Protocol Title:	***SCManage*: Improving Self-Management in Adolescents with Sickle Cell Disease**
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1. ABSTRACT

Background: Sickle cell disease (SCD) is the most common life-shortening genetic disorder and affects primarily African American youth in the U.S.[12] In addition to the progressive biological impact of SCD, which requires a higher level of disease self-management, adolescence is also a time when parents/caregivers begin transferring responsibility for disease management. Adolescents with chronic diseases have some of the lowest adherence rates[17,18] and for those with SCD, minority race and economic disadvantage compound the risk.[19] Crucial for the success of any self-management intervention is behavioral activation (BA), which is the knowledge, skills, readiness to change, and self-efficacy, needed to make effective decisions to manage health.[1] No existing interventions address broader BA skills that underlie many of the specific health behaviors and lifestyle changes that are required for effective self-management of SCD and its impact. Furthermore, to effectively motivate and engage AYAs with SCD in sustainable health behavior change, the social context (e.g. connection with peers) is developmentally important, but has not been considered in existing programs. **Objective**: In this study, we will refine and test an innovative, technology-enhanced, group self-management intervention, *SCThrive,* which uses a mixed in-person and online format and is supported by a tailored mHealth tool, *iManage*. The objective of the current proposal is to determine the feasibility and acceptability of *SCThrive,* and to evaluate its initial efficacy for increasing BA in adolescents with SCD. **Methods**: We will achieve our objective via two specific aims: Aim 1: we will conduct a small pilot to determine the feasibility and acceptability of the *SCThrive* intervention for adolescents and young adults with SCD (N = 8; 4 adolescents ages 13-17; 4 young adults ages 18-21). Aim 2: we will conduct a small single-site, randomized control trial (N = 64) to determine whether the refined *SCThrive* intervention is superior to attention control in improving BA in adolescents and young adults (AYAs) with SCD ages 13-21. We hypothesize that *SCThrive* will be engaging, beneficial, increase BA in adolescents with SCD, and, ultimately, change health behaviors (long-term goal) that result in improved quality of life, decreased SCD symptoms, and decreased acute care visits (i.e. emergency room); in other words, participation in the intervention will help adolescents with “sickle cell thrive.” **Conclusions/Next Steps**: Results from this developmental/exploratory project will lay the foundation for a competitive R01 application to examine SCThrive’s efficacy in a fully powered randomized multisite trial.

2. PURPOSE OF STUDY

The objective of this study is to determine the feasibility and acceptability of *SCThrive*, an innovative, technology-enhanced, group self-management intervention that uses a mixed in-person and online format and supported by a tailored mHealth tool, *iManage*. The study will also evaluate the initial efficacy of *SCThrive* for increasing behavioral activation (BA) in adolescents with Sickle Cell Disease (SCD) ages 13 to 21. We will achieve our objective through two specific aims:

Aim 1: Determine the feasibility and acceptability of the *SCThrive* intervention for adolescents and young adults with SCD (N = 8; 4 adolescents ages 13-17; 4 young adults ages 18-21).

Aim 2: Conduct a pilot randomized trial (N = 64) to determine whether the refined *SCThrive* intervention is superior to attention control in improving BA in AYAs with SCD ages 13-21.
Hypothesis 1: Participants in the *SCThrive* group will show greater BA (primary outcome) at post-treatment than the attention control group.
Hypothesis 2: Participants in the *SCThrive* group will continue to show significantly greater BA at the six week follow-up compared to the attention control group.

Exploratory Aim: Explore whether *SCThrive* is associated with greater improvements in self-management behaviors and quality of life (secondary outcome) compared to attention control at the six-week follow-up assessment.

3. BACKGROUND

Adolescents and young adults (AYAs) with SCD have poor health outcomes. SCD is the most common genetic disorder in the U.S. affecting approximately 100,000 individuals, the majority of whom are African-American (approximately 1 in 400 African-American births).[24] SCD is first identified during infancy, but the AYA years are a particularly vulnerable time when complications (e.g. chronic pain due to organ or bone damage, pulmonary hypertension, renal and cardiac dysfunction, or stroke) increase.[11,25,26] SCD pain is severe, unpredictable, and recurrent, and accounts for the majority of Emergency Room (ER) visits and hospitalizations.[15] AYAs with SCD have more ER visits than other age groups of SCD patients(3.61 per patient per year vs. 2.59 per patient per year).[27] SCD accounts for approximately 100,000 hospitalizations per year (estimated $488 million in healthcare costs).[28,29] AYAs with SCD have higher 30 day and 14 day re-hospitalization rates than other SCD patients (41.1% and 28.4% respectively).[15] Mortality rates for AYAs are also high, ranging from 6-20 percent. [30,31] Approximately, 11% of AYAs with the most severe genotype (Hb SS) are at risk for over strokes.[32] Silent strokes are frequent in all genotypes (37% of patients age 14 or older).[33] Regrettably, the risk of stroke increases into adulthood and 50% of adults with SCD with no documented history of stroke have neurocognitive limitations.[33-36] Furthermore, empirical studies confirm that AYAs with SCD are at risk for depression and anxiety, impairments in quality of life, and delays in social functioning.[37-39]

Behavioral Activation (BA) is a potentially important mechanism for improving disease self-management and preventing poor outcomes. Effective disease self-management is critical to decreasing complications and early mortality in SCD. BA (also referred to as “patient activation” or “patient engagement in health behaviors”) plays an intermediary role in improving self-management behaviors.[1,40,41] BA is composed of several different constructs (knowledge, self-efficacy, skills, and readiness for change[1]) that are linked to health outcomes in SCD and other chronically painful conditions.[2-4] Although individual components of BA have shown links with health outcomes, the direct association between the larger construct of BA and health outcomes

is understudied (*Table 1 summarizes SCD and BA research*). Studies suggest that increased BA precedes improvements in self-management.[1] Moreover, high levels of BA are associated with positive health outcomes (i.e. healthy eating, exercising, medication adherence, fewer EF visits and hospitalizations).[1,41-43] Our prior research and extensive clinical experience suggests that AYA with SCD lack the skills components of BA: goal setting, self-monitoring, communication, and action planning.[53,54]

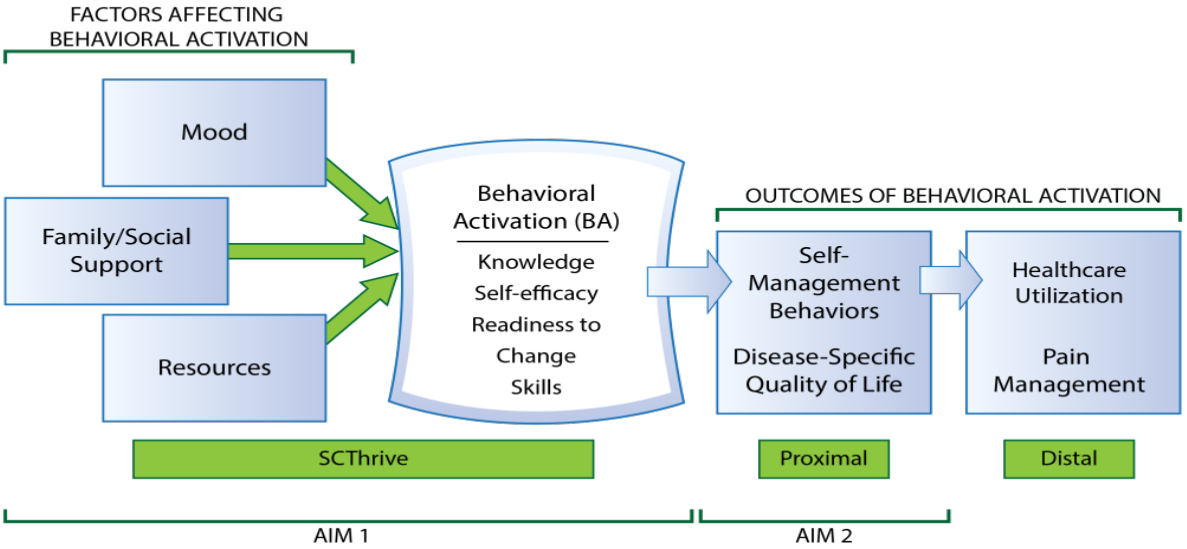
Table 1. Summary of Prior Research on BA Constructs in SCD

BA Construct	Research Findings
Knowledge	Maternal disease knowledge associated with positive health outcomes for AYA with SCD; increased disease knowledge may improve self-efficacy in children with SCD.[44,45]
Self-Efficacy	Lower self-efficacy associated with high pain severity, healthcare utilization and physical and psychological symptoms in adults with SCD. Higher self-efficacy associated with better quality of life in adults with SCD; lower self-efficacy associated with adverse physical and psychological symptoms and poor transition (self-management) outcomes in adolescents.[2,46-49]
Readiness to Change	AYA with SCD demonstrate poor preparation for self-management and transition (low readiness); higher levels of readiness for self-management or transition associated with high HRQL; Negative attitudes about the transition process of self-management associated with disease severity.[3,50-52]

BA is particularly important during the AYA years when the demands for self-management increase and have a significant impact on health. Although AYAs are expected to be more independent, many AYAs with chronic conditions have not developed the self-regulation skills (e.g. daily monitoring of health status) needed to manage their illness.[55,56] Furthermore, self-management rates are especially low for AYAs with limited exposures to healthy behavior role models and who lack access to health resources due to risk factors such as minority race and economic disadvantage, like our proposed sample.[57] Likewise, the complexity and demands of the SCD treatment regimen present unique challenges that may undermine BA. For example, AYAs with severe disease may be required to take daily medications (e.g. hydroxyurea), receive monthly blood transfusions, and/or frequent lab draws (4-12 times per year) all of which require strong healthcare navigation skills,[58] and yet, data suggest that families of youth with SCD identify these skills as a significant barrier to care.[59] In addition, the episodic and unpredictable nature of SCD may contribute to AYAs feeling unprepared when a flare-up occurs and reinforce inaccurate beliefs about the consequences of non-adherence (low motivation).

The SCD research community has called for intervention to increase activation and self-efficacy during AYA to improve self-management.[5,6] SCD Transition and Centers for Disease Control guidelines recommend the development of broad-based self-management skills for patients with SCD, particularly AYA.[5-7] Moreover, self-management research in pediatric chronic disease and SCD shows that multicomponent interventions are superior to those focusing on a single domain of self-management.[8,9,49] Additionally, public health research supports the use of peer-based intervention to effectively engage and motivate AYA to sustain health behavior changes.[60] Nevertheless, existing SCD self-management interventions have focused on a single dimension of self-management (e.g. adherence), used an individual approach rather than including peers, and been primarily designed by investigatorys.2 While these interventions have shown some positive effects (such as increased daily functioning and decreased school

Figure 1. Relationship between Behavioral Activation, Self-Management and Outcomes



Model is informed by research on patient and consumer activation, the Wagner chronic care model, health action process approach and self-determination theories[40,63-68]

absences); they assume a high level of motivation and engagement and fail to address the full range of behaviors required to manage SCD.[2,61]

We developed and prototyped a novel, tailored, group-based BA intervention, *SCThrive*, supported by an mHealth self-monitoring tool co-designed by AYAs with SCD (*iManage*), that works to systematically target BA constructs knowledge, self-efficacy, skills, readiness to change) and influencing factors (mood, family/social support, resources; see Figure 1). The *SCThrive* intervention gives patients a structure for sharing their illness narrative (builds importance and confidence which promotes readiness for change), choosing self-management goals and developing action plans to achieve them (self-efficacy), setting reminders to complete action plans (skills), tracking daily symptoms (build knowledge through *iManage*), and receiving support from others on goals and action plans (family/social support from peers and caregivers). *SCThrive* uses evidence-based, developmentally appropriate, interactive teaching methods including brainstorming, video vignettes, skills-training methods (modeling, role-playing, and rehearsal), small group exercises, large group discussions (sharing action plans) and social reinforcement via *iManage*.[62]

AYAs with SCD are a particularly vulnerable group at risk for serious disease complications that could be minimized or prevented with effective self-management. The new *SCThrive* intervention is a multicomponent, developmentally tailored intervention to increase BA with the potential to significantly improve their quality of life and health outcomes.

3.1 Preliminary Data Informing the Proposed Study Design

Data from our preliminary studies as well as the larger literature highlight the persistence of motivational and environmental barriers to self-management in AYAs with SCD[5,49,72,73] and support the need for an intervention focused on BA. Preliminary data from 33 AYAs with SCD confirmed that they have an elevated risk for self-management difficulties due to environmental or psychosocial barriers such as lack of family social support, family medical/behavioral problems, and parental stress (as measured by the Psychosocial Assessment Tool 2.0; M=1.32; SD = .68).[74] In partnerships with University of Cincinnati (UC) design students, the PI used qualitative and design thinking research methods to identify barriers to self-management

for AYAs with SCD ages 16-24. Eighteen AYAs with SCD (M age = 20.4; 61.11% female; SS type 77.77%) and eight SCD providers completed in-depth interviews and co-creation (validation) session. The following barriers emerged: 1) inaccurate beliefs about the consequences on non-adherence (low SCD knowledge and self-efficacy); 2) negative perceptions of overall health status (low readiness to change, low mood); and 3) lack of self-management support (from peers, family, and the healthcare team) and lack of self-management resources (educational resources).[75] *SCThrive* addresses these barriers by targeting BA constructs to increase the likelihood of engaging AYA in self-management.

Development of the *iManage* tool. In another collaboration with US design students, eight AYAs with SCD (m age=19; 60% male) and six SCD providers participated in interviews, focus groups, and visit observations.[82] Results revealed that AYA desired a self-management tool that would educate them about the impact of SCD, help monitor progress on self-management goals, send reminders to complete self-management goals (e.g. take daily medications, drink fluids, develop a medication list), facilitate communication with healthcare team and other AYAs with SCD. These themes informed the development of the *iManage* app, which was refined with patient and provider input. Usability testing (N=5 AYA with SCD) found that *iManage* is easy to use, increases AYA knowledge about SCD, facilitates peer communication and tracking progress on self-management goals.[75]

Self-management online portal. As part of her K-Award, the PI designed a web-based portal and examined the feasibility and preliminary efficacy of a six-week intervention to promote portal use in AYA with SCD aged 16-24.[83] Data from 42 AYAs indicated that 95% found the portal easy to use, 90% found it beneficial, 98% reported that the portal increased SCD knowledge, and 95% reported that it improved their self-management. Yet, outcome data for BA and other measures were not impressive (pretest PAM-13 M=72.0; posttest PAM-13 M=65.6; i.e. no significant reduction in BA) suggesting that online-only interventions were unlikely to lead to measureable behavior change.

In-Person Delivery of SM Intervention for AYAs with SCD**.** The PI also conducted a pilot study of a six-week in-person group self-management intervention (Chronic Disease Self-Management Program – CDSMP)[84] with 74 AYAs with SCD aged 16-24. Intervention participants were highly satisfied with the CDSMP (9.05 out of 10), yet barriers to regular attendance at sessions posed a strong impediment to study participation.[85,86] Session completion was defined as 4/6 sessions; 34% of completers attended less than six sessions and another eight participants who started the intervention dropped out due to illness or family issues (e.g. hospitalization, family member ill). Participants rated sessions focused on physical activity and exercise, managing difficult emotions, and communicating with healthcare providers as most beneficial and reported that interacting with other AYA with SCD enhanced their ability to learn and continue to use self-management skills. Multivariate analyses found significant improvement from pre to post on AYA confidence in: 1) using exercise to deal with health problems ($p = .005$), 2) keeping fatigue from interfering with pleasurable activities ($p = .020$), and 3) exercising three times per week ($p= .057$). Study findings are highly promising and suggest that in-person interventions have strong potential to improve AYA self-efficacy for self-management.

In summary, our pilot work underscores the need for multicomponent, peer-based interventions that include easily accessible technology enhanced tools combined with at least some in-person contact to enhance knowledge, peer support, and self-monitoring, but also to produce greater engagement and clinically significant changes in self-management in AYA with

SCD. *SCThrive* uses a mixed format (online and in-person sessions) to overcome participation barriers, but also maintain engagement. For example, results from a pilot study of three *SCThrive* online sessions with four AYA with SCD found high ratings on engagement (4.5/5 on returning for another session) and skills (4.75/5 on improving their management of SCD).

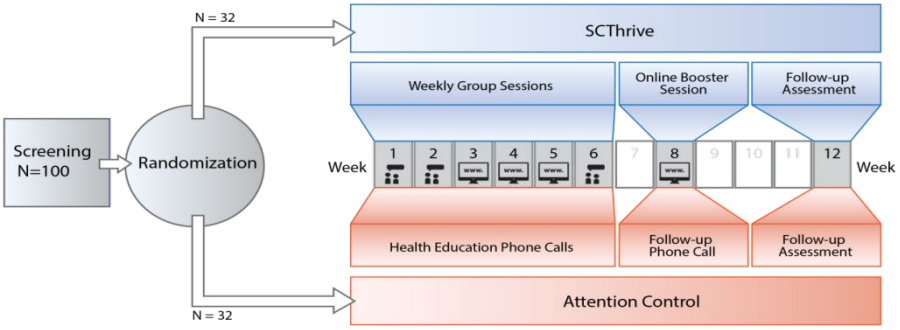
4. STUDY DESIGN

Aim 1: We will conduct a mixed-methods study (quantitative and qualitative). Eight AYA with SCD ages 13-21 will participate in the *SCThrive* six-week, mixed format (in-person and online) intervention. Participants will complete measures at baseline and post-intervention to assess feasibility and acceptability of data collection and management procedures. We will also obtain qualitative feedback (via focus groups) from participants about *SCThrive* content, format, feasibility and acceptability. Data will be used to refine and finalize the intervention protocol.

Aim 2: We will conduct a pilot 2-arm randomized controlled trial to test the initial efficacy of *SCThrive* in improving BA relative to an Attention Control in AYAS with SCD ages 13.21. AYA with SCD will first be dichotomized by age (13-17 and 18-21) and disease severity (severe/non-severe). Participants will be categorized as severe if they have a history of acute chest syndrome, prior stroke or more than three hospitalizations for vaso-occlusive crises in the prior 3 years. Participants will be categorized as not severe if these complications are not present. Participants within each of the 2 (age; 13-17 years or18-21 years) by 2 (disease severity; severe or not severe) cells will be randomized into the *SCThrive* intervention arm or an attention control arm (e.g., stratifying participants based on age and disease severity prior to random assignment).

Study participation includes a baseline assessment, after which participants will be randomized to the *SCThrive* intervention arm or attention control arm. This is followed by 6 weeks of intervention (*SCThrive*) and post-treatment assessment. Given the grant timeline, only a subset of participants will be followed in the post-treatment period. Fourteen *SCThrive* intervention arm participants will complete an online/in-person booster session at 6 weeks post-treatment and 14 attention control participants (N=14) will receive a follow-up phone call at 6 weeks post-treatment. These participants will also complete a follow-up assessment 6 weeks after treatment ends.

Aim 2 Study Design



Our **primary outcome** will be for participants in the *SCThrive* group to demonstrate greater BA at post-treatment than the attention control group. Our *secondary outcome and exploratory aim* will be greater improvements in self-management behaviors and quality of life at the six-week follow-up.

SCThrive Intervention: SCThrive consists of six weekly group sessions. Three sessions will be held in-person at CCHMC while the other three will be held online via Skype for Business or Zoom™, group video chat programs. To promote engagement during video chats, therapists will call AYAs by name to join in discussions and brainstorms consistent with the intervention. In addition, AYAs will designate another individual (most likely their caregiver) to receive reminders about their action plans. Two therapists (doctoral level clinical psychologists or graduate students) trained in delivering *SCThrive* and in cultural sensitivity will co-facilitate all sessions (see Table 2 for information on Intervention Sessions). *SCThrive* incorporates several components of culturally-sensitive clinical interventions with African-Americans including its emphasis on becoming an active member of the healthcare team (advocacy), assessment of stress related to SES and ethnic minority status (PAT 2.0), flexible and home-based design, and inclusion of culturally-relevant content (AYA with SCD co-designed *iManage*; use of culturally sensitive and age appropriate book on SCD management, Hope and Destiny Jr.[87]; developmentally appropriate scenarios/exercises for the 13-17 and 18-21 age groups).[88] Participants will also receive the Living a Healthy Life with Chronic Conditions book.[89] The *iManage* app is accessible on smartphone or tablet; it is an essential component of the intervention because it: 1) visually reinforces the connection between SCD symptoms and self-management behaviors; 2) provides visual feedback on self-management goal progress; 3) facilitates peer support for self-management; and 4) allows AYA to track daily pain, fatigue and mood symptoms. We will ask participants in the first three SCThrive groups to participate in usability testing to ensure the iManage app is easy to navigate and that that is it having the desired result. Pilot group participants reported that they would need the ipad to log on for the 8th session so we changed the 8th session to an in-person session so they could turn in their ipads at that session. Since feedback from the pilot group was so informative and beneficial, we have asked two young adults from the pilot group to participate as members of the Intervention Development Team (we will enroll up to 4 to ensure that at least 2 can attend meetings regularly). They will be responsible for advising on study recruitment and retention, study procedures and dissemination of study results. They will be compensated for their participation and sign a consent form. These team members will also be asked to pilot accelerometers to evaluate whether they would be a value add to the SCThrive intervention and should be incorporated in future iterations (next grant application).They will be asked to sign an accelerometer use agreement.

Table 2. Intervention Target by Treatment Sessions

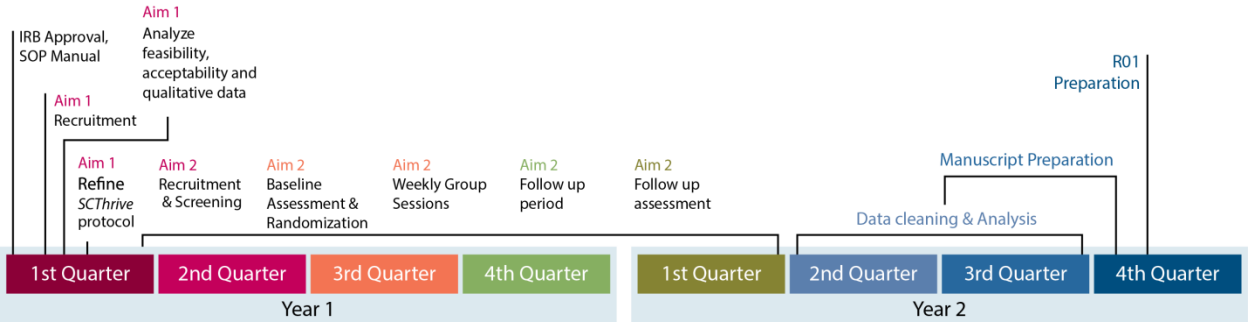
Week (Location)	Topics	Behavioral Activation (BA) Target
1 (in-person)	SCD Knowledge, Self-Monitoring, Action Planning	Knowledge, Self-Efficacy, Readiness for Change, Family/Social Support
2 (in-person)	Communication, Problem Solving, Action Planning	Skills, Self-Efficacy, Family/Social Support
3 (online)	Pain Management, Mood Management, Action Planning	Mood, Self-Efficacy, Skills, Family/Social Support
4 (online)	Cognitive Restructuring, Action Planning	Self-Efficacy, Skills, Family/Social Support
5 (online)	Managing Emergencies, Treatment Adherence, Action Planning	Knowledge, Skills, Self-Efficacy, Resources, Family/Social Support
6 (in-person)	Decision Making, SCD Health Behaviors, Action Planning	Skills, Knowledge, Self-Efficacy, Resources, Family/Social Support
Booster (in-person/online)	Review of skills, Progress Updates, Action Planning	Self-Efficacy, Readiness to Change, Family/Social Support

Attention control arm: Additional trained therapists (not conducting *SCThrive*) will conduct the attention control intervention which consists of 6 weekly 15-20 minute individual phone calls and a follow-up up phone call on the following educational topics: Session 1: What is Sickle Cell Disease?; Session 2: It's in the Genes; Session 3: SCD Complications; Session 4: Treatments for SCD; Session 5: Healthy Living with SCD; and Session 6: Navigating Health Insurance.[91-93]

5. DURATION

The project will begin in April 2016 and conclude in March 2018. *Figure 2 displays the project timeline.*

Figure 2. Study Timeline



6. SELECTION & RECRUITMENT OF PARTICIPANTS

Study Population

The study population will consist of 72 AYAs with SCD recruited from the CCHMC Sickle Cell Clinic. Eight (8) participants will be recruited for Aim 1 (feasibility, acceptability, intervention refinement) and 64 participants for Aim 2 (pilot two-arm randomized trial comparing efficacy of *SCThrive* to Attention Control) with the goal of retaining 54 for analyses (see recruitment strategies).

Inclusion Criteria

We will use the following inclusion criteria for study participants:

1) Patient of CCHMC Sickle Cell Clinic.
2) Confirmed diagnosis of SCD with SS, SB^0Thal or SC genotype.
3) 13-21 years of age.
4) On or eligible for disease-modifying therapies.
5) Caregiver (or AYA $\geq$ 18 years) consent that the participant will be the sole user of the tablet, report immediately if it is damaged or lost, return it at the end of the study, and log on to sessions from a private location.

Exclusion Criteria

We will use the following exclusion criteria for study participants:

1) another chronic disease (which would complicate measurement of behavioral activation);
2) Non-English-speaking (<5% of the target population); or
3) cognitive or psychiatric disorder that the physician or study therapists believe would impair study participation. Patients who desire participation but are not eligible will be referred to the SCD Clinic social worker for assistance with self-management as this is the usual procedure.

Recruitment

Potentially eligible AYAs will be identified through CCHMC's electronic medical record (EMR). Those meeting entry criteria will be sent a letter and flyer signed by the PI and the hematology clinical director telling them about the study and offering them the opportunity to call if interested. A trained clinical research coordinator will follow-up with a phone call to eligible participants to describe the study, answer any questions and schedule a time for interested participants to come in for a baseline visit. Eligible participants with a scheduled clinic visit will be approached to see if they would like to enroll during the visit. Eligible patients who are hospitalized will be approached only if the medical team feels it is appropriate or the patient requests more information about the study. After written informed consent/assent is obtained, AYAs and caregivers will complete baseline measures.

We will screen 85-100 AYAs with SCD (eligible pool) with the goal of recruiting 64 new AYAs with SCD (did not participate in Aim 1) using Aim 1 inclusion/exclusion criteria. After baseline assessment, we will review EMR data to determine disease severity (severe = history of acute chest syndrome, prior stroke or more than three vaso-occlusive crises in the past three years; not severe = these complications are not present) [90].

The study statistician will use computer-generated randomization tables. Participants will be blocked on age (ages 13-17; ages 18-21) and disease severity (severe/not severe) and then randomized to one of the study arms to ensure equal distribution across groups.

Retention

To promote retention, AYAs will provide emails, all phone numbers, and contact information for others (i.e. parent-guardian, grandparents) in case they cannot be reached. In addition, participants will receive a calendar of study visits and electronic appointments. To facilitate communication, study staff will use a dedicated texting enabled cell phone.

7. PROCESS OF OBTAINING CONSENT

Written informed consent/assent will be obtained by trained research staff when this is not possible phone consent will be obtained and written consent faxed or mailed to the CRC. All pertinent aspects of consent/assent will be covered including study purpose, risks/benefits, confidentiality, and right to withdraw. Patients will be informed that their care at CCHMC will not be affected by whether they choose to participate in the study. Caregivers and/or patients and study staff (co-investigators or research assistants) will sign and date the consent and permission form to document the informed consent process. Caregivers and/or patients will receive a copy of the signed and dated consent form to keep. Patients under age 18 will be asked to sign an assent form that is written at the 7th grade reading level or below.

8. STUDY PROCEDURES

Aim 1: We will conduct two successive groups of 4 AYAs with protocol refinements after the first group and further refinements after completion of the second group. These AYAs will participate in focus groups at the end of treatment to provide additional information about *SCThrive's* format, content and acceptability. Participants will also complete measures at baseline and post-treatment (see Table 3).

All *SCThrive* participants will receive a Wi-Fi enabled, insured, tablet computer with a cellular data plan that will facilitate: 1) standardization of intervention delivery; 2) consistent access to a computer and internet service; and 3) study personnel monitoring of tablet use. During the first session, AYAs will be assigned a unique username and password for the *iManage* tool and sign a iPad use agreement (see epas). The CRC will provide instructions, demonstrate system features, and assist AYAs in starting their patient profile, selecting a self-management goal (action plan), and scheduling reminders. The CRC will be available by cell phone for troubleshooting.

After obtaining consent, a member of the research team will schedule the first study visit with the participants. Subsequent study visits will be scheduled via phone, e-mail, or in-person contact with a member of the research team. All study visits will last approximately one to two hours and will be conducted in a conference room in the D building, Behavioral Medicine and Clinical Psychology clinic space or online.

Aim 2: Participants will complete two or three study visits as part of this study. Study visits will occur at baseline (screening), post-intervention, 2 weeks post-intervention (week 8), and 4 weeks- post-intervention (week 12). The SCD population has a high rate of no-shows and cancellations due to psychosocial factors that interfere with access to treatment but to increase the likelihood of participant retention while minimizing participant burden, measures can be completed within a one month window of each study visit date. To minimize participant burden, follow-up study visits will be coordinated with SCD clinic appointments when possible or scheduled at another time convenient for the participant and their family. To maximize attendance at study visits, a member of the research team will remind the participants of upcoming research visits via phone call, text, or e-mail as preferred by the participant.

SCThrive arm. Four successive groups with four to eight participants per group will be conducted. Participants will receive the finalized six-week *SCThrive* intervention sing procedures described in Aim 1. To encourage retention and skill maintenance, participants will receive one online/in-person booster session two weeks after treatment ends. Based on feedback from the Intervention Development Team we will allow participants who cannot attend the in-person session due to illness or other factors to attend online via ZOOM. We will also allow participants to review a missed session recording before the next session with the CRC.

Attention control arm. Additional trained therapists (not conducting *SCThrive*) will conduct the attention control intervention which consists of six weekly 15-20 minute individual phone calls via Zoom. Participants will receive one online booster session two weeks after treatment ends.

Assessment Strategy. AYAs will complete questionnaires assessing BA, self-management behaviors (including healthy lifestyle behaviors), quality of life, and depressive symptoms (which can impact BA; Beck Depression Inventory-II)[94], at baseline, post-treatment, and six-weeks after treatment (see Table 3). Caregivers or AYAs ≥ age 18 will complete demographic (e.g. parental

education, family income), psychosocial (Psychosocial Assessment Tool – PAT 2.0 General)[74,95], barriers to care (Barriers to Care Questionnaire – BCQ)[96] measures at baseline. Caregivers will also complete a quality of life measure at baseline and post-treatment. We will collect ER visits, disease severity, and hospitalization data from the EMR. *SCThrive* satisfaction and usefulness will be assessed after each session. Feasibility, acceptability, and *iManage* usage measures will be completed at post-treatment. The *iManage* tool will provide usage data on the number and frequency of logins, pages visited, time spent on each page, and number and time of action plan reminders. Based on feedback from the pilot group, we added a health motivation measure (Treatment Self-Regulation Questionnaire – TSRQ[109]) to capture the social support and healthcare knowledge and skills participants reported were significant benefits of participating in the intervention. In addition, since our original submission an SCD-specific measure of self-management/ transition readiness has been published[110-111]. We have now added these two measures to the battery and will increase our compensation accordingly. We also added a feasibility measure for the SCHealthEd treatment and a qualitative interview for the SCThrive treatment to help us better understand participant perceptions and experiences with the intervention.

Table 3. Assessment Strategy

Construct	Measure	Brief Description/Score Used/ Psychometrics
Primary Outcome Measure		
Behavioral Activation (BA) (AYA report)	PAM-13[97]	Measures skills, knowledge, confidence and readiness for self-management; Total Score; used in many studies of BA and self-management[22,40,98,99]; α = .87
Secondary and Exploratory Outcome Measures		
Self-management behaviors (AYA report)	TRAQ-5[100] ; Youth Risk Behavior Survey items[101]	Measures managing medications and appointments, tracking symptoms, provider communication, daily interference and physical activity, eating, sleeping and fluid intake; TRAQ Total Score (α = .82-.92) and Youth Risk Behavior Survey item mean scores; N/A
Self-management behaviors (clinician rating)	TRxANSIT Scale V4[102]	Semi-structured interview that assesses knowledge of chronic health condition, medications, adherence, nutrition, self-management skills, insurance, and finding a new health care provider); Knowledge of Chronic Health Condition, Medications, Adherence, Self-Management Skills Subscales; *r* = .71
Medication Adherence (clinician rating)	Medical Adherence Measure (MAM)[103]	Semi-structured interview with four general modules to assess adherence with medication, diet, exercise, and clinic attendance; Medication Domain; *r* = −.40; *r* =.89
SCD-specific quality of life (Caregiver & AYA report)	Peds-QL SCD Module[90]	Measures several domains of health-related quality of life including pain impact, fatigue, pain management, emotions, communication and treatment adherence; Total Score; α = .95
SCD Knowledge (AYA report)	SCD Knowledge Questionnaire[10]	Measures SCD knowledge including pathophysiology, treatments and self-management; Total Score; α = .79
SCD Self-Efficacy (AYA report)	Sickle Cell Self-Efficacy Scale[4]	SCD self-efficacy scale validated in adolescents with SCD; Total Score; α = .87
Self-Regulation (AYA Report)	Treatment Self-Regulation Questionnaire (TSRQ)	Measures the degree of motivation an individual has towards changing/maintaining health behaviors; Total Score; α > .73.
SCD Transition Readiness	Transition Intervention Program Readiness for Transition (TIP-RFT)	Measures healthcare knowledge and skills, education and vocation planning, social support skill set, and independent living skills.
SCD Readiness to Change (AYA report)	SCD Readiness to Change for Self-Management Scale[3]	Measures amount of prior thought, knowledge, interest, anticipated difficulty and perceived importance about self-management; Mean Scores; N/A
Covariates		
Medical Covariates (EMR review)	Medical Background Case Report Form	ER visits, Hospitalizations, Treatment type
Demographic Covariates (AYA or Caregiver)	Demographics Form	AYAs age, gender, SES, SCD type, parental education, family income level
Treatment barriers (AYA or Caregiver)	Barriers to Care Questionnaire (BCQ)[68]	Sociobehavioral factors that interfere with successful interaction with the health care system

Table 3. Assessment Strategy		
Construct	**Measure**	**Brief Description/Score Used/ Psychometrics**
Psychosocial barriers (AYA or Caregiver)	Psychosocial Assessment Too [74,95]*	Assesses level of psychosocial risk for families of patients with a chronic illness
Feasibility & Acceptability		
Feasibility/ Acceptability/ Satisfaction (AYA report)	SCThrive Feasibility & Acceptability SCThrive Satisfaction Survey SCThirve Follow-up Questionnaire SCHealthED Feasibility & Acceptability	AYA opinion regarding the format, content, satisfaction and usefulness of SCThrive and SCHealthEd
Feasibility/ Acceptability/ Satisfaction (AYA report)	iManage Feasibility & Acceptability Survey iManage Usage Survey	App characteristics, usefulness and computer/internet use
iManage Usability	Internet Background Questionnaire & Post Questionnaire	Assesses usability of the iManage app
SCThrive Group Qualitative Interview	SCThrive Feasibility Interview	Assesses usefulness and satisfaction with SCThrive in an interview format

**Psychosocial Assessment Tool: Patients complete this annually during clinic visits in hematology. We will get permission from participants to use this data. We will only administer it if it has not been completed in the last 12 months. To decrease participant burden, we will then provide the PAT data to the clinic (so the participant will not have to complete it again – see consent form).*

Independent evaluators. Trained independent evaluators blinded to treatment assignment (doctoral psychology graduate students) will administer self-management and treatment adherence measures (clinician ratings); one evaluator will review 25% of intervention sessions for fidelity.

9. DATA ANALYSIS/METHODS

Analytic Plan. We will use Mplus (Version 7.20)104 to conduct our analyses. Descriptive statistics (e.g. proportions for dichotomous variables, means, and standard deviations) will be calculated for all measures of interest. Outliers will be examined and kept in final analyses, unless substantial evidence is available for their deletion (e.g., data errors). When testing statistical hypotheses, statistical model assumptions will be examined.

Aim 1: Determine the feasibility and acceptability of the SCThrive intervention for adolescents and young adults with SCD. ***Feasibility*** of SCThrive will be assessed by the proportion of eligible patients approached for the study who consent to participate and attend at least 4/6 sessions. ***Acceptability*** will be assessed by qualitative analysis of focus groups at the end of treatment. The focus groups will elicit the AYAs overall impression of the program, the mixed format, how well they perform skills, and the progression of activities, as well as content- and format-specific feedback on the integration of iManage and SCD content, interest level, and length of sessions.

Aim 2: Conduct a pilot randomized trial (final N=54 assuming 15% attrition) to determine whether the refined *SCThrive* intervention is superior to attention control in improving BA in AYAs with SCD ages 13-21. A 2 (group; treatment vs. control) by 2 (time; Pre-/Post-test) mixed ANCOVA analysis will be used, with BA (PAM-13) as our primary outcome, time and group as main effects, and a time*group intervention effect, to determine the needed effect size estimates. The statistical test of the interaction will be the primary tests of the efficacy of the *SCThrive* intervention. If statistically significant, the group*time interaction would indicate BA changed differently across time between the two groups and effect sizes (d) will be calculated

for all significant simple main effects and simple comparison effect size calculations described above.

Exploratory Aim: A MANOVA will be used to test for significant group (*SCThrive* vs. attention control) differences on improvements in self-management behaviors and quality of life scores at three months. A significant omnibus test will be followed with simple comparisons and computation of effect size estimates (d).

Power Analysis. We chose the PAM-13 (BA) as our primary outcome for power estimates because the General Linear Modeling analyses found a significant improvement in PAM-13 means from pre-test to post-test for the in-person self-management versus the self-management online portal groups, whereas the responsiveness of the other measures (e.g. SCD quality of life) may require a longer time-frame. The average effect size (eta-squared) for the change in BA was η^2= 0.14, which is a large effect. A 2 (treatment vs. control) by 2 (pre-test, post-test) mixed effects ANCOVA power analysis was conducted using the internal Monte Carlo simulation capabilities of Mplus (Version 1.20)[104] under the following assumptions: 1) the attention control arm will show a d = 0.30 effect size improvement in BA from pre-test to post-test, 2) based on the effect size obtained from pilot data analyses (i.e., η^2= 0.14), the *SCThrive* intervention arm will show a d = 0.90 effect size improvement from pre-test to post-test, 3) participants assigned to the SCThrive intervention arm will show in incremental effect of (0.90 – 0.30 = 0.60) d = 0.60 over participants assigned to the attention control arm, and 4) the inclusion of two control covariates (treatment type and baseline healthcare utilization), together with blocking on participant age and disease severity prior to randomization, will explain 40% (i.e., R2 = 0.40) of post-test BA score variance. Results from the Monte Carlo simulation analyses based on 5,000 simulated datasets showed power will be > 0.80 to detect the d = 0.60 anticipated incremental improvement for the *SCThrive* intervention arm if recruitment, N = 64, results in a post-attrition N = 54 (N =27 per group) available for statistical analysis.

10. FACILITIES & PERFORMANCE SITES

The research will take place in the following locations:

a. Location D Conference Rooms
b. Location A – CBDI clinic, day hospital, inpatient rooms
c. Location T - BMCP or CRC conference rooms

11. POTENTIAL BENEFITS

Based on our prior work with group self-management interventions, we expect that *SCThrive* participants will most likely experience direct benefits including improved behavioral activation, self-management, better ability to cope and improved mood and functioning. In addition, all participants may receive some benefit from completing disease self-management measures. If successful, this line of research has the potential to significantly impact clinical care for all AYAs suffering from SCD and improve their psychological and physical health outcomes.

12. POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES, AND PRECAUTIONS

Overall, this study presents minimal risk to participants. To further minimize risks and protect participants' confidentiality, all members of the study team will have completed mandated training procedures and certifications. Specific risks are noted below.

1. **Emotional/clinical distress.** Asking AYA with SCD to complete self-report measures about their symptoms, physical and psychological functioning typically does not result in distress. However, some AYA may report depressive affect or suicidal thoughts or become emotionally distressed when discussing their disease self-management.
2. **Hassles/frustrations.** It is possible that teens may not like the *iManage* app or receiving messages (electronic reminders) from other group members or the individual they designate for their secondary reminder.
3. **Confidentiality & Privacy.** The primary risk of this study is the loss of confidentiality in three main ways: 1) considering focus groups and the group-based intervention involve collaboration and support among the participants, there is an inherent loss in privacy between group members; 2) loss of confidentiality or privacy that may occur if participants log onto to the group video chat from a public or semi-public location; 3) inadvertent and unauthorized release of PHI to individuals outside the study or research team.

Protections Against Risk

1. **Emotional Distress**. In the event that a participant becomes emotionally distressed during their study participation or a participant reveals severe depressive symptoms or suicidal ideation (e.g. on the Beck Depression Inventory-II), the PI (Dr. Crosby, a licensed psychologist) will be immediately notified. A risk assessment, including detailed information about suicidal ideation, intent and/or plans, access to means to hurt themselves, major stresses, availability of social supports, access to treatment, and plans for safety will be discussed in detail with the subject. The assessment will be conducted by either the PI or Dr. Joffe, also a licensed clinical psychologist, with extensive experience in the treatment of SCD patients. A referral to the Emergency Room (if necessary), and/or a referral to the Psychiatry Division or our outpatient Psychology clinic, as appropriate, will be made. All actions taken will be documented in the participant's confidential folder. The *SCThrive* intervention will be delivered by a highly trained psychologist (Dr. Joffe) and an experienced clinical psychology graduate student (Ms. McCuistian) supervised by the PI (Dr. Crosby) who is an expert in cognitive behavioral and self-management interventions.
2. **Hassles/Frustrations**. During the consent process, participants are told of the possible hassle/frustration caused by the receipt of reminders to complete self-management goals and action plans. Study personnel will be trained to give participants the proper instructions to change the frequency, alter the sound (new ringtone, vibrate), or delete the reminders at any time. Additionally, the participant is given the contact information of a research coordinator who is able to assist them in making necessary changes to reminders.

3. **Confidentiality & Privacy.** All personnel will participate in training on protecting the rights and welfare of human participants in research. Personnel will all complete an online tutorial and satisfactorily complete an electronically-administered examination testing knowledge and application of the ethical principles and Federal regulations protecting human participants in research as described in the Belmont Report and Title 45 Code of Federal Regulations Part 46.

Adverse events will be reported to the IRB during continuing review, while serious adverse events will be reported to the IRB within 24 hours.

13. RISK/BENEFIT ANALYSIS

Based on a risk/benefit judgement and our knowledge of the study procedures, the risk of adverse effects is minimal. The potential benefits to participants such as improved ability to self-manage, which lead to overall improved quality of life may outweigh any minimal risks participants may experience. The potential benefits of this study including improvement of knowledge of SCD, self-management, and quality of life in adolescents with SCD serve as justification for the minimal risks associated with this study.

14. DATA SAFETY & MONITORING

This project includes a small scale clinical trial in Phase 2 and we recognize the need to provide a plan to ensure scientific integrity and safeguard the well-being of study participants. As such, the PI and research team will plan regular monthly meetings to monitor the progress of the study, the integrity of the treatment and safety monitoring, including a review of any adverse events. If participants experience any adverse events, investigators will follow up participants and provide treatment until the event has subsided. Investigators will be available 24 hours via pager. The PI will report any significant study-related or unanticipated adverse events to the Institutional Review Board and to the study sponsor based upon institutional and sponsor guidelines. Given that this study is an initial exploratory study with a single treatment arm, it is felt that monitoring at the level of the PI and research team, with oversight from the IRB and study sponsor, is sufficient.

15. PRIVACY & CONFIDENTIALITY

The informed consent process will address various aspects of participant privacy including the level of control over the circumstances and extent of sharing one's personal information. As stated above, participants will only be approached by study personnel after initial interest is obtained through their provider. The nature of the intervention (e.g. group self-management sessions) leads to a loss of privacy as participants will be able to identify each other. They may also be identified by others if a participant logs onto the group video chat in a public location. This will be explained to participants as a compromise of the security of the data and part of the consent form. If a participant logs on from a public place, the clinical research coordinator will end the call with the participant and call them individually to problem solve an alternate location. If a suitable private location cannot be found, the participant will be asked to turn off their webcam and participate by phone or set an appointment to review the recorded session at a later date. During the informed consent process, the study personnel will explain these risks and the nature of the interaction with other participants. At that time, the potential participant may 1) decline to participate or 2) agree to participate with the understanding that they may withdraw at any time. This will give the participant control over the circumstances of sharing their personal information. To minimize privacy risks, all participants will also be required to sign an agreement that the AYA will log on to sessions from a private location. Study personnel will screen all questionnaires for completeness; participants are allowed to skip any survey questions they do not wish to answer, thereby providing additional control over the extent of sharing personal information.

15.1 Data De-Identification

All data will be de-identified with the use of unique assigned study identifier codes. Study identifier codes will be used on study measures for data entry and adherence electronic monitor

data download. No other identifying data such as date of birth, address, phone numbers, social security number, or zip code will be entered on electronic measures. Electronic data files (including downloads of data from REDCap or DDC measures) will only identify participants via study identifier codes and will be password protected. Electronic data files will be maintained on CCHMC hard drives.

15.2 Data Storage

Informed consent documents will be maintained in locked storage cabinets within Dr. Crosby's locked office at CCHMC. Consent and permission forms will be kept separate from participant's data. Only the study investigative team will have access to the keys to the cabinets. Medical chart data will be collected by trained study staff under the supervision of the PI. These risk protection methods have been effectively used by the PI and her mentors and consultants for numerous studies.

Individual data will not be available to anyone not directly associated with the study. All study personnel have been trained in data safety and monitoring, privacy and confidentiality, minimizing risks related to loss of privacy and confidentiality. We will closely monitor performance of our research personnel to ensure the strictest standards. Study-related information will not be released without written permission of the participant (and parent or legal guardian, when applicable).

16. COST OF PARTICIPATION

No payment from participants will be required to participate in this study. Participants will be responsible for the usual costs of medical care.

17. PAYMENT FOR PARTICIPATION

17.1 Assessments (baseline, post-intervention, 2 weeks post-intervention, 6 weeks post-intervention)

Compensation for baseline measure completion (est. completion time: 50 minutes) is set at $35 based on previous studies. The goal is that baseline questionnaires will be completed directly following a clinic visit, but subsequent study visits may require additional trips to CCHMC so a graduated incentive schedule will be used. *SCThrive* Pilot Group*, SCThrive* Intervention Arm*, and* Attention Control Arm participants will be compensated $35 for the baseline assessment, $55 for the post-treatment (week 6), and $60 for the week 12 assessment ($150 total). All payments will be in the form of a reloadable debit card (ClinCard) and participants will receive a handout that will explain how to use the card. Money will be loaded onto their cards after each visit based on the schedule listed below.

Assessment Compensation	
Visit Type	**Compensation**
Baseline Measure Completion	$35
Post-Treatment Measure Completion	$55 ($25 if complete SCThrive qualitative interview for a total of $80)

12 week Measure Completion	$60

17.2 Intervention Compensation

Intervention Development Team:

$360 for attending the majority of the study meetings by phone/in-person as well piloting new intervention tools and completing measures. These measures will help us evaluate the usefulness of the intervention tools.

Participants will be compensated for their time and participation in *SCThrive* sessions and Attention Control phone calls ($35 per session/phone call). Based on feedback from the intervention development team, we will clearly identify the portion of the compensation that is for tracking pain/mood via the iManage app for *SCThrive* Intervention Arm participants. If all 6 sessions/phone calls are completed, participants will receive a total of $245. Attention control participants will receive $35 for the booster phone call (making the total possible $245).*SCThrive* Intervention Arm participants will be asked to return their tablet at the 8th session (booster session); therefore, this treatment session offers a significantly higher compensation rate of $60. All payments will be in the form of a reloadable debit card (ClinCard) and participants will receive a handout that will explain how to use the card. Money will be loaded onto their cards after each visit based on the schedule listed below.

Pilot and Intervention Studies Compensation	
Visit Type	**Compensation Total**
***SCThrive* Pilot Group**	$210
Intervention Study	
SCThrive Intervention Arm (6 sessions +1 booster)	$270
Attention Control Arm (6 sessions + 1 booster)	$245

17.3 Transportation

Many families report that transportation is a barrier to participation. Therefore, participants will receive compensation for their travel to complete assessments (baseline, post and 3-month). Data from our previous 6 week group self-management intervention indicates that approximately 25% of participants needed taxi cabs. On average, taxi roundtrip transportation is < $35. The participants not using taxi services also required transportation assistance for gas or to pay a family member/friend for gas. Pilot group participants reported that $10 was sufficient for transportation reimbursement given current gas prices.

To minimize transportation needs, we will have participants in the *SCThrive* pilot group and *SCThrive* Intervention arm complete the post-assessment on the same day as their last intervention session.

1. The *SCThrive* pilot group will consist of 8 participants who will have 3 in-person visits (session 1, session 2 & session 6/post-assessment). We are planning that 25% (3) of

participants in the *SCThrive* pilot group will require taxi compensation for study visits, and the other 75% (5) of participants will require $10 for transportation compensation.

2. The *SCThrive* Intervention Arm will consist of 32 participants who will have 3 in-person visits (sessions 1, 2 & 6), 14 of whom will have an additional 2 in-person visits (booster session and 3 month follow up). We are planning that 25% (8) of participants in the *SCThrive* Intervention Arm will require taxi compensation for study visits, and 75% (24) of participants will require $10 for transportation compensation.

3. The Attention Control Arm will consist of 32 participants who will have 1 in-person visit for their post-assessment. We are planning that 25% (8) of participants in the *Attention Control* Arm will require taxi compensation for study visits, and 75% (24) of participants will require $10 for transportation compensation.

All payments will be in the form of a reloadable debit card (ClinCard) and participants will receive a handout that will explain how to use the card. Money will be loaded onto their cards based on the parameters described above.

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