3:
Descriptive statistical analyses will be conducted to characterize and highlight unique aspects of this population. The statistics used to summarize the responses to the various instruments and their scales will be based on standard and recommended practice. Frequencies and percentages will be used for categorical data, means and standard deviations for continuous measures that are normally distributed, and the median and inter-quartile range for continuous measures that are skewed or otherwise not normal. To examine relationships between measures, crosstab tables with chi-square will be used for categorical variables, a t-test or ANOVA for a categorical and continuous variable (or the equivalent non-parametric test), and a Pearson correlation or Spearman rank correlation as appropriate for the association between two continuous measures. Interview data gathered during the visits will be transcribed and de-identified as described in aim 1. We will use a combined inductive-deductive approach, which will be informed by knowledge of SCD, design of usable apps, and social science theory.

4.2 Sample size calculation
Aim 1:
As the primary outcome for step 1 is to create feedback useful for modifying the app, we will conduct a sufficient number of focus groups to reach data saturation (estimate 3-4 groups). For step 2, usability testing with five participants has been shown to uncover the majority of issues has been shown to uncover the majority of issues[53], therefore we will test with five participants per usability round.

Aim 2&3:
As the primary outcome of this aim is the change in SCD-specific knowledge, we calculated the power for our sample size of 50 participants based on improvements in SCD-specific knowledge from preliminary data from St. Jude[35] and a study that used a private online computer network within the hospital.[33] These studies showed an improvement of about 10-20% in test scores for SCD-specific knowledge, with a baseline mean score of around 7.5 and standard deviation of about 2.5. If we use an improvement of 15%, and assume a baseline score of 7.5, our target sample size of 50 achieves 86.2% power to detect a mean of paired differences of 1.1 with an estimated standard deviation of paired differences of 2.5, at a significance level (alpha) of 0.05 using a two-sided paired t-test.

4.3 Data Integrity, Management, and Missing Data
This project will utilize the REDCap platform for data collection and management. Data will be manually retrieved from the EHR and entered into REDCap.
This study will utilize REDCap (Research Electronic Data Capture), a software toolset and workflow methodology for electronic collection and management of clinical and research data, to collect and store data. The OSU Center for Clinical and Translational Science (CCTS) Research Informatics Services will be used as a central location for data processing and management. REDCap provides a secure, web-based application that provides an intuitive data manipulation interface, custom reporting capabilities, audit trail functionality, real-time data monitoring/querying of participant records, and variations of data exporting/importing. REDCap is hosted by OSUWMC IT in the Ackerman Datacenter (640 Ackerman Road; Room 345). The OSU REDCap instance is located on internal

OSUWMC network. Remote access to this network can be obtained over an encrypted VPN tunnel (AnyConnect) This VPN uses Protocol: DTLS and Cipher: RSA_AES_128_SHA1. Background checks are performed on all staff that are on the network or obtaining VPN access.

We will take the following steps to ensure rigor and reproducibility of this study. Data will be de-identified, and survey responses will be securely stored in REDCap or both a password protected computer and external hard drive. A standard analysis file will be created for use in the analysis of the trial for manuscripts and reports. The analysis file will include data from screening and baseline forms, treatment forms, mHealth application data, and outcomes. First and foremost, we plan to minimize the amount of missing data through various strategies. However, in the case of missing data, randomness of missing data will be assessed and when feasible, imputation will be performed.[54] We will minimize nonadherence and attrition by employing retention strategies and adequate follow-up of all participants (e.g. contact from study coordinator; increasing reimbursement over time for study participation). We will employ techniques to ensure self-administered survey completion by requiring needed questions in REDCap so a participant cannot submit a final survey without answering each question, and by following up on incomplete surveys through telephone contact and possibly completing the survey over the telephone.

5.0 DATA MONITORING

The local principal investigator and/or members of the research team will monitor the study for inclusion/ exclusion criteria, accrual/withdrawal rates, and breech of confidentially annually prior to submission to the IRB. Any adverse events will be reviewed immediately with the Principal Investigator and will be reported to the Ohio State IRB per IRB regulations. All study events will be summarized once a year for the IRB, during the annual continuing review reporting.

6.0 REGISTRATION AND STUDY ORGANIZATION

Approval for use of this protocol and consent forms by the Institutional Review Board (IRB) must be obtained prior to patient participation on the trial. All reasonable measures will be taken to protect the confidentiality and identity of the patient and patient's records according to State and Federal laws. Patient identity will not be revealed in any publication.

The parent/legal guardian of each patient will be given consent forms to read and sign on paper or through REDCap e-consent prior to the patient's entry into the trial, if eligible. These forms will contain a description of the objectives of the trial, a description of the examinations and tests which will be given to the patient as each part of the trial, as well as expectations of the patient as a trial participant. These consent forms will be given to the patient by a KSP.

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8.0 APPENDICES

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