CORRELATION BETWEEN BARRIERS TO ADHERENCE AND TREATMENT SATISFACTION OF HYDROXYUREA IN INDIVIDUALS WITH SICKLE CELL DISEASE

by

Anusha Vaidyanathan

B.Sc Advanced Zoology and Biotechnology, Madras University, India 2012

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This thesis was presented

by

Anusha Vaidyanathan

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and approved by

Thesis Director:
Lakshmanan Krishnamurti, M.D., Ph.D.
Director of BMT Program and Professor of Pediatrics
Department of Pediatrics, Emory University School of Medicine

Committee Members:
Dr. Gregory Kato, M.D.
Professor of Medicine, Department of Pediatrics, School of Medicine, University of Pittsburgh

John Shaffer, Ph.D.
Assistant Professor, Human Genetics, Graduate School of Public Health, University of Pittsburgh

Robin Grubs, M.S., Ph.D.
Assistant Professor, Human Genetics, Graduate School of Public Heath, University of Pittsburgh

Jeremy Martinson, PhD.
Assistant Professor, Infectious Diseases and Microbiology, Graduate School of Public Health, University of Pittsburgh

Lakshmanan Krishnamurti, M.D., PhD.

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Anusha Vaidyanathan, M.S.

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ABSTRACT

Sickle cell Disease (SCD) is an autosomal recessive disorder that affects 50,000 to 100,000 people in the United States. This disorder is characterized by pain episodes, acute chest syndrome, splenic sequestration, infection, stroke, aplastic crisis, and priapism. Hydroxyurea (HU) is a drug that is clinically effective in reducing pain episodes, hospitalizations, and total health care costs. However, studies show that HU continues to be underutilized in individuals with SCD. There is evidence to suggest poor adherence to HU among people in this population and studies have identified a number of barriers at the patient, caregiver, provider and system wide levels. Issues with adherence strongly impacts Health Related Quality of Life (HRQOL) of individuals with SCD, making it a public health concern. While there are reports available in the literature on the qualitative analyses of barriers experienced by this population, there have been no known studies that have examined patient reported treatment satisfaction. Our hypothesis is that barriers to adherence of HU and treatment satisfaction play a significant role in medication adherence.

The objective is three-fold:

1. To determine the barriers to adherence of hydroxyurea for individuals with SCD
2. To determine the treatment satisfaction of hydroxyurea in individuals with SCD
3. To determine any correlation between the treatment satisfaction and the barriers to HU

The participants in this study include individuals who have been on HU for at least 6 months. Pediatric, caregiver and adult participants were recruited from the University of Pittsburgh Medical Center and Children's Healthcare of Atlanta. Only adult participants were recruited from Children's National Medical Center, Washington DC. The information was collected using two surveys administered to all individuals. The TSQM-9 (Treatment Satisfaction Questionnaire for Medication) was used to evaluate Hydroxyurea treatment satisfaction in patients. The Adherence Starts with Knowledge (ASK-12) survey along with the additional barriers survey were used to evaluate the barriers to adherence of Hydroxyurea. All surveys were modified for caregiver responses in the pediatric settings. The surveys were administered over a period of one year.

The results of this study revealed low levels of barriers and moderately high levels of treatment satisfaction. The survey results indicate that two specific questions present in the additional barriers surveys may be examined in greater detail. Weak linear correlation was observed between several categories of barrier surveys and the subsets of the treatment satisfactions survey.

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1.0 INTRODUCTION

Sickle cell disease (SCD) is an inherited blood disorder that affects 50,000 to 100,000 people in the United States and over 250 million people worldwide. It is a chronic disabling disorder that can decreases one's life expectancy by 25-30 years.[1] This disorder is clinically characterized by vaso-occlusive episodes and hemolysis. Individuals with SCD are often hospitalized for acute complications such as painful episodes, acute chest syndrome, splenic sequestration, infection, stroke, aplastic crisis and priapism. [2] Treatment and management of complications related to SCD involves home remediation or treatment in the Emergency Department (ED). This condition has a negative impact on the quality of life for children, adolescents and adults who are affected. [2; 3]

In the United States, it is mandatory that all newborns be screened for hemoglobinopathies (including SCD) in order to start prophylactic treatment and anticipatory guidance. Hydroxyurea (HU) was approved in 1996 for treatment of symptoms in individuals with sickle cell anemia.[1; 4] HU is a myelo-suppresive agent that raises the levels of fetal hemoglobin in the bloodstream. This effectively decreases the rate of vaso-occlusive and acute chest syndrome episodes by 50%. [5] Clinical studies show that individuals regularly using HU over a period of time show reduced mortality, lower hospitalizations, and lower medical costs among people with SCD.[6; 7] HU is currently administered as an oral daily drug. [4]

Although HU has been established as an important therapeutic agent, there is evidence to support that it is underutilized in individuals with SCD. Adherence to HU has been determined to be a very important concern for individuals being treated. Physician reports claim that two thirds of their patient population has concerns with adherence.[8] In two large clinical studies involving pediatric patients, 10% to 20% of participants stopped taking HU because of non-adherence. Non-adherence is also expected to be higher outside of a clinical trial. [9]

Barriers to adherence of HU have been identified at the patient, provider and system level and are described in the National Institutes of Health (NIH) Consensus Development Conference. At the patient level, barriers that have previously been outlined include lack of access, lack of knowledge, fear of side effects, concerns for male infertility, cost of medication, patient compliance with blood tests and taking medication.[10] Other barriers that have been determined include frequent monitoring, unavailability in pharmacies and time taken for benefits to become apparent. [1; 9] There is limited research that has assessed patient perceived treatment satisfaction to HU as a medication.

This project recognizes the need to identify patient reported barriers to the use of hydroxyurea and understand patient reported treatment satisfaction of HU. It aims to determine hydroxyurea specific barriers for sickle cell disease, as well as patient perceived treatment satisfaction for this drug and to check for any correlation between HU specific barriers and patient reported treatment satisfaction. One hundred and forty nine individuals from three different locations participated in this study by completing qualitative surveys for treatment satisfaction and barriers to Hydroxyurea adherence. The surveys were administered over a period of one year.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 SICKLE CELL DISEASE

Every year, around 2000 babies are born in the United States with sickle cell disease (SCD). SCD is both a chronic and a lifelong condition and has often been associated with a decreased lifespan. [1] This condition is most common in individuals of African, South or Central American, Caribbean, Mediterranean, Indian and Saudi Arabian ancestry. [1]

SCD is a genetic blood disorder of hemoglobin that damages and deforms the red blood cells (RBCs) or erythrocytes. In individuals with SCD, the red blood cells become deoxygenated, dehydrated, and crescent shaped. The sickle shaped RBCs sometimes break down and causes anemia. These cells tend to form aggregates or stick to the walls of the blood vessels. This blocks the blood flow in limbs or organs that causes the painful episodes characteristic of this condition. These episodes can cause damage to the eyes, brain, heart, lungs, kidney, liver, bones, and spleen. [1; 5; 11]

2.2 IMPACT ON INDIVIDUAL AND SOCIETY

2.2.1 Clinical presentation

Clinical manifestations vary with the genotype of SCD. Signs and symptoms of this condition can manifest in individuals by 5-6 months of age and continue throughout their life. Fetuses and new born children produce a high level of fetal hemoglobin (different from adult hemoglobin) and it helps them to be relatively free of the manifestations of SCD. [12] SCD can show variable presentation ranging from asymptomatic individuals to episodic pain events referred to as "crisis" events. Persistent pain is a complex phenomenon of SCD.[11] This condition can impact a variety of organ systems and cause multiple different disease-related complications. [2] Individuals with SCD are frequently seen in Emergency Departments and hospitals for their pain episodes.

Symptoms associated with Sickle cell disease:

Pain is seen in the form of vaso-occlusive episodes and can be observed in individuals as young as 6 months of age. [2; 12] Vasocclusion is an unpredictable ischemic event that occurs when the sickled RBCs block blood vessels. They can be frequent, severe and last from a few hours to weeks. [11; 13]

Some of the complications associated with SCD include Acute Chest Syndrome (ACS), aplastic crisis, acute vaso-occlusive pain, priapism in males, stroke, leg ulcers, splenic sequestration, susceptibility to serious infections, transfusion related iron overload, retinopathy, avuncular necrosis of the hip and shoulders, hemolytic anemia, chronic damage to the lungs, bones and kidneys.[1; 3; 9; 14; 15]

Organ damage often results in other long term disease related outcomes such as delayed puberty and decreased lung function.[11] Infections and lung disease are the leading causes of death in people with SCD. [1]

Sickle cell crisis can be caused by dehydration, exposure to cold, infection and environments with low oxygen tension. Pain episodes can be acute, chronic or both and are unpredictable and recurrent. [11]

2.2.2 Health Related Quality of Life (HRQOL)

The World Health Organization (WHO) defines health as being not only the absence of disease and infirmity but also the presence of physical, mental and social well-being. Health related quality of life (HRQOL) refers to the "physical, psychological and social domains of heath seen in areas influenced by a person's experiences, beliefs, expectations and perceptions". If a person has a life closer to the standard of normalcy, he/she is said to have better HRQOL. [2] A comparison of HRQOL in children with SCD and matched controls showed significantly lower overall HRQOL reported by both the children with SCD and their parents. [2]

The relationship between sickle cell complications leading to decreased health related quality of life has been well documented in both adults and youth with SCD. Sickle cell related pain events are common manifestations of this condition and are recurrent, acute and unpredictable. Studies show that more effective management of persistent pain can lead to improved quality of life in adults with SCD. [2] Fuggle and colleagues demonstrated that sickle cell pain events are associated with decrements in social and recreational functioning as well as school attendance for youths with SCD. [16] It is essential to understand the association of pain with HRQOL to improve pain management and other health related outcomes.[16] The

hospitalizations and school absences could be expected to have a negative impact in the HRQOL for children and adolescents with SCD. [2]

2.2.3 Public health implications

The HRQOL impairments for youth with SCD are associated with personal and healthcare costs in pediatric populations.[16] Adults living with Sickle cell disease have high rates of unemployment. Studies propose that the unemployment may be caused by irregular school attendance that could prevent children from acquiring adequate job skills. Studies display weak evidence to support direct links between pain severity, SCD symptoms and unemployment. [17]

SCD poses to be an enormous financial burden for individuals, families and even third-party payers. Studies suggest interventions designed to control pain episodes could help avoid hospitalizations and may help reduce personal and economic burden of the disease. [5] Pain accounts for around 80% of all hospitalizations for children with SCD. Research shows that pain is also often managed at home and therefore goes unreported.

The public health issues and policies associated with SCD vary widely by country according to the population frequency of the relevant genes and the availability of healthcare in those locations.[12]

2.3 GENETICS AND INHERITANCE

2.3.1 Molecular genetics and pathophysiology

Sickle cell disease was the first genetic disease for which a specific molecular defect in a gene was identified. It is one of the genetic conditions screened for by the newborn screening program in the United States. [1]

Sickle hemoglobin is produced when the sickle mutation is present in the beta globin coding gene. This gene is present on chromosome number 11. It is estimated that close to 2 million individuals in the United States has one sickle hemoglobin gene and one normal hemoglobin gene. They are said to have sickle cell trait.

Sickle cell disease occurs when an individual inherits the gene for sickle hemoglobin from both parents. Individuals who inherit one sickle hemoglobin gene and one abnormal hemoglobin gene from the other parent also have sickle cell disease and are said to be "compound heterozygotes". There are several genotypes that can cause sickle cell disease, namely, SS, $S\beta^0$, SC, SD, $S\beta^+$ SO_{arab}**1**

SCD is used as a broad term to define a group of autosomal recessive disorders. [12] This condition is characterized by the production of abnormal hemoglobin by the inherited sickle hemoglobin gene. The genotype of an individual is often seen to have a direct correlation with the severity of disease. [12]

2.4 PREVENTION AND MANAGEMENT

2.4.1 Prevention

Preventive approach to genetic conditions involve primary, secondary and tertiary measures. Primary preventive strategies involve taking measures to prevent the disease from occurring. They include carrier screening and genetic counseling to encourage informed decision making. Secondary prevention measures involve early detection and preclinical interventions such as newborn screening followed by prophylactic treatment of young children. These measures also include education of parents.

Tertiary prevention measures are developed to minimize the effects of the disease. They include hydroxyurea therapy, prophylactic transfusions to prevent stroke recurrence, daily folic acid supplementation to prevent megaloblastic anemia, outpatient administration of analgesics and hydration for pain control. Efforts to cure sickle cell disease using bone marrow transplantation or gene therapy are currently being investigated.[12]

2.4.2 Management and treatment

Treatment of pain episodes involve symptomatic care.[10] The current non-specific treatments involve penicillin prophylaxis, hydroxyurea, pain medications, blood transfusions and vaccines.[11] Management of complications related to sickle cell disease may require hospitalization or treatment at home, in an ambulatory setting or in the ED. Standard treatments for acute pain crisis include painkilling medications, hydration and oxygen. [1]

2.5 HYDROXYUREA

2.5.1 History

Hydroxyurea (HU) was initially synthesized in Germany in the year 1869. Around 50 years ago, it was used as an anticancer drug to treat myelo-proliferative syndromes, some types of leukemia, melanoma and ovarian cancer. It was also previously used to treat psoriasis.

The first trial conducted to observe the effects on HU in individuals with SCD was in 1984. Studies revealed increased production of the fetal hemoglobin-containing erythrocytes and diminished number of sickled erythrocytes in circulation for individuals on this medication. A HU case-control research study in the 1990s ended early because it clearly showed reduced number and severity of pain episodes in individuals on HU compared to those on the placebo.

In 1995, a randomized controlled trial for adults with SCD called the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH trial) found HU significantly reduced the number of painful events, ACS and transfusions. A nine year follow up to this study showed that HU was associated with reduction in mortality, minimum side effects, and was safe.[10] In 1998, the United States Food and Drug Administration approved HU for prevention of pain crisis in adults with SCD. [1]

HU is a myelo-suppressive agent. This drug helps increase the level of fetal hemoglobin present in the blood stream which in turn causes a general increase in the amount of hemoglobin in the blood stream that decreases the rate of pain crisis events by 50% in adults. [5]

2.5.2 Drug action and drug use

It often takes 3 to 6 months of treatment for the patient to have a clinical response to HU therapy. In 2002, NIH published recommendations for HU in children and adults which stated that HU therapy should be initialized in individuals with “frequent pain episodes”. Preventive methods for pain are limited and HU is the only drug shown to decrease the frequency of SCD associated pain events. [10]

2.5.3 Drug Efficacy

Drug efficacy can be defined as the therapeutic effect of HU in a controlled setting like a clinical trial. Response to HU therapy has been seen to vary by haplotype or genotype. HU is the only drug available for individuals with SCD that can modify disease process. The evidence for this is strongly observed in adults but is limited in children due to the nature of clinical trials in this population.[1]

2.5.4 Drug effectiveness

Drug effectiveness is the therapeutic effect of an intervention as seen or observed in patients in their usual care setting. Data suggests that specific treatments such as hydroxyurea or stem cell therapy (SCT) may improve HRQOL in children and adolescents. Ballas and colleagues (2010) used information collected in the multicenter study of HU in sickle cell anemia to report that HU improves some aspects of Quality of Life (QOL) in adult patients who have moderate to severe sickle cell anemia.[2]

Many studies indicate strong evidence to support HU's role in reducing frequency of hospitalization in children with SCD and moderate evidence to show its role in decreasing the frequency of pain events. [5]

An issue faced when determining effectiveness is that precise estimates of the number of people with sickle cell disease in the United States and the number of people receiving HU treatment is lacking. Another concern that plays a role in determining effectiveness of HU is the adherence to medication. Although data on the effectiveness of HU treatment in individuals with SCD is limited, it appears to be highly effective but underutilized. [1]

2.5.5 Cost effective

The results from a multicenter study of HU in individuals with SCD shows that adult patients treated with HU had a 44% decrease in hospitalizations compared to those taking placebo. This translated into cost savings for individuals in HU and suggests that HU therapy is cost effective.[5]

2.5.6 Short and long term effects

Leukopenia, thrombocytopenia and anemia are frequent and expected short term effects of HU therapy that usually resolve within 1 to 2 weeks. They can be anticipated and prevented by discontinuing HU treatment. Skin rash and pneumonitis are infrequently observed short term effects of HU therapy. Nausea is infrequently observed with this treatment and there is no evidence to suggest that this side effect is related to HU. Temporarily decreased sperm count or sperm abnormalities have been observed in this population but have not been sufficiently evaluated.

Side effects that have been infrequently associated with HU use include skin and nail darkening. There is insufficient or low evidence to support the association of increased risk for superficial skin cancer and permanently decreased sperm count with this treatment.

HU when taken during pregnancy can increase risk for miscarriage, birth defects, restricted fetal growth or postnatal development. There is limited research available about this and the NIH Consensus statement observes that sexually active couple should avoid pregnancy if they are on HU.

2.6 CONCERNS WITH NON ADHRENCE

Although Hydroxyurea has been established as an important therapeutic option, research shows that HU is underutilized in patients with SCD.

Patel et al. (2010) determined that in a cohort of children with SCD on HU, patients were only partially adherent to HU based on their medication refill records and therefore did not receive the full benefits of the medication. [4] Another research study reported 4% non-adherence in 17 patients who were started on HU. In two large clinical trials, it was observed that 10% to 20% of children stopped taking HU due to non-adherence.

Some issues about the use of HU include concerns about overall safety and effectiveness of drug. Researchers have found that 70% of patients who were candidates for HU were either not prescribed the medication or were not taking the medication. [5]

2.6.1 Effect of poor adherence

Pharmacotherapy can have a range of benefits including symptom reduction, preservation of physical function and improving quality of life. However the effectiveness of any medication depends on the patient's adherence to the treatment regimen. Poor adherence can limit the benefits of treatment, leading to decreased efficacy, greater adverse effects potential, disease relapse, increased medical expenditure and decreased quality of life. [18]

Poor adherence can contribute to substantial worsening of disease and increased healthcare costs. Due to this, it is essential to identify specific patients who are at increased risk for non-adherence. [4]

2.7 BARRIERS TO ADHERENCE

Barriers to HU treatment can arise at 4 levels – patient, provider, caregiver and system. The NIH consensus states that there have been no interventions performed to address such barriers. [1] The most common provider reported barrier is compliance. A survey of pediatric hematologists identified that medication compliance, laboratory monitoring compliance and contraception compliance as major barriers from the physician. [8] Providers reported that the most common reasons for patient's refusal of HU included fear of cancer and other side effects, not wanting to take medication, not wanting lab monitoring and patient's perception that the drug would not work. [10]

3.0 SPECIFIC AIMS

This study has three specific aims:

1. To determine patient reported barriers to adherence of hydroxyurea for individuals with Sickle Cell Disease
2. To determine the patient reported treatment satisfaction of hydroxyurea therapy in Sickle Cell Disease
3. To determine any correlation between patient-reported barriers to Hydroxyurea and satisfaction with medication

4.0 STUDY DESIGN AND METHODS

4.1 PROJECT DEVELOPMENT

This project was conducted in collaboration with the "Patient Centered Comprehensive Medication Adherence Management System to Improve Effectiveness of Disease Modifying Therapy with Hydroxyurea in Patients with Sickle Cell Disease" Study (also called Mobile DOT study). The Mobile DOT Study was funded by the Patient Centered Outcome Research Institute (PCORI) and is a two year research study that aims to improve adherence to Hydroxyurea in the Sickle Cell population using individualized structured interventions. This study was approved by the University of Pittsburgh IRB and began recruiting participants in February 2014. It is being conducted in three different sites – University of Pittsburgh Medical Center Hospitals, Children's Healthcare of Atlanta and Children's National Medical Center. The Mobile DOT study was reviewed and approved by the Institutional Review Boards of all three Universities (Please refer **Appendix A** for IRB approval).

This project was designed as a sub-study to analyze the patient reported barriers to adherence and treatment satisfaction of hydroxyurea. The surveys used in this project were administered as part of the baseline questionnaires in all three participating sites.

4.2 PARTICIPANT POPULATION

4.2.1 Description of study population

The participants for this study were recruited from pediatric and adult sickle cell patients who received care from the sickle cell programs at the University of Pittsburgh Medical Center Hospitals, Children's National Medical Center and Children's Healthcare of Atlanta. The participant population consists of male and female patients who were evaluated at one of the above clinics to determine eligibility as compared to the inclusion/ exclusion criteria. Patients with SCD were eligible if they have Hemoglobin SS, SC, Sß^{D}, Sß^{0}, Sß$^{0\text{-Arab}}$ or Sß$^{+}$ disease, were greater than two years of age, had been prescribed Hydroxyurea for greater than six months and were willing and able to participate in the intervention for the Mobile DOT study. Unwillingness to participate in the intervention for the Mobile DOT study was a criterion for exclusion from this study.

4.2.2 Patient recruitment

The multidisciplinary care team at the sickle cell clinics assisted in identifying individuals currently on Hydroxyurea for at least six months as prospective subjects for the study. The prospective adult participants and the parent/legal guardian of the pediatric participants were mailed a notification of the study. They were also approached directly at clinical appointments about the study by either the investigators or research staff. Prospective participants and their parent/legal guardian as applicable received an explanation of the study, were offer the opportunity to enroll in the study.

A member of the research team provided an introduction/ review of the research study, including potential risks and benefits, protocol procedures and research team expectations. Patients and/or parent/legal guardian were encouraged to ask questions. All prospective participants were informed about the voluntary nature of the study and that they can withdraw from the study at any time. Consent was obtained from participants 18 years or older, and from a parent/legal guardian for participants under 18 years of age. Assent was obtained from all minors whenever possible. A copy of the signed consent was offered to all participants, as well as parent/ legal guardian as applicable.

4.3 SURVEYS

Patients who consented to be a part of the study received the following surveys during a scheduled clinical visit.

4.3.1 Adherence Starts with Knowledge (ASK-12) Survey

The ASK-12 Survey can be used to measure adherence behavior and barriers to treatment adherence. It is a survey designed to measure and determine the barriers to adherence of a particular medication. The ASK-12 survey is a validated patient-reported measure of barriers to medication adherence and adherence-related behavior. It is a generic instrument applicable to patients regardless of their medical conditions.[19] It has also been described as a condensed tool that offers quick identification of patient specific barriers. The ASK-12 survey was developed by GlaxoSmithKline in July 2008 and was reported to demonstrate “adequate reliability and

validity".[18] Previous studies have determined that ASK-12 is a reliable and valid questionnaire for assessing patient perceptions of potential barriers to medication adherence and adherence related behavior. The questions in this survey are designed to address 3 domains or subscales, namely, inconvenience/forgetfulness (3 items), health beliefs (4 items) and behavior (5 items). (See **Appendix B** for survey questions). The ASK-12 Survey contains twelve questions and each question is scored on a Likert scale ranging from 1 to 5 for each question. The total scores can range from 12 to 60 with a higher score representing greater barriers to adherence.[18]

4.3.2 Additional barriers survey

The additional barriers survey was designed to address the barriers specific to hydroxyurea in the SCD population. This survey was created by the research team at the Children's Hospital of Pittsburgh of UPMC in February 2014 to better understand and characterize the hydroxyurea specific barriers previously reported in this patient population. The ASK-12 survey is a validated tool to look at adherence barriers to any medication while the additional barriers survey was designed to address barriers that are not present in the former survey. This survey contains ten questions that focus on issues specific to hydroxyurea that were determined after reviewing the literature. (See **Appendix B** for survey questions). This survey tool was created as part of the Mobile DOT study and has not been used before and is not a validated tool.

The survey questions are unique to different aspects influenced by Hydroxyurea consumption and are analyzed individually. Answers to each question were scored from 1 to 5 based on a 5-point Likert scale similar to the ASK-12 Survey ("Strongly agree", "Agree", "Neutral", "Disagree" and "Strongly Disagree").

4.3.3 Treatment Satisfaction of Medication Adherence (TSQM-9)

The TSQM survey was designed to evaluate and compare patients' satisfaction with a given medication.[20] Previous studies with this survey use it to compare medication adherence and treatment satisfaction. In this study, we use the TSQM-9 to measure the participant's satisfaction with hydroxyurea. This questionnaire was created by Quintiles in 2004 and modified to the current version in 2009. Several versions of the TSQM surveys have been validated and the TSQM-9 was reported as a validated measure in the article "Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medication" in April 2009. The survey is described as "a reliable and valid measure to assess treatment satisfaction in naturalistic study designs".[20] It has been reported that patient satisfaction with their medication is shown to affect treatment-related behavior such as likelihood to continue using medication, use medication correctly and adherence to medication regimens.[21] The questions in the TSQM survey are designed to address 3 domains or subscales – Effectiveness (3 items), Convenience (3 items) and Global Satisfaction (3 items). (See A**ppendix B** for survey questions). Each question is scored on a scale of 1 to 5 or on a scale of 1 to 7 using a Likert scale system. The questions are grouped into domains and each domain is scored on a scale of 0 to 100 with higher score indicating higher satisfaction.[15]

4.3.4 Survey types

Each of the above surveys were designed to be administered to adults and pediatric participants. The survey was adapted to be eligible to be administered to caregivers of pediatric participants.

4.4 DATA COLLECTION AND ANALYSIS

4.4.1 Data handling and storage

The surveys were administered as paper questionnaires to the participants during their regular clinical visits at each of the three sites. The completed surveys were uploaded onto a secure online server by a member of the research team. This server was developed and maintained by Data Warehouse Consultants.

The survey data was extracted from the online secure database on May 15th 2015 as an excel file. The data was exported to Minitab® 16 statistical software for analyses.

4.4.2 Data cleaning and scoring

The responses to all surveys were coded using the data coding function in the Minitab® 16 software. The ASK-12 and TSQM-9 surveys were coded as described in the literature.[15; 18; 20; 22; 23] The additional barriers survey were created mirroring the style of the ASK-12 survey. Thus data coding and analysis of this survey was performed similar to the ASK-12 data.

The responses to the ASK-12 survey and additional barriers survey were coded on a Likert scale from 1 to 5 with a higher score indicating higher barriers (**Appendix B)**. Raw scores were used for questions numbered 1 to 3 and 8 to 12. Reverse scores were used for questions numbered 4 to 7 in the ASK-12 Survey. Raw scores were used for questions numbered 13 to 16 and 18 to 22 in the additional barriers survey. The reverse score was used for question number 17 in the additional barriers survey.

The responses to the TSQM-9 survey were coded on a Likert scale with a higher score indicating higher satisfaction with hydroxyurea. Questions numbered 1 to 6 and question number 9 were coded on a scale of 1-7. Questions numbered 7 and 8 were coded on a scale of 1 to 5. Raw scores were used for all TSQM-9 survey responses.

Surveys completed by two participants from Children's Healthcare of Atlanta and one participant from Children's National Medical Center were disregarded as each participant attempted only one of the above two surveys.

4.4.3 Analytical methods for specific aim 1

Table 1. Categorical Classification of the ASK-12 survey

	ASK-12 Survey questions	Category
1	I just forget to take my medicines some of the time	Inconvenience/Forgetfulness
2	I run out of my medicine because I don't get refills on time	
3	Taking medicines more than once a day is inconvenient	
4	I feel confident that each one of my medicines will help me	Treatment beliefs
5	I know if I'm reaching my health goals	
6	I have someone I can call with questions about my medicines	
7	My doctor/nurse and I work together to make decisions	
8	Have you taken a medicine more or less often than prescribed?	Behavior
9	Have you skipped or stopped taking a medicine because you didn't think it was working?	
10	Have you skipped or stopped taking a medicine because it made you feel bad?	
11	Have you skipped, stopped, not refilled, or taken less medicine because of the cost?	
12	Have you not had medicine with you when it was time to take it?	

The ASK-12 survey and additional barriers survey were analyzed separately. The ASK-12 survey questions were divided into 3 main categories – inconvenience/forgetfulness, health beliefs and behavior based on instructions from validated literature.[18; 23] **Table 1** displays the categorical classification of the ASK-12 questionnaire.

The additional barriers survey were divided into 4 categories – side effects, difficulty, transportation and follow up. **Table 2** displays the categorical classification of additional barriers questionnaire.

Table 2. Categorical Classification of Additional Barriers Survey

	Additional Barriers Survey Questions	Category
1	I do not like taking Hydroxyurea because I have to get monthly blood draws	Side effects
2	It is hard for me to get to monthly clinical visits because of my schedule	Difficulty
3	It is hard for me to get refills of Hydroxyurea from the pharmacy on time	Difficulty
4	I am afraid Hydroxyurea will cause me to gain weight or lose my hair	Side effects
5	There is a someone who keeps track of my Hydroxyurea schedule	Follow up
6	It is difficult to take hydroxyurea at a regular time because of my work or school schedule	Difficulty
7	It is difficult to get time off from work or school to attend doctor's appointments	Difficulty
8	I cannot arrange transportation to go to clinic visits	Transportation
9	I do not like to take Hydroxyurea because I am worried about how it will affect my fertility	Side effects
10	I do not like to take Hydroxyurea because I am worried about how it will affect me in the long term.	Side effects

Graphical representation of ASK-12 survey subsets and individual additional barriers questions was performed to visually represent the survey responses. Interpretation of graphical

data was performed whenever possible. Multiple regression analyses was performed with site of survey administration and participant type as predictors. This was used to check for significant differences in all subsets of ASK-12 and additional barriers survey based on location of survey administration or type of survey participant (Adult, caregiver or pediatric participant). The above analyses was performed with a critical level of significance of $P<0.05$ for each survey. General descriptive statistics such as mean, standard deviation and median were determined for each survey subset.

4.4.4 Analytical methods for specific aim 2

The TSQM-9 survey questions were divided into 3 main subsets – effectiveness, convenience and global satisfaction based on instructions from previous literature.[15; 20; 22] **Table 3** displays the categorical classification of TSQM-9 questionnaire.

Graphical representation of TSQM-9 survey responses was constructed for each survey subset to visually represent survey responses. Multiple regression analyses was performed with site of survey administration and participant type as predictors. The above analyses was performed to check for significant differences in the subsets of TSQM-9 survey based on the location of survey administration and the type of participant (adult, caregiver or pediatric) responding to the surveys. Analyses were performed with a critical level of significance of $P<0.05$. General descriptive statistics such as the mean, standard deviation and median was determined for each survey subset.

Table 3. Categorical Classification of TSQM-9 Survey

	TSQM-9 Survey questions	Category
1	How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?	Effectiveness
2	How satisfied or dissatisfied are you with the way the medication relieves your symptoms?	
3	How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?	
4	How easy or difficult is it to use the medication in its current form?	Convenience
5	How easy or difficult is it to plan when you will use the medication each time?	
6	How convenient or inconvenient is it to take the medication as instructed?	
7	Overall, how confident are you that taking this medication is a good thing for you?	Global Satisfaction
8	How certain are you that the good things about your medication outweigh the bad things?	
9	Taking all things into account, how satisfied or dissatisfied are you with this medication?	

4.4.5 Analytical methods for specific aim 3

Correlation was determined between each subset of the barrier surveys (ASK-12 and Additional Barriers Survey) and each subset of the treatment satisfaction survey (TSQM-9). The Pearson moment correlation coefficients were determined along with their P-value to check for linear relationships between the above two variables. Scatterplots with regression lines were graphed to determine the magnitude of the association and effect of each participant type. Data from subsets that displayed significant difference between participating sites were adjusted for by calculating partial correlation.

5.0 RESULTS

5.1 DEMOGRAPHICS

A total of 152 participants took part in this study. Three participants did not attempt both surveys and were removed from the analysis. Responses from the remaining 149 participants were used in the analyses and interpretation of survey data. The Children's National Medical Center in Washington obtained surveys only from adults and did not have any pediatric or caregiver participants. The University of Pittsburgh Medical Centers and the Children's HealthCare of Atlanta had all three types of participants.

Table 4. Enrollment Data and Demographics

Site Name	Site Number	Number of Adult Participants	Number of Pediatric Participants	Number of Caregiver Participants	Site Total N (%)
University of Pittsburgh Medical Centers	1	21	12	15	48 (32.2 %)
Children's Healthcare of Atlanta	4	6	36	40	82(55.0 %)
Children's National Medical Center, Washington DC	3	19	-	-	19 (12.7 %)
TOTAL N (%)		46 (30.8 %)	48 (32.2 %)	55 (36.9 %)	149

Table 4 displays the classification of participants based on location of survey administration and type of participant. Out of the 149 total participants, 48 (32.21%) completed the surveys at the University of Pittsburgh Medical Centers and 82 (55.03%) took the survey at Children's Healthcare of Atlanta. Of all participating individuals, 48 (32.87%) were minors ($\leq$17 years of age) at the time of survey administration. 55 participants (36.91%) were caregiver participants of minors with SCD. The caregiver participant data and pediatric participant data were not paired in this study.

5.2 BARRIERS TO ADHERENCE

5.2.1 Distribution of ASK-12 and additional barriers survey responses

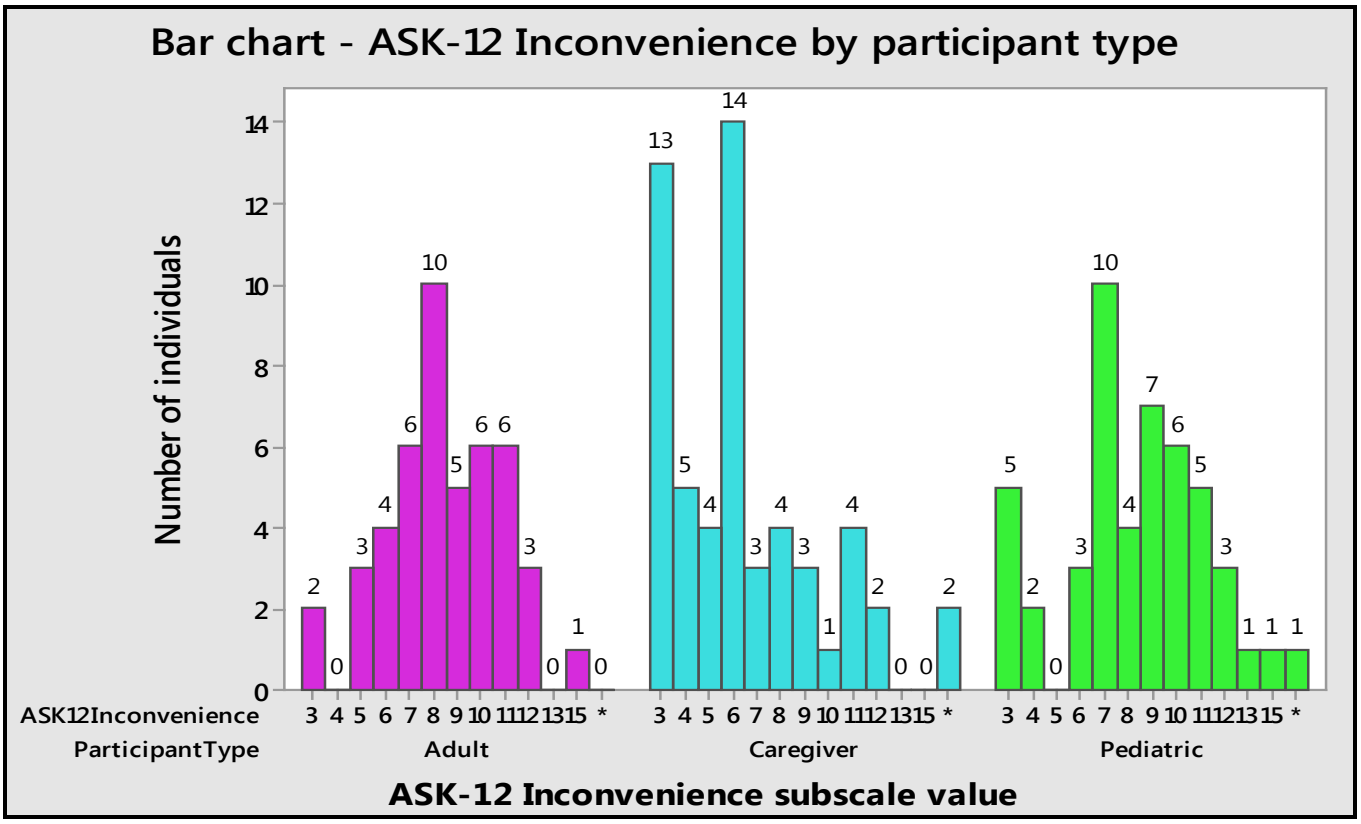

Figure 1. Bar chart - ASK-12 Inconvenience

Figure 1 displays the number of individuals who responded to each value of the ASK-12 inconvenience subset. An ASK-12 subset value $\geq$12 represents a high barrier score. 11 individuals scored $\geq$12 for this subscale which indicates that around 7% of the study population considered issues related to inconvenience a barrier to consumption of hydroxyurea. Out of the 11 individuals, there are 2 are caregiver responses, 4 adult responses and 5 pediatric responses.

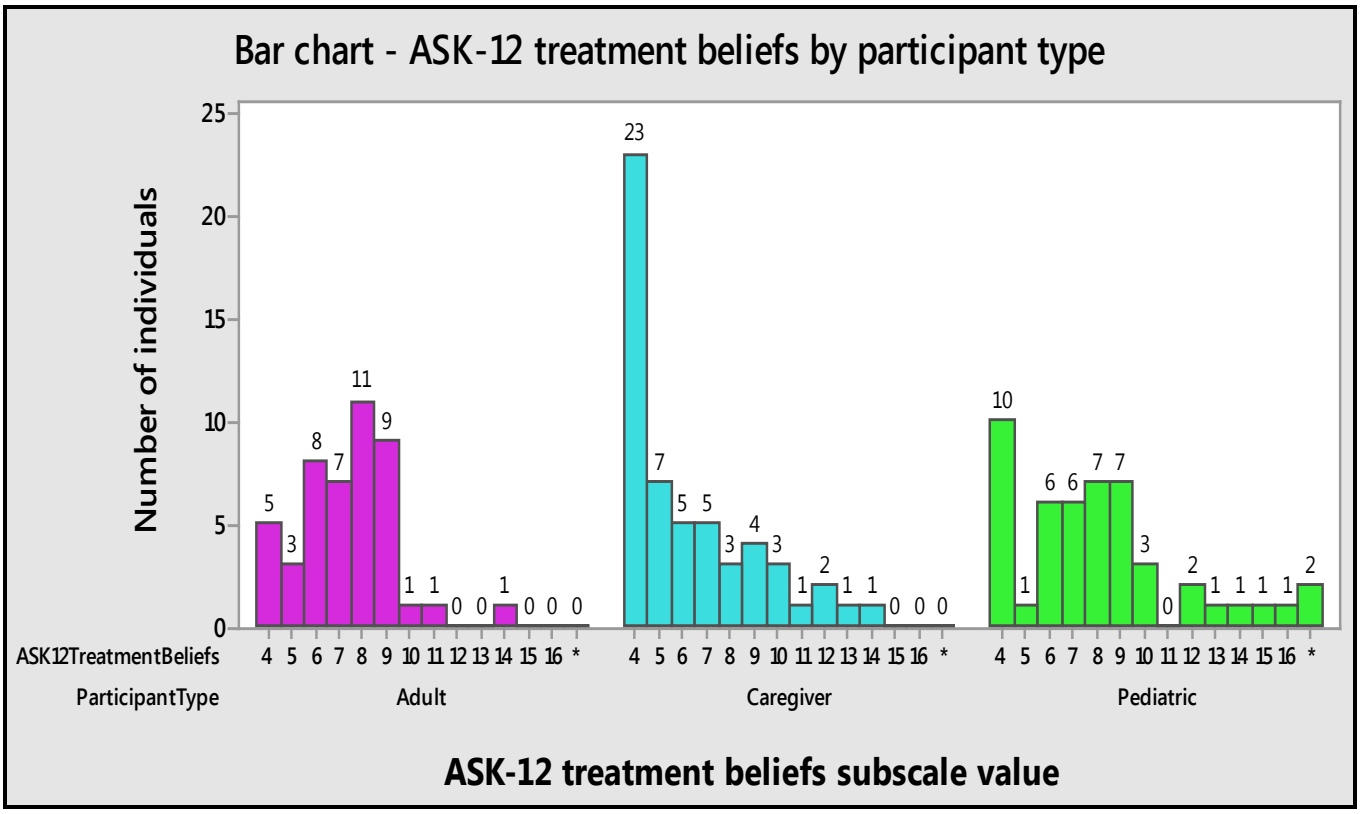

Figure 2. Bar chart - ASK-12 treatment beliefs

Figure 2 displays the number of individuals who responded to each value of the ASK-12 treatment beliefs subscale. An ASK-12 treatment beliefs value of ≥16 represents a high barrier score. Only 1 pediatric response had a score of ≥16 for this subscale which indicates that less than 1% of the study population considers issues related to treatment beliefs a barrier to consumption of hydroxyurea.

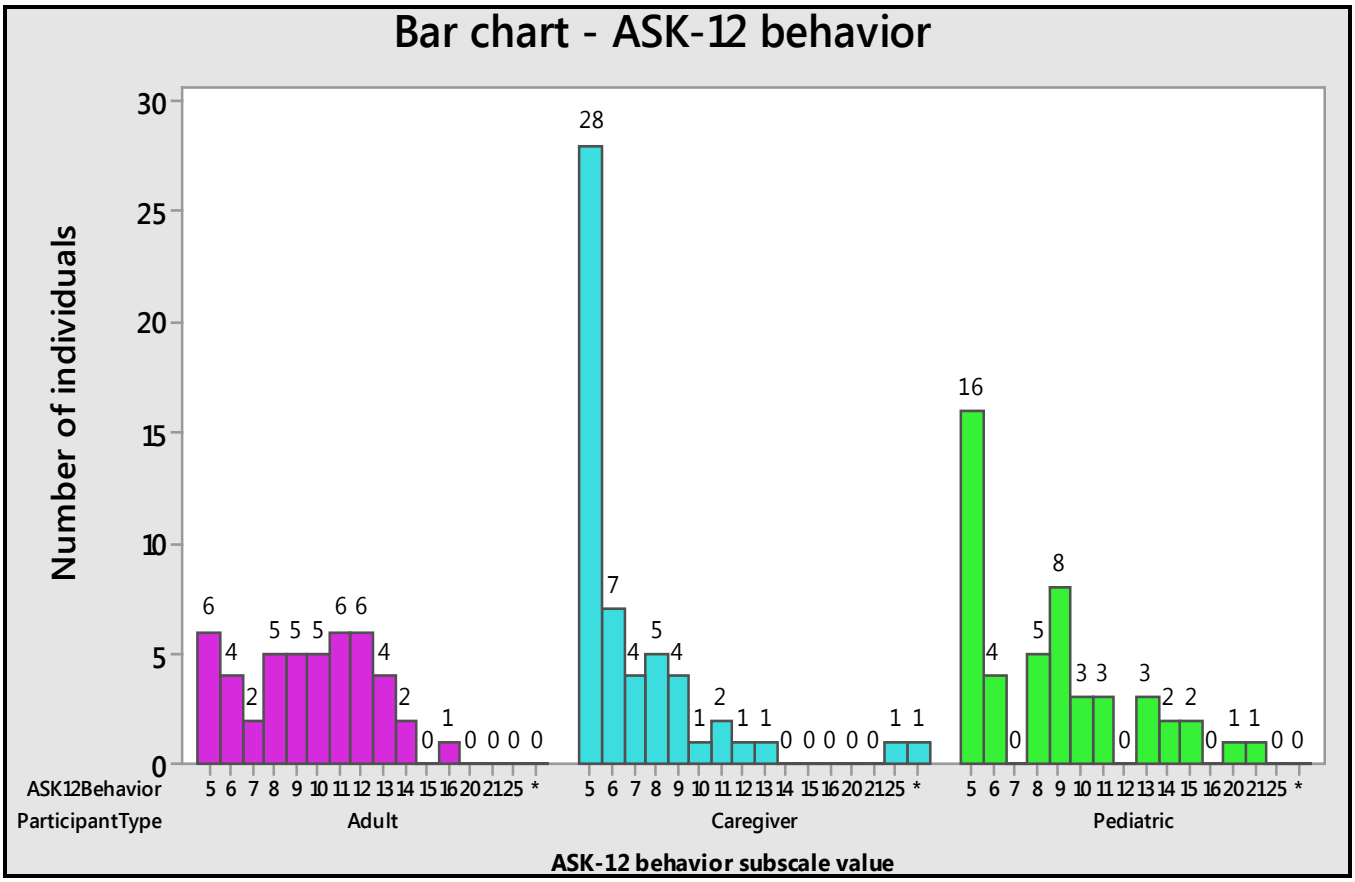

Figure 3. Bar chart - ASK-12 behavior

Figure 3 displays the number of individuals who responded to each value of the ASK-12 behavior subscale. An ASK-12 behavior subscale value of ≥20 represents a high barrier score. 3 individuals scored ≥20 for this subscale which indicates that around 2% of the study population considers issues related to behavior to be a barrier to consumption of Hydroxyurea. Out of the 3 individuals 1 is a caregiver response and 2 are pediatric responses.

The number of individuals experiencing barriers to adherence of HU appears to be low in this population.

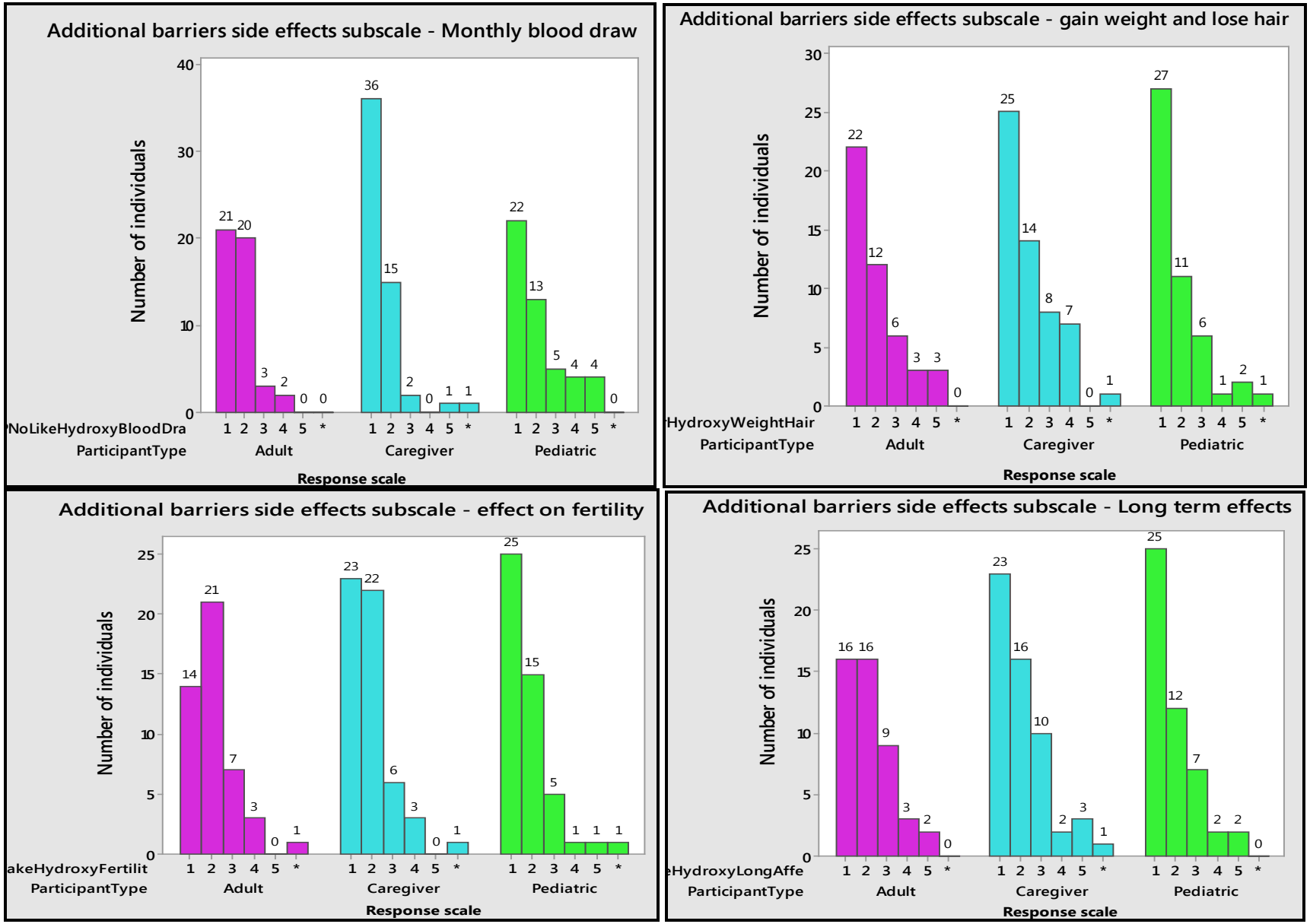

Figure 4. Additional barriers survey side effects subscale responses

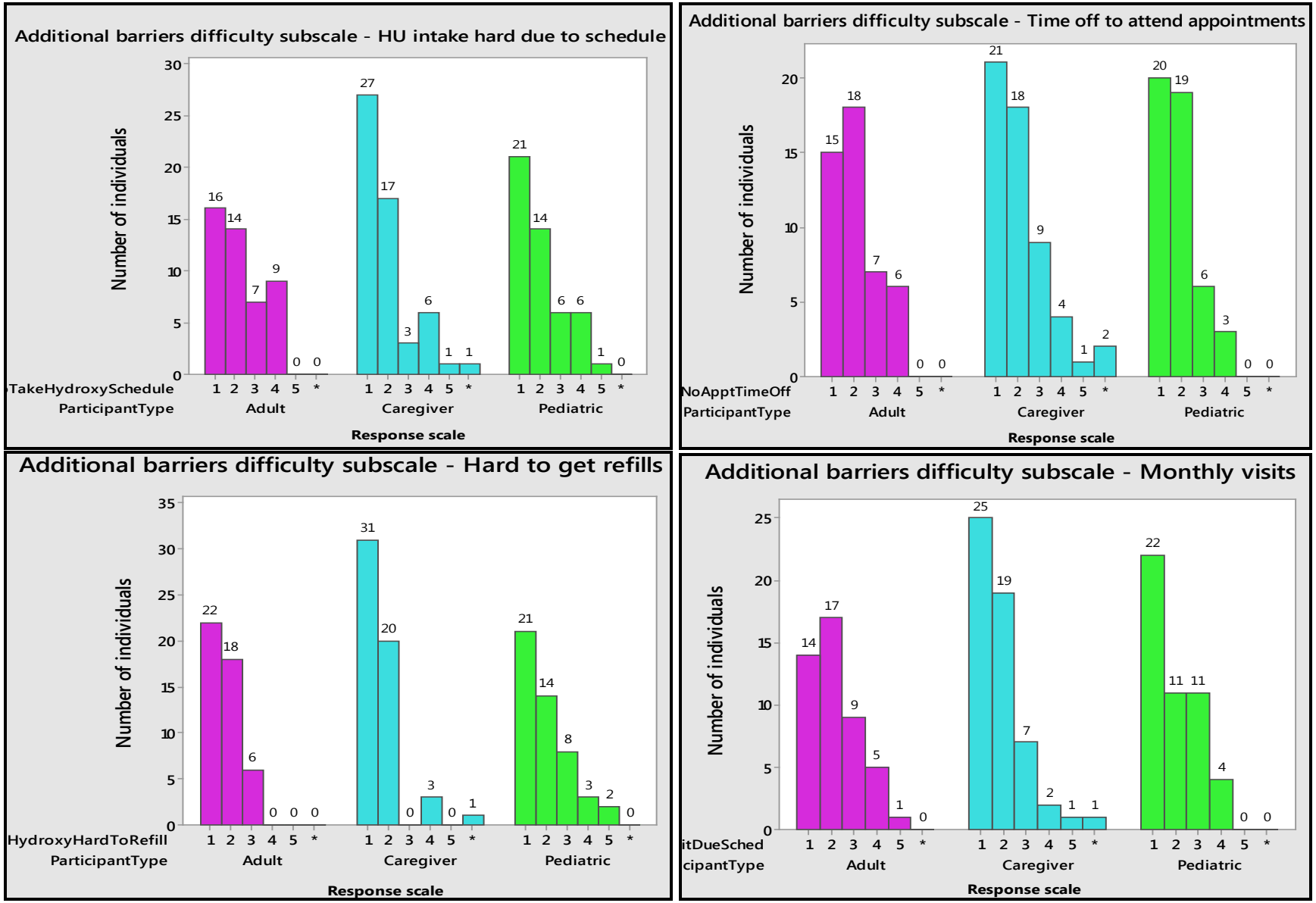

Figure 5. Additional barriers survey difficulty subscale responses

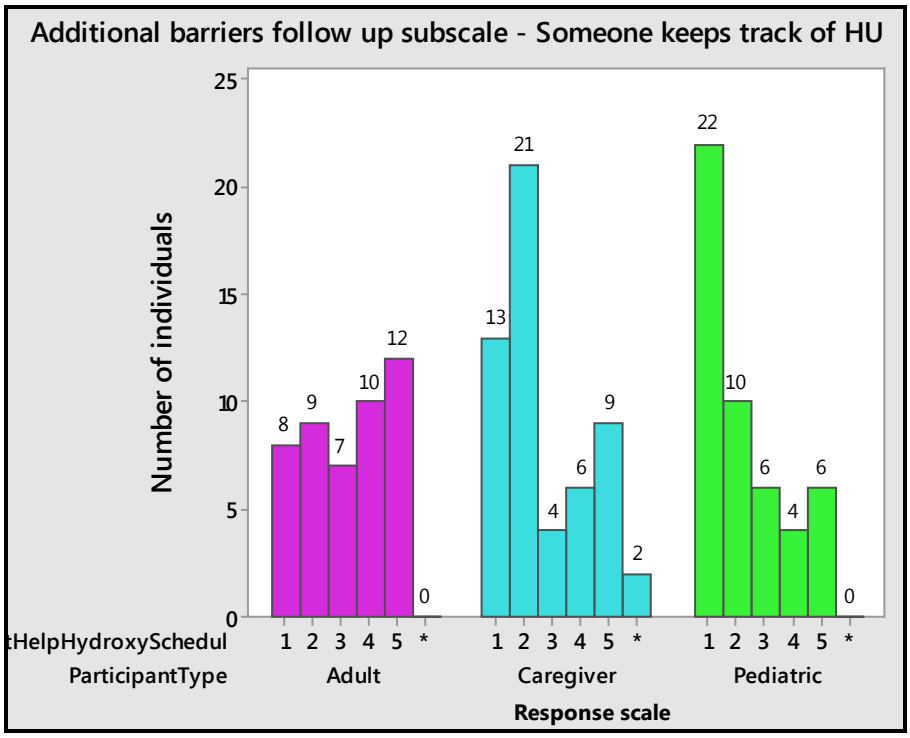

Figure 6. Additional barriers survey follow up subscale response

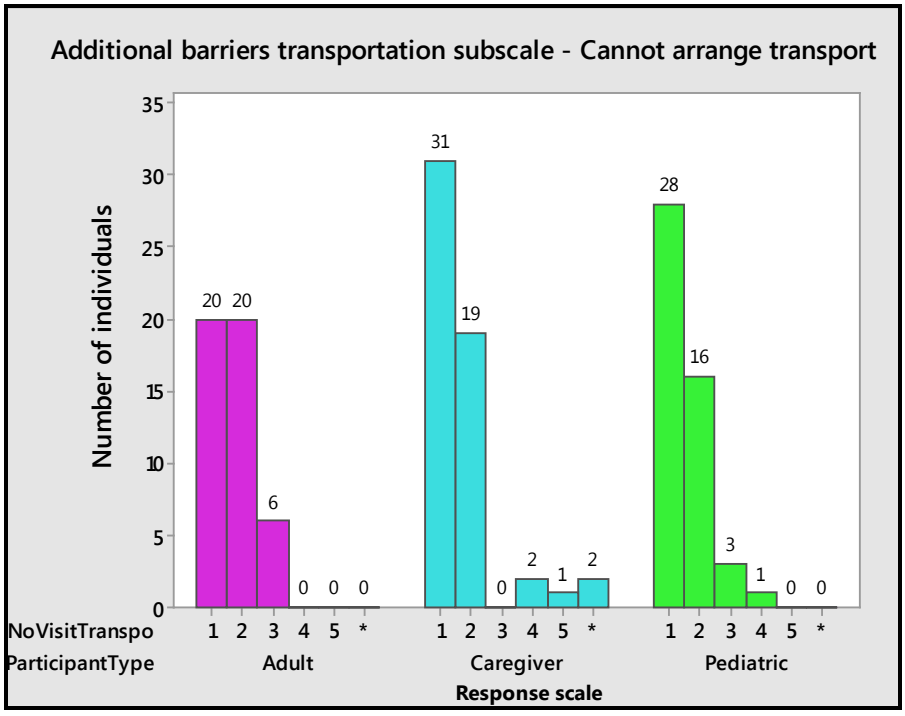

Figure 7. Additional Barriers Survey transportation subscale response

Figures 4, 5, 6 and **7** are graphical representations of responses to the additional barriers survey questions in this study population. **Table 5** shows the number of individuals who scored ≥4 for each question. The observation of above data shows that an increased number of individuals have reported higher level of barriers for questions of this survey compared to the ASK-12 survey.

Table 5 indicates two questions in the additional barriers survey show a larger number of individuals reporting increased level of barriers. The statement "There is a someone who keeps track of my hydroxyurea schedule" was reported as a high level of barrier by 47 individuals (33%). This finding is difficult to interpret in adults with SCD due to the phrasing of question, which may have confused adult participants. However, in the pediatric and caregiver populations, it is possible that this question is still applicable because most pediatric patients have a caregiver to assist them with medication management and refills. Therefore, this may represent a true barrier in these two groups.

"It is difficult to take HU at a regular time because of my work or school schedule" is another question that 23 individuals (15%) reported as a high level of barrier. This could indicate that scheduling a specific time for HU intake may be a challenge for individuals. "I cannot arrange transportation to go to clinic visits" yielded a much lower number of individuals reporting this as a high level barrier compared to previous literature. [24; 25]

Table 5. Number of responses - Additional barriers survey

	Additional Barriers Survey Questions	N
1	I do not like taking Hydroxyurea because I have to get monthly blood draws	11
2	It is hard for me to get to monthly clinical visits because of my schedule	13
3	It is hard for me to get refills of Hydroxyurea from the pharmacy on time	8
4	I am afraid Hydroxyurea will cause me to gain weight or lose my hair	16
5	There is a someone who keeps track of my Hydroxyurea schedule	47
6	It is difficult to take hydroxyurea at a regular time because of my work or school schedule	23
7	It is difficult to get time off from work or school to attend doctor's appointments	14
8	I cannot arrange transportation to go to clinic visits	4
9	I do not like to take Hydroxyurea because I am worried about how it will affect my fertility	8
10	I do not like to take Hydroxyurea because I am worried about how it will affect me in the long term.	14

5.2.2 Regression analysis

A multiple regression analysis was performed to investigate the relationship between the survey responses and its association with two predictors – site of survey administration and participant

type. The model compared survey responses to each predictor independent of the other predictor. The least squares estimation fit regression model was used to perform a multiple regression analysis with each survey subset as the continuous response variable and survey site and participant type as categorical predictor variables. Significance is determined by establishing $P<0.05$ for entire survey which would translate into $P<0.013$ for each survey subset to counteract multiple comparisons using Bonferroni correction.

In the tables describing the results of the regression analyses, Coef refers to the beta coefficient of the analysis (change in the response variable caused by a unit change in the predictor variable), SEcoeff refers to the standard error of this coefficient and the T value refers to the test statistic.

The P-value for estimated coefficients between all three sites is greater than the established α level of 0.013 for the ASK-12 survey subsets and the additional barriers survey subsets. We observed no significant difference between the survey responses based on the location of survey administration for any subset of ASK-12 and additional barriers surveys.

Table 6. Results of Simple Regression for ASK-12 Survey and Participant type

ASK-12 Inconvenience				
Term	**Coef**	**SEcoef**	**T value**	**P-value**
Adult and Caregiver	-2.349	0.690	-0.3.41	**0.001***
Pediatric and Caregiver	2.129	0.538	3.96	**0.000***
Adult and Pediatric	-0.220	0.708	-0.31	0.756
ASK-12 Treatment Beliefs				
Term	**Coef**	**SEcoef**	**T value**	**P-value**
Adult and Caregiver	-0.920	0.673	-0.37	0.174
Pediatric and Caregiver	1.415	0.524	2.7	**0.008***
Adult and Pediatric	0.495	0.698	0.71	0.4791
ASK-12 Behavior				
Term	**Coef**	**SEcoef**	**T value**	**P-value**
Adult and Caregiver	-2.122	0.878	-2.42	0.017
Pediatric and Caregiver	1.884	0.674	2.79	**0.006***
Adult and Pediatric	-0.238	0.896	-0.27	0.790

Table 6 displays the results of regression analyses between each subset of the ASK-12 survey and type of participant attempting the survey. The P-values for estimated coefficients between adult and pediatric participants are greater than the established α level of 0.013 for all three categories. This implies there is no significant relationship between adult and pediatric participant's response to all three ASK-12 categories.

The P-value for the coefficients between the pediatric and caregiver participants are consistently less than 0.013 for each subset. We conclude from this information that there is a difference between the ASK-12 survey responses by the caregivers and the pediatric participants to all three survey categories. This finding could indicate that caregivers' understanding of barriers experienced by the pediatric population could be different. This finding could also be a representation of a difference in barriers expressed by adolescents who independently consume medication and their caregivers' understanding of these barriers.

When examining the relationship between adults and caregivers based on survey response, we see that the P-value of the coefficient in the inconvenience subset is 0.001. This result suggests a difference in response between adults and caregivers in the inconvenience category of the ASK-12 survey. No significant relationship was seen between adults and caregivers in the treatment beliefs and behavior categories of the ASK-12 survey.

To summarize, there appears to be an association between the participant type and certain subsets of the ASK-12 survey.

Table 7. Results of Regression for Additional Barriers Survey and Participant Type

HU Side Effects				
Term	**Coef**	**SEcoef**	**T value**	**P-value**
Adult and Caregiver	-0.123	0.783	-0.16	0.876
Pediatric and Caregiver	0.081	0.613	0.13	0.894
Adult and Pediatric	-0.041	0.806	-0.05	0.959
HU Difficulty				
Term	**Coef**	**SEcoef**	**T value**	**P-value**
Adult and Caregiver	-1.302	0.709	-1.84	0.069
Pediatric and Caregiver	0.599	0.551	1.09	0.279
Adult and Pediatric	-0.703	0.727	-0.97	0.335
HU Transportation				
Term	**Coef**	**SEcoef**	**T value**	**P-value**
Adult and Caregiver	-0.279	0.195	-1.43	0.154
Pediatric and Caregiver	-0.027	0.151	-0.18	0.858
Adult and Pediatric	-0.306	0.200	-1.53	0.128
HU Follow Up				
Term	**Coef**	**SEcoef**	**T value**	**P-value**
Adult and Caregiver	-0.942	0.367	-2.57	**0.011****
Pediatric and Caregiver	-0.355	0.285	-1.25	0.215
Adult and Pediatric	-1.297	0.376	-3.45	**0.001****

Table 7 describes the result of the regression analysis between the additional barriers survey subsets and the type of participant who attempted the survey. The P-value for estimated coefficients were all greater than the established α level of 0.013 for three subsets - HU Side effects, HU difficulty and HU transportation. The above three categories of the Additional Barriers Survey show no significant relationship with participant type.

The P-value of the coefficient between adult and caregiver responses in the HU follow up subset showed significance at 0.011 indicating presence of a difference in response between adults and caregivers to this category of the survey. Additionally, the relationship between participant type and, pediatric and adult responses showed significance with a P-value of 0.001. This indicates the presence of a difference between adult and pediatric responses to the follow up subset of the Additional barriers survey.

5.2.3 Descriptive statistics

Table 8 and **Table 9** display the descriptive statistics of the ASK-12 survey and additional barriers survey respectively. The tables show the number of individuals who responded to each survey subset (N), number of missing responses (N*), mean, standard deviation and median by participant type. The last two columns of the table reports the results of a one sample two tailed T-test to check for significant difference from the neutral response for each subset of the barriers survey. The T-value represents the size of the difference with respect to variation in the response means. The greater the T-value the more evidence against the hypothesis that the population mean is equal to the neutral value.

Table 8. Descriptive statistics of ASK-12 Survey

Variable	Participant Type	N	N*	Mean	StDev	Median	T-value	P-value
ASK-12 Inconvenience (3 items with a neutral score of 9)	Adult	46	0	8.457	2.44	8.00	-1.51	0.138
	Caregiver	53	2	6.057	2.685	6.00	-7.98	0.000
	Pediatric	47	1	8.191	2.856	8.00	-1.94	0.058
ASK-12 Treatment Beliefs (4 items with a neutral score of 12)	Adult	46	0	7.304	2.010	7.500	-15.85	0.000
	Caregiver	55	0	6.255	2.743	5.000	-15.61	0.000
	Pediatric	46	2	7.696	3.054	7.500	-18.45	0.000
ASK-12 Behavior (5 items with a neutral score of 15)	Adult	46	0	9.500	2.904	10.00	-12.86	0.000
	Caregiver	54	1	6.815	3.263	5.000	-11.69	0.000
	Pediatric	48	0	8.688	3.974	8.000	-11.00	0.000
ASK-12 Total (12 items with a neutral score of 36)	Adult	46	0	25.261	5.268	25.000	-13.85	0.000
	Caregiver	52	3	19.038	6.039	18.500	-20.25	0.000
	Pediatric	45	3	24.71	7.65	24.0	-9.90	0.000

In **Table 8**, the mean and median of the caregiver response to all three categories of the ASK-12 survey is lower in comparison to that of adult and pediatric participants. This could indicate lower barriers with respect to all categories indicated by the caregiver participants. The inconvenience subset shows that the responses of the adult and pediatric participants are not significantly different from neutral response but the caregiver response is significantly different from the neutral value.

The negative T value indicates that the mean of the subscales are lower than the neutral value. It can be observed from the T-value of each subset that the treatment beliefs subscale has the most significant difference from the neutral response followed by the behavior subset and lastly by the inconvenience subscale.

The total ASK-12 responses can be scored from 12 to 60 for all participants. The ASK-12 total response for adults, caregivers and pediatric participants are 25.261, 19.038 and 24.71 which indicates a low threshold of barriers.

Table 9. Descriptive statistics of Additional Barriers Survey

Variable	Participant Type	N	N*	Mean	StDev	Median	T-value	P-value
HU Side Effects (4 items with a neutral score of 12)	Adult	45	1	7.733	2.895	7.000	-9.89	0.000
	Caregiver	54	1	7.167	3.161	7.000	-11.24	0.000
	Pediatric	46	2	7.239	3.042	7.000	-10.61	0.000
HU Difficulty (4 items with a neutral score of 12)	Adult	46	0	8.109	2.885	8.500	-9.15	0.000
	Caregiver	53	2	7.132	2.602	7.000	-13.62	0.000
	Pediatric	48	0	7.750	2.787	8.000	-10.57	0.000
HU Follow Up (1 item with a neutral score of 3)	Adult	46	0	3.196	1.470	3.000	0.90	0.371
	Caregiver	53	2	2.566	1.421	2.000	-2.22	0.031
	Pediatric	48	0	2.208	1.429	2.000	-3.84	0.000
HU Transportation (1 item with a neutral score of 3)	Adult	46	0	1.696	0.695	2.000	-12.73	0.000
	Caregiver	53	2	1.547	0.845	1.000	-12.52	0.000
	Pediatric	48	0	1.521	0.714	1.000	-14.35	0.000

Table 9 shows the mean and median values for the different types of participants in all subsets of the additional barriers survey. The value of the T-tests shows significant difference from the neutral value for three of the four survey subsets. Transportation subset showed the most significant difference from the neutral value while the side effects and difficulty subscales appeared to have similar significant differences from the neutral value. The adult and the caregiver responses appear to have no significant difference from the neutral value for the follow up category indicating that the responses by the adult and caregivers were not significantly different from a neutral response.

The negative T-value indicates that the mean of the subscales are lower than the neutral values. The pediatric participant subset showed presence of a significant difference but the T value is much lower than the other subsets indicating lesser deviation of the mean from the neutral response.

5.3 TREATMENT SATISFACTION

5.3.1 Distribution of TSQM-9 survey responses

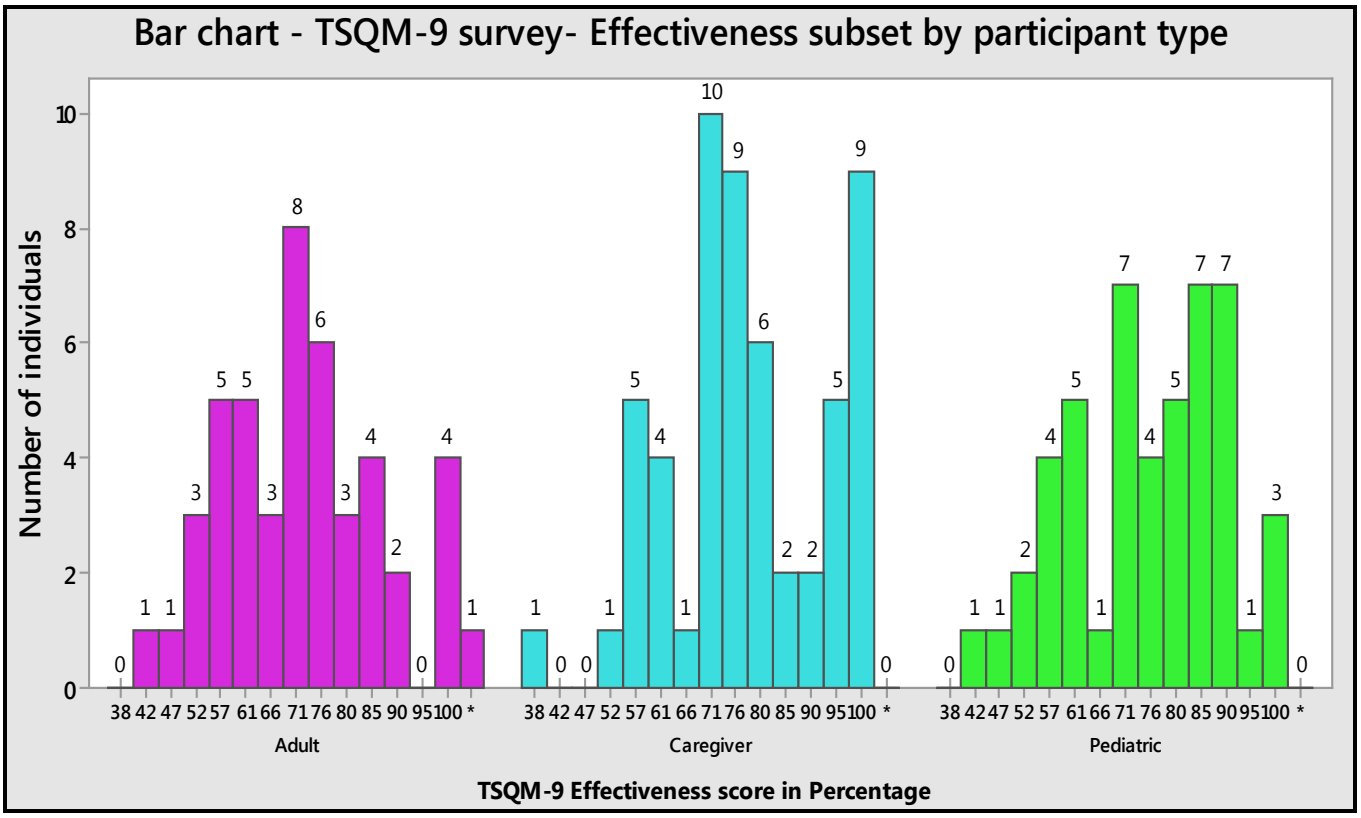

Figure 8. Bar chart - TSQM-9 effectiveness subset

Figure 8 displays the distribution of responses to the TSQM-9 survey effectiveness subscale based on participant type. The TSQM-9 subscale values are converted into a numeric response between 0 and 100. 13% of adults, 29% of caregivers and 22% of pediatric participants have reported a score $\geq$87 for the effectiveness subscale. This indicates that a larger percent of caregiver participants experienced a higher level of satisfaction compared to pediatric and adult participants in the effectiveness category of the TSQM-9 survey.

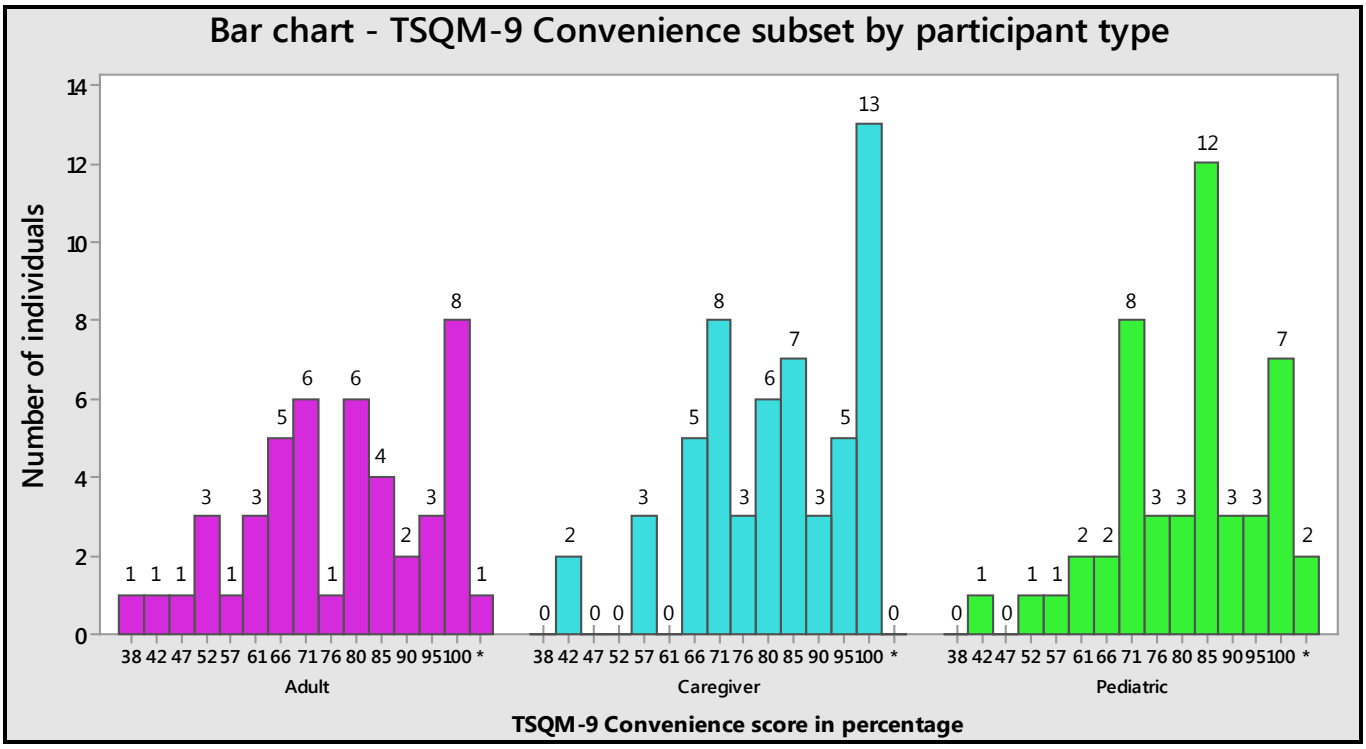

Figure 9. Bar chart - TSQM-9 Convenience subset

Figure 9 shows the distribution of the adult, pediatric and caregiver responses to the TSQM-9 convenience subset. 28% of adults, 38% of caregivers and 27% of pediatric participants report a score $\geq$87 for this subset. This subset also displays a larger percentage of caregiver participants experiencing higher levels of satisfaction when compared to pediatric and adult participants.

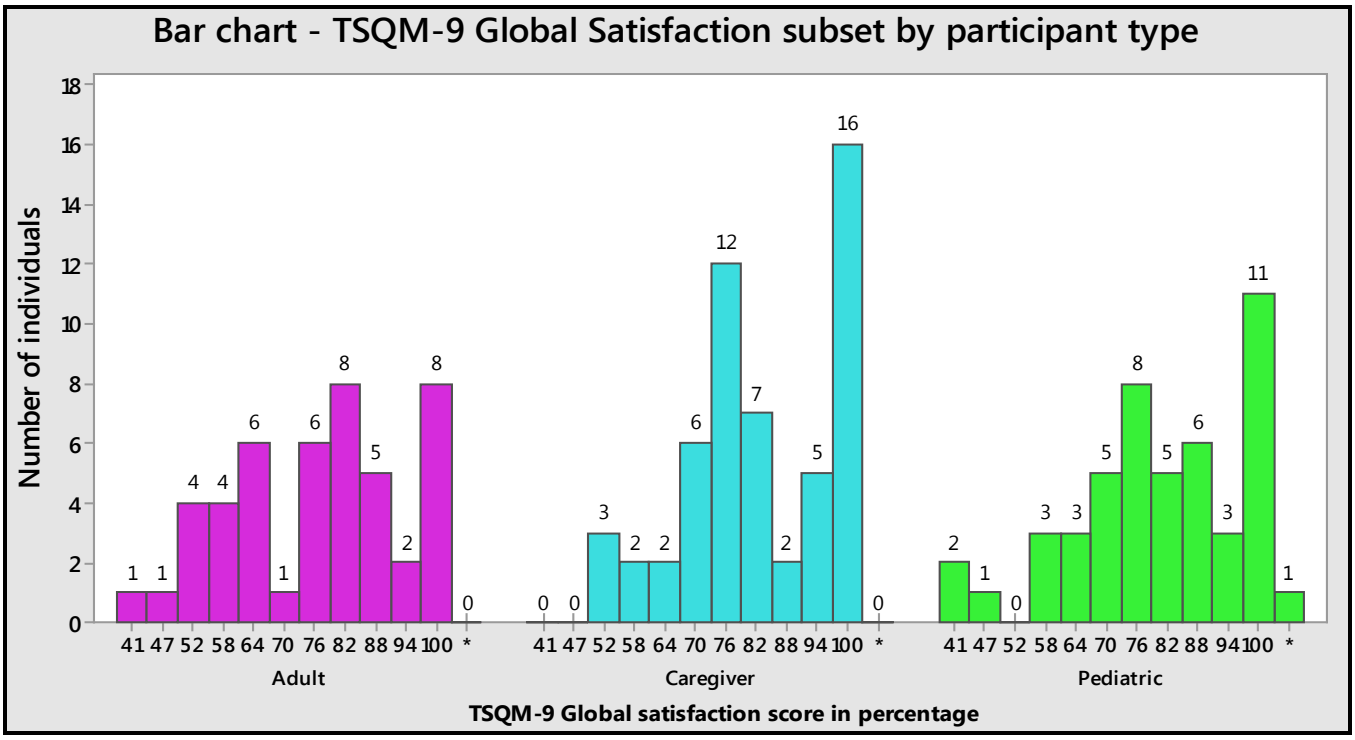

Figure 10. Bar chart - TSQM-9 Global satisfaction

Figure 10 represents the distribution of the TSQM-9 survey responses in the global satisfaction subsets based on participant type. 32% of adult participants 42% of pediatric participants and 42% of caregiver participants provided a response ≥87 for this category of the TSQM-9 survey. This subset indicates a smaller percent of adults experiencing high treatment satisfaction compared to caregiver and pediatric participants.

5.3.2 Regression analysis

A multiple regression analysis was performed to investigate the relationship between the TSQM-9 survey responses and its association with two predictors – Site of survey administration and participant type.

The results of regression analysis for the subsets of the TSQM-9 survey with participant type shows no significant difference for any of the three subsets. P-values for estimated coefficients of all types of participants were greater than the established α level of 0.013. This implies that all the TSQM-9 survey subsets show no significant relationship with adult, caregiver or pediatric participants.

Table 10. Results of Regression for TSQM-9 Survey and Participant Sites

TSQM-9 Effectiveness				
Term	**Coef**	**SEcoef**	**T value**	**P-value**
Site 1 and 3	-0.0840	0.0445	-1.89	0.061
Site 1 and 4	0.0107	0.0295	0.36	0.717
Site 3 and 4	0.0947	0.0496	1.91	0.058
TSQM-9 Convenience				
Term	**Coef**	**SEcoef**	**T value**	**P-value**
Site 1 and 3	-0.0751	0.0474	-1.58	0.116
Site 1 and 4	0.0033	0.0315	0.11	0.916
Site 3 and 4	0.0784	0.0529	-1.48	0.141
TSQM-9 Global Satisfaction				
Term	**Coef**	**SEcoef**	**T value**	**P-value**
Site 1 and 3	-0.1270	0.0461	-2.75	**0.007****
Site 1 and 4	0.0304	0.0311	0.98	0.330
Site 3 and 4	0.1573	0.0516	3.05	**0.003****

Table 10 shows the results of regression analysis for the subsets of the TSQM-9 survey with participant site. P-value for estimated coefficients of all participant sites are greater than the established α level of 0.013 for the effectiveness and convenience subsets of this survey. This implies that the two subsets show no significant relationship with participant site.

The P-value of the coefficient between site 1 and 3 for the responses of the global satisfaction shows significance at P=0.007 indicating the presence of a significant difference in response between Site 1 and Site 3 for this part of the survey. Also, the P-value of Site 3 and 4 show a significant relationship at 0.003. Thus there is a significant difference in responses between site 3 and 4 as well. The significant difference between site responses could be explained by the type of participants in each of the sites. Site 3 enrolled only adult participants while sites 1 and 4 enrolled pediatric, adult and caregiver participants.

5.3.3 Descriptive statistics

Table 11. Descriptive statistics for TSQM-9 survey subsets

Variable	Participant Type	N	N*	Mean	StDev	Median	T-value	P-value
TSQM-9 Effectiveness (3 items with a central value of 57.14)	Adult	45	1	70.26	13.96	71.43	6.30	0.000
	Caregiver	55	0	78.26	15.14	76.19	10.35	0.000
	Pediatric	48	0	77.38	14.45	76.19	9.70	0.000
TSQM-9 Convenience (3 items with a central value of 57.14)	Adult	45	1	77.04	16.13	80.95	8.28	0.000
	Caregiver	55	0	82.25	15.21	85.71	12.24	0.000
	Pediatric	46	2	81.16	15.06	83.33	10.82	0.000
TSQM-9 Global Satisfaction (3 items with a central value of 58.82)	Adult	46	0	75.96	16.02	76.47	7.97	0.000
	Caregiver	55	0	83.10	14.46	82.35	13.31	0.000
	Pediatric	47	1	81.60	16.53	82.35	10.14	0.000

Table 11 show the number of individuals who responded to each survey subset (N), number of missing responses (N*), mean, standard deviation and median by participant type. The last two columns of the table reports the results of a one sample two tailed T-test to check for significant difference from the central value for each subset of the TSQM-9.

The T-test shows all T-values to be positive with significant difference from the central value. The positive nature of the T-values implies the sample means for all subsets are greater than the central value. Thus all participants show significantly high treatment satisfaction for all categories.

The mean for the effectiveness subset of the treatment satisfaction survey is lower for the adults at 70.26 compared to the caregiver and pediatric means of 78.26 and 77.38. Similarly the mean for adult participants is lower than the means of the caregiver and pediatric participants for Convenience and Global Satisfaction subsets. This indicates that adults may experience a lower level of treatment satisfaction to hydroxyurea compared to the pediatric participants. This is supported by the lower T-value of adult survey participants compared to the pediatric and caregiver participant types.

The similar means for all three subsets in pediatric and caregiver category of the surveys indicate that caregivers may have an accurate understanding of the treatment satisfaction of the minor under their care.

5.4 CORRELATION BETWEEN BARRIERS AND TREATMENT SATISFACTION

The third aim of this study is to determine the presence of correlation between the subsets of barriers and the subsets of the treatment satisfaction survey. Correlation between data is obtained by determining the Pearson Correlation Coefficient. Partial correlation analyses were performed to adjust specific categories for predictor variables:

1. ASK-12 categories – partial correlation while adjusting for the effects of participant type
2. TSQM9 Global Satisfaction – Partial correlation while adjusting for the effects of participant sites
3. Additional Barriers Follow Up – Partial correlation while adjusting for the effects of both participant sites and participant type

5.4.2 Correlation

The Pearson product moment correlation evaluates the presence of a linear relationship between continuous variables. A linear relationship is defined as the association of a change in one variable to a proportional change in another variable.

Table 12 displays the results of the correlation analyses between treatment satisfaction and barriers survey responses while adjusting for the appropriate factors. All the correlation coefficients obtained are negative (except for the last value that shows no correlation) which implies an inverse relationship between the two variables, i.e, as one variable decreases, the other variable increases.

Table 12. Correlation Analyses

SURVEY CATEGORY	ASK12 Inconvenience	ASK12 Treatment beliefs	ASK12 Behavior	Additional Barriers – Side Effects	Additional Barriers – Difficulty	Additional Barriers – Follow Up	Additional Barriers - Transportation
TSQM9 Effectiveness	**-0.281*** **(0.001)**	-0.163 (0.049)	-0.086 (0.303)	**-0.260*** **(0.002)**	-0.186 (0.025)	-0.077 (0.356)	-0.051 (0.541)
TSQM9 Convenience	**-0.339*** **(0.000)**	-0.134 (0.109)	-0.176 (0.034)	**-0.233*** **(0.005)**	**-0.236*** **(0.004)**	-0.086 (0.307)	-0.119 (0.115)
TSQM9 Global Satisfaction	**-0.303*** **(0.000)**	-0.091 (0.276)	-0.065 (0.436)	**-0.272*** **(0.001)**	-0.094 (0.260)	-0.116 (0.163)	0.000 (0.996)

Cell Contents: Pearson correlation
P-Value

There is a weak linear relationship observed between all categories of the TSQM-9 survey and the ASK-12 inconvenience subset. The strongest linear relationship observed is between the TSQM-9 convenience and ASK-12 inconvenience subset. This indicates that as the barriers in the inconvenience subset decrease, the treatment satisfaction in the convenience subscale increases. There is another weak linear relationship observed between all subsets of the TSQM-9 survey and the side effects subset of the additional barriers survey. This implies that as the side effects are reduced the treatment satisfaction for hydroxyurea increases. The last weak linear relationship observed is between the convenience subset of TSQM-9 survey and the difficulty subset of the Additional barriers survey. This could imply that as the barriers in the difficult subset are reduced, it improves the convenience of medication use.

5.4.3 Exploring statistical interaction effects

Scatterplots are statistical tools used to display the association between two variables by plotting the values on a graph. The regression line in scatterplots illustrates the relationship between the two groups and is graphical representation of the regression equation. A scatterplot with regression and groups is used to display the association of two variables and plot regression lines based on a specified categorical group. This type of scatterplot was used to examine the potential relationship between the barriers subsets and the treatment satisfaction subsets by participant type. A scatterplot was created between each barriers subset and each treatment satisfaction subset. The plots were grouped based on participant type to check for any difference between the association of the two variables for adults, caregivers and pediatric participants.

Ideally, we expect all regression lines for each graph to have similar slopes and therefore indicating equal contribution to the correlation between the two subsets. This analysis was

performed check if a particular participant type influenced the correlation more than the other two participant types.

Figure 11, Figure 12 and **Figure 13** display the scatterplots between the barriers subsets and treatment satisfaction subsets grouped by participant type. Most of the scatterplots display regression lines with similar slopes indicating equal contributions by each participant type to the correlation between the two subsets. However a few graphs show a difference in slope between participant types which could indicate that one particular group is driving the correlation with limited contribution from the other two groups. In the scatterplot between the ASK-12 treatment beliefs barriers subset and global satisfaction subset of TSQM-9, the regression lines of both the pediatric and adult participants are almost parallel to the X axis while the caregiver regression line shows a negative slope. This indicates that any correlation seen between these two subsets is driven by the responses of the caregiver participants. The same pattern is observed in the scatterplot between the additional barriers difficulty subtype and convenience subset of TSQM-9, indicating that any correlation observed between the two subsets is driven by the caregiver participant responses. While there was no significant correlation observed for the former scatterplot, the latter showed presence of weak linear correlation. Further analyses is required to provide more concrete interpretation on this finding which is outside the scope of this project.

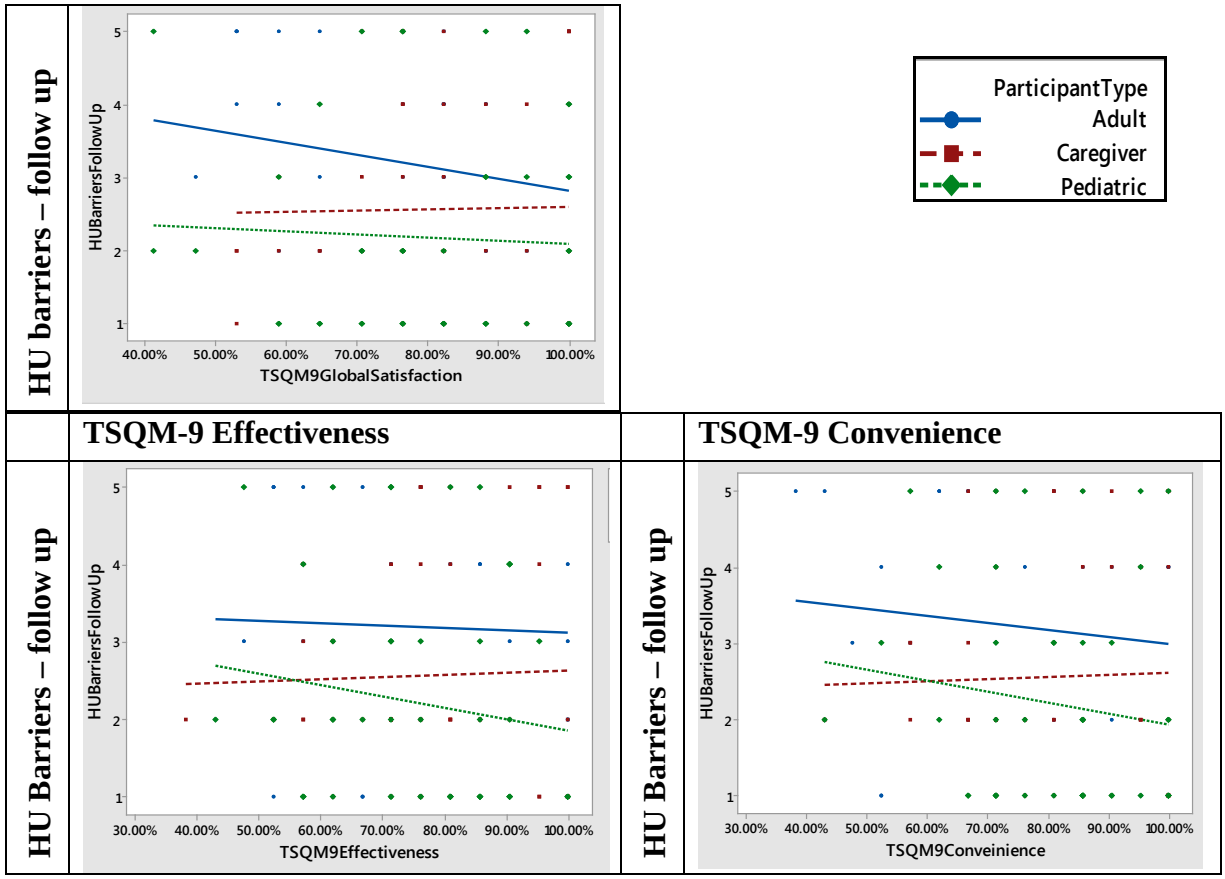

Figure 11. Scatterplot Additional barriers follow up VS TSQM-9

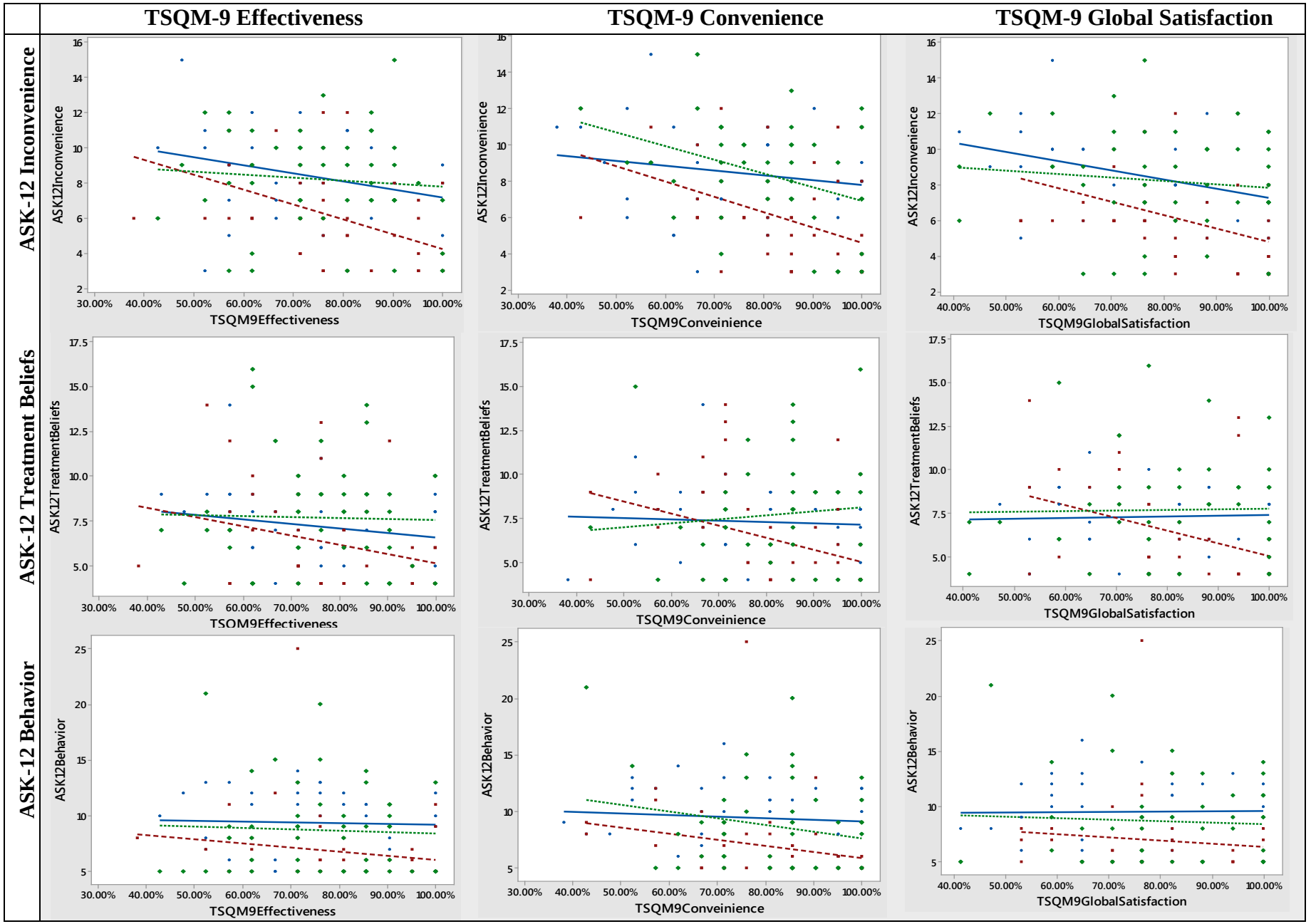

Figure 12. Scatterplot - ASK-12 vs TSQM-9

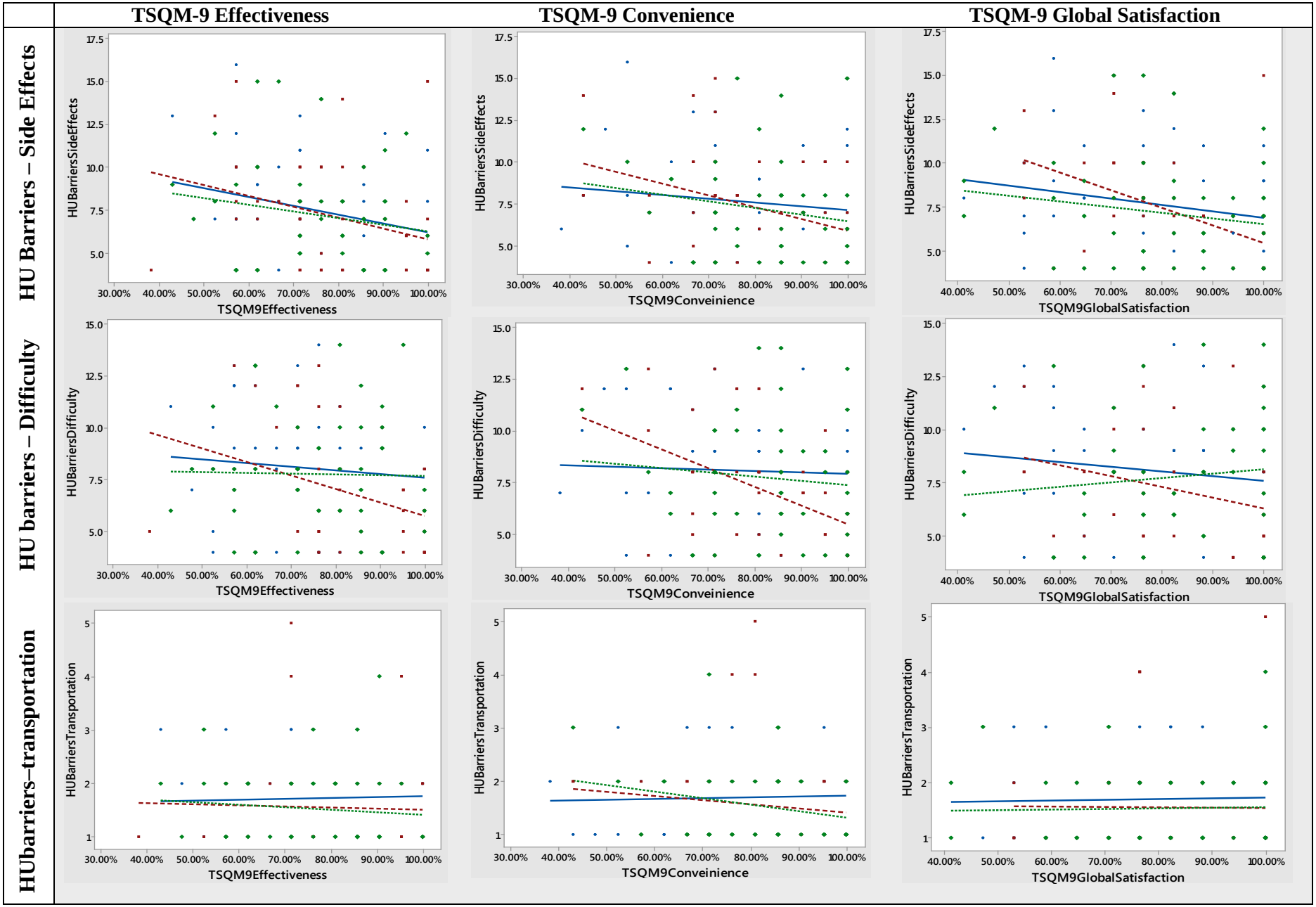

Figure 13. Scatterplot – Additional Barriers survey vs TSQM-9

6.0 DISCUSSION

Sickle cell disease (SCD) is a genetic disorder that is characterized by pain episodes, acute chest syndrome, splenic sequestration, infection, stroke, aplastic crisis, and priapism. While there are reports available in the literature on the barriers experienced by this population[1; 24; 26], there is little research that has examined patient reported treatment satisfaction. This study examined patient reported barriers to adherence of hydroxyurea and patient reported treatment satisfaction. It also investigated the possible association between barriers and satisfaction.

The first aim of this study was to determine the barriers to adherence of hydroxyurea in individuals with SCD (self-reported and/or parent proxy for minors). Due to an increased number of caregiver participants (55) compared to pediatric participants (48), unpaired testing was performed for all participant types. However, a large proportion of the data contains paired responses between the caregiver and pediatric participants. The significant difference in responses of the caregiver and pediatric participants in all three subsets of the ASK-12 survey indicates the possibility of a difference in perception of barriers experienced by the pediatric individuals by caregiver and pediatric participant groups. Interestingly, lower barrier means were found for caregiver participants for all three subsets of the ASK-12 survey when compared to pediatric and adult participants. Lack of agreement between pediatric and caregiver participants has been previously observed in literature with respect to other medication.[27] It may be important to consider that caregivers report lower level of barriers because they do not experience the

disease themselves. A study comparing caregiver reported barriers for caregivers who are affected with SCD to caregivers who do not have the disease would help determine if caregiver bias is a possible cause for this difference. Overall, the number of individuals experiencing barriers to adherence of hydroxyurea appears to be low in this population. There is no previous literature outlining quantitative analysis of patient reported barriers to adherence of hydroxyurea thus limiting the interpretation of this data. [9]

The additional barriers survey follow up subset showed several significant results. The significant difference between the adult responses when compared to both pediatric and caregiver responses may indicate a difference in perception of medication follow up. This subset is limited in its interpretation for adults due to the phrasing of the question which may be confusing for adults (Please refer **Table 2** for categorical classification of survey). However, a high number of caregivers and pediatric participants have also reported this to be a barrier to adherence encouraging further research to determine the nature of this barrier. Categorical examination of the ASK-12 survey revealed lower levels of barriers than what has previously been reported in studies.[9] This difference could be due to population bias as we only included individuals already on hydroxyurea from tertiary care centers. The responses could also be influenced by reporting bias of caregivers and adults who may wish to provide more socially acceptable answers.[9] 15% of individuals reported one question from the difficulty subset - "It is difficult to take hydroxyurea at a regular time because of my work or school schedule" – to be a barrier. This indicates that scheduling a specific time for hydroxyurea intake may be a challenge for individuals. Less than 2% of individuals have expressed transportation to be a barrier to adherence of hydroxyurea. This result is different from the previous qualitative studies that have

often described transportation to be a barrier to use of hydroxyurea[24; 25]. This could indicate the presence of patient reporting bias in this population or a population selection bias.

The second aim of the study was to examine treatment satisfaction with the use of hydroxyurea. Analysis revealed that responses to the global satisfaction category of TSQM-9 survey were influenced by the location of the study participants. This could indicate that satisfaction may have a geographical influence with individuals from site 3 having a consistently different satisfaction compared to the other two sites. The presence of only adult participants at site 3 compared to the three different participant types at the other two sites may also have played a role in generating this difference. The mean for all three categories of the treatment satisfaction survey is a lower for the adults compared to the caregiver and pediatric means indicating that adults may experience a lower level of treatment satisfaction compared to the other participant types. However, available literature, though limited, show no such relationship existing in previous studies of medication treatment satisfaction.[28] The similar means for all three categories in pediatric and caregiver category of the surveys indicate that caregivers may have an accurate understanding of the treatment satisfaction of the minor under their care.

The third aim of the study was to examine any correlation that may exist between the data from the ASK-12 and additional barriers survey and the treatment satisfaction observed from the TSQM-9 survey. All the correlation coefficients obtained were negative implying an inverse association between the two variables. The absence of a strong correlation between any of the barriers subsets and the treatment satisfaction subset indicates that no single barrier has a strong effect on treatment satisfaction. A weak linear relationship was observed between all categories of the TSQM-9 survey and the ASK-12 Inconvenience subset as well as the side effects subset of the additional barriers survey. This implies that as the side effects and inconvenience barriers are

reduced the treatment satisfaction for hydroxyurea increases. This leads to avenues of potential research that could address fear of side effects to improve treatment satisfaction to hydroxyurea. Another weak linear relationship was observed between the convenience subscale of TSQM-9 survey and the difficulty subset of the additional barriers survey. This could indicate that as the barriers in the difficult subset are reduced, it improves the convenience of medication use. However, the scatterplot of the above two subsets show that the correlation is largely driven by the caregiver participant population.

6.1 LIMITATIONS

The patient population used in this study was selected based on their use of hydroxyurea. Therefore, the study sample does not capture the barriers and thoughts of individuals who have not been offered this drug, who have declined this drug or who have been on the medication for less than 6 months. Subjective measures of adherence like the ASK-12 survey as well as the TSQM-9 are subject to potential inaccuracy because they depend on the participant's memory and willingness to report poor adherence or low treatment satisfaction.

This study has only examined a linear relationship between the two survey variables. However other relationships are possible between these variables. Since the Pearson correlation coefficient is very sensitive to extreme values, a single outlier can change the value of the correlation coefficient.

6.2 FUTURE STUDIES

This study provides a novel quantitative analysis of barriers to adherence of hydroxyurea and treatment satisfaction to this medication. As part of an ongoing study, this data will help analyze the barriers expressed by the same population after implementing an intervention for a period of time. Exploring specific barriers and their relationship to treatment satisfaction will provide valuable information for clinicians and future studies. Educational interventions that address individuals' fear of side effects and difficulty with scheduling medication could potentially improve medication adherence.

A paired analysis of caregiver and pediatric responses could provide more information on their perceptions of barriers to medication. This study also brings into question the degree of a caregiver's understanding of barriers faced by children with SCD. Another potential avenue for future research would include qualitative and quantitative analysis of caregivers with this disorder to explore the ways in which their perceptions may differ from caregivers without SCD.

7.0 CONCLUSION

This is the first study that examines patient reported barriers to hydroxyurea and patient reported treatment satisfaction in adults and pediatric individuals with SCD as well as caregivers of pediatric individuals with SCD. It offers insight to patients' understanding of barriers and their level of satisfaction with medication adherence. The survey results suggest that two specific questions present in the additional barriers surveys may be examined in greater detail to understand the role of barriers. Overall, it appears that this study population has low concerns for barriers and a moderate to high level of treatment satisfaction. The study also provides information on correlation between the barriers and treatment satisfaction survey. A weak correlation was found between several subsets of barriers survey and treatment satisfaction subsets. Further research could define how interventions to these barriers influence the outcomes of adherence to hydroxyurea.

APPENDIX A: IRB APPROVAL AND RELAVANT DOCUMENTS

A.1 UNIVERSITY OF PITTSBURGH INSTITUTIONAL REVIEW BOARD APPROVAL

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Ground Level
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Gregory Kato
From: IRB Office
Date: 1/30/2015
IRB#: MOD13110186-06 / PRO13110186
Subject: Patient Centered Comprehensive Medication Adherence Management System to Improve Effectiveness of Disease Modifying Therapy with Hydroxyurea in Patients with Sickle Cell Disease

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The University of Pittsburgh Institutional Review Board reviewed and approved the requested modifications by expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110.

Modification Approval Date: 1/30/2015
Expiration Date: 12/18/2015

The following documents were approved by the IRB:
Amendment 1 from Emory (Protocol Version 3 8.29.2014)

For studies being conducted in UPMC facilities, no clinical activities that are impacted by the modifications can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

A.2 PERMISSION TO USE ASK-12 SURVEY

Christopher M. Hanes
Senior Counsel
Legal: Global Trademarks

VIA FACSIMILE: (412) 692-7580

February 25, 2014

Anusha Vaidyanathan
One Children's Hospital Drive
4401 Penn Avenue
Plaza Building, 5th Floor
Pittsburgh, PA 15224
(412) 692-6467

Re: Permission to Reproduce and Use the ASK-12 Adherence Scale

Dear Ms. Vaidyanathan,

Thank you for your request of January 31, 2014 for permission to reproduce and use the ASK-12 adherence scale. We understand the material will be used to administer to patients in your research study entitled *Patient Centered Comprehensive Medication Adherence Management System to Improve Effectiveness of Disease Modifying Therapy with Hydroxyurea in Patients with Sickle Cell Disease.*

GSK is pleased to grant such permission to reproduce the material for the specific use as described in your request dated January 31, 2014. We do ask that you do not modify the material, and maintain all trademark and copyright notices as they appear. Further, GSK requests appropriate acknowledgment be made as to the source and authorization for use of this material. Accordingly, please list credits as follows: "Copyright GSK. Used with permission."

Furthermore, we would like to inform you and request of you the following:

- For information on scoring the ASK-12, refer to the article by Matza LS, Park J, Coyne KS, et al. entitled Derivation and validation of the ASK-12 adherence barrier survey. *Ann Pharmacother.* 2009;43:1621-1630;
- The five behavioral questions from the ASK-12 are not validated outside of the ASK-12. In any publication, you will be required to make a note of this circumstance; and
- Provide notification of the publication of your results.

This permission is granted solely for the specific purpose as stated in your request, and GSK strictly prohibits reproduction of this content in any other matter. We reserve the right to revoke our permission at any time; however, such revocation will not affect any use by you of the reproduction in accordance with the permission granted herein prior to such revocation. Unfortunately, we cannot make, and hereby disclaim, any warranties as to the necessity of any other grant of permission, or any other warranties of any kind with regard to this content.

Thank you for your interest in GSK. If you have any questions regarding this matter, please contact me at your convenience.

A.3 PERMISSION TO USE TSQM-9 SURVEY

QUINTILES

Quintiles, Inc.
4820 Emperor Boulevard
Durham, North Carolina 27703
Telephone 919.998.2109
Fax 919.998.7838

January 9, 2014

Children's Hospital of Pittsburgh of UPMC
Angela Martino, BSN, RN
One Children's Hospital Drive
4401 Penn Avenue
Plaza Building, 5th Floor
Pittsburgh, PA 15224

Re: Treatment Satisfaction Questionnaire for Medication ("TSQM") and TSQM Scoring Algorithm

Dear Ms. Martino,

With this letter, we are providing Children's Hospital of Pittsburgh of UPMC ("you") with the 9-item abbreviated Treatment Satisfaction Questionnaire for Medication [TSQM-9] ("TSQM") and TSQM Scoring Algorithm, and one (1) translation thereof, as specified in Attachment A (collectively, the "Licensed Materials"), solely for use in connection with the Protocol PRO13110186, entitled "Patient Centered Comprehensive Medication Adherence Management System to Improve Effectiveness of Disease Modifying Therapy with Hydroxyurea in Patients with Sickle Cell Disease" (the "Project").

All rights, title and interest in and to the Licensed Materials are owned by Quintiles Transnational Corp., Quintiles, Inc.'s corporate affiliate and licensor. The Licensed Materials are protected by copyright, trade secret and other laws. The TSQM may only be administered by you in connection with patients participating in the Project. The TSQM Scoring Algorithms may only be provided to your Personnel (defined below) participating in the Project for the sole purpose of scoring the TSQM.

In the event that you need a translation of the Licensed Materials which Quintiles Transnational Corp. and Quintiles, Inc. (individually and collectively, "Quintiles") do not already have in their possession, you may, following receipt of the written consent of Quintiles, translate the Licensed Materials into the requested language; provided that the translation (a) is carried out in accordance with applicable standards for linguistic adaptation, and (b) is carried out in accordance with Quintiles' instructions and subject to Quintiles' final approval. Upon completion of the translation of the Licensed Materials pursuant to this procedure, you will promptly provide Quintiles, Inc. with a copy of the translated Licensed Materials together with a copy of the translation certificate executed by the official translator. While you will not be charged a license fee for a translation conducted under this process, any such translation will be deemed Licensed Materials under this agreement and all rights that you and any party acting on your behalf may have therein shall be assigned to Quintiles Transnational Corp.

All Licensed Materials are provided by Quintiles subject to terms regarding confidentiality as set forth in this paragraph and in the following paragraph. You will receive, maintain, and hold the Licensed Materials in strict confidence and will use at least the same level of care in safeguarding them that you use with your own confidential material. You will not reveal the Licensed Material to your employees, directors, or staff (collectively, "Personnel") except to the extent required to administer the Project, and you will ensure that all Personnel treat the Licensed Material as strictly confidential and abide by the terms of this letter. You will not disclose the Licensed Materials to any third party or utilize Licensed Materials, except as provided herein, without first having obtained Quintiles' written consent to such disclosure or utilization.

The obligations of confidentiality set forth herein shall not apply to the Licensed Materials to the extent the Licensed Materials are required by law to be disclosed by you, provided that you notify Quintiles prior to such disclosure and offer Quintiles an opportunity to contest such disclosure.

You agree to indemnify and hold harmless Quintiles and each of its directors, officers, employees and agents from and against all liabilities, losses, claims, demands, damages, costs and expenses (including but not limited to reasonable legal fees and disbursements) suffered or incurred by Quintiles and arising as a direct or indirect result of (a) any claim, proceeding, civil, criminal or administrative action, inquiry, suit or legal action instituted against Quintiles and in respect of your use of the Licensed Materials, or (b) your negligence or willful misconduct or that of any of your directors, officers, employees or agents.

Quintiles shall not be responsible for any special, incidental, consequential, exemplary or punitive damages relating to this letter or the License Materials even if Quintiles has knowledge of the possibility of such potential damages.

You will ensure that any paper, article or other publication reporting results obtained using the Licensed Materials will include the following reference:

> Bharmal M, Payne K, Atkinson MJ, et al. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes 2009 Apr 27;7:36. Those seeking information regarding or permission to use the TSQM are directed to Quintiles, Inc. at www.quintiles.com/TSQM or TSQM@quintiles.com

You agree to inform Quintiles upon the completion of the Project. Following completion of your use of the Licensed Materials as contemplated by this letter, or upon termination of your rights to such materials hereunder, you agree to provide to Quintiles all data from the Project that could be used to build the psychometric properties of the Licensed Materials. Any data provided will be used by Quintiles only to improve the psychometric properties of the Licensed Materials.

The rights granted to you hereunder are subject to your acceptance of the terms of this letter as shown below. The nonrefundable license fee is waived for your institution.

Upon completion of your use of the Licensed Materials as contemplated by this letter, or upon termination of your rights to such materials hereunder, you shall destroy all copies of the Licensed Materials and have an officer of your company certify in writing that all Licensed Materials have been destroyed, however you may retain one copy of the Licensed Materials under seal for regulatory purposes.

The terms of this offer letter shall be considered effective as of the date signed below ("Effective Date").

This letter agreement may be executed in any number of counterparts, each of which when executed and delivered, shall constitute an original, but all of which together shall constitute one agreement binding on all parties, notwithstanding that all parties are not signatories to the same counterpart. Transmission by fax or by electronic mail of an executed counterpart of this letter agreement shall be deemed to constitute due and sufficient delivery of such counterpart. This letter agreement and any amendment or modification may not be denied legal effect or enforceability solely because it is in electronic form, or because an electronic signature or electronic record was used in its formation.

Should you have any questions, please contact us immediately. To confirm your acceptance of these terms and conditions, please sign below and return via pdf to Elizabeth Moskowitz at elizabeth.moskowitz@quintiles.com.

Sincerely,

Quintiles Inc.

APPENDIX B: SURVEYS

B.1 ASK-12 AND ADDITIONAL BARRIERS SURVEY

Pt ID: ☐☐☐ PT INITIALS: ☐☐☐ STAFF ID : ☐☐☐ DATE: ☐☐/☐☐/☐☐☐☐

ASK-12

	Strongly agree	Agree	Neutral	Disagree	Strongly Disagree
1. I just forget to take my medicines some of the time					
2. I run out of my medicine because I don't get refills on time					
3. Taking medicines more than once a day is inconvenient					
4. I feel confident that each one of my medicines will help me					
5. I know if I'm reaching my health goals					
6. I have someone I can call with questions about my medicines					
7. My doctor/nurse and I work together to make decisions					

HAVE YOU.....	In the last week	In the last month	In the last 3 months	More than 3 months ago	Never
8. Taken a medicine more or less often than prescribed?					
9. Skipped or stopped taking a medicine because you didn't think it was working?					
10. Skipped or stopped taking a medicine because it made you feel bad?					
11. Skipped, stopped, not refilled, or taken less medicine because of the cost?					
12. Not had medicine with you when it was time to take it?					

Pt ID: ☐☐☐ PT INITIALS: ☐☐☐ STAFF ID : ☐☐☐ DATE: ☐☐/☐☐/☐☐☐☐

Additional Barriers survey

	Strongly agree	Agree	Neutral	Disagree	Strongly Disagree
13. I do not like taking Hydroxyurea because I have to get monthly blood draws					
14. It is hard for me to get to monthly clinical visits because of my schedule					
15. It is hard for me to get refills of Hydroxyurea from the pharmacy on time					
16. I am afraid Hydroxyurea will cause me to gain weight or lose my hair					
17. There is a someone who keeps track of my Hydroxyurea schedule					
18. It is difficult to take hydroxyurea at a regular time because of my work or school schedule					
19. It is difficult to get time off from work or school to attend doctor's appointments					
20. I cannot arrange transportation to go to clinic visits					
21. I do not like to take Hydroxyurea because I am worried about how it will affect my fertility					
22. I do not like to take Hydroxyurea because I am worried about how it will affect me in the long term.					

B.2 TSQM-9 SURVEY

Pt ID: ☐☐☐ PT INITIALS: ☐☐☐ STAFF ID : ☐☐☐ DATE: ☐☐/☐☐/☐☐☐☐

TSQM-9

Abbreviated Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it.* For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

Pt ID: ☐☐☐ PT INITIALS: ☐☐☐ STAFF ID : ☐☐☐ DATE: ☐☐/☐☐/☐☐☐☐

4. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

5. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

6. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

8. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

APPENDIX C: DATA CODING

C.1 ASK-12 SURVEY AND ADDITIONAL BARRIERS SURVEY

Results for: Barriers

Code

Summary

Original Value	Recoded Value
Agree	4
Disagree	2
Neutral	3
Strongly Agree	5
Strongly Disagree	1
	*

Source data columns BTAPForgetMedSomeTime, BTAPNoMedRefillOnTime, BTAPMedMoreOPDInconvenient
Recoded data columns Coded BTAPForgetMedSomeTime - Coded BTAPMedMoreOPDInconvenien

Source data columns BTAPNoLikeHydroxyBloodDraws, BTAPNoVisitDueSched, BTAPNoHydroxyHardToRefill, BTAPFearHydroxyWeightHair
Recoded data columns Coded BTAPNoLikeHydroxyBloodDra - Coded BTAPFearHydroxyWeightHair

Source data columns BTAPNoTakeHydroxySchedule, BTAPNoApptTimeOff, BTAPNoVisitTranspo, BTAPNoTakeHydroxyFertility, BTAPNoLikeHydroxyLongAffect
Recoded data columns Coded BTAPNoTakeHydroxySchedule - Coded BTAPNoLikeHydroxyLongAffe

Code

```
Summary

                  Recoded
   Original Value    Value
            Agree        2
         Disagree        4
          Neutral        3
   Strongly Agree        1
Strongly Disagree        5
                         *


Source data columns   BTAPMedWillHelp, BTAPReachHealthGoals,
BTAPCanCallMedQuestion, BTAPDoctorNurseHelpDec
Recoded data columns  Coded BTAPMedWillHelp - Coded BTAPDoctorNurseHelpDec


Source data column   BTAPGetHelpHydroxySchedule
Recoded data column  Coded BTAPGetHelpHydroxySchedul
```

Code

```
Summary

                       Recoded
        Original Value    Value
  In the last 3 months        3
     In the last month        4
      In the last week        5
More than 3 months ago        2
                 Never        1


Source data columns   BTAPMedMoreLess, BTAPMedNotWork, BTAPMedFeelBad,
BTAPMedCost, BTAPMedNotWith
Recoded data columns  Coded BTAPMedMoreLess - Coded BTAPMedNotWith
```

C.2 TSQM-9 SURVEY

Results for: TSQM-Participant

Code

Summary

Original Value	Recoded Value
Dissatisfied	3
Extremely Satisfied	7
Satisfied	5
Somewhat Satisfied	4
Very Dissatisfied	2
Very Satisfied	6
*	

Source data columns TSQM9DissatisfiedTreatCond, TSQM9DissatisfiedRelieveSymp, TSQM9DissatisfiedTimeToWork
Recoded data columns Coded TSQM9DissatisfiedTreatCon - Coded TSQM9DissatisfiedTimeToWo

Source data column TSQM9OverallSatisfaction
Recoded data column Coded TSQM9OverallSatisfaction

Code

Summary

Original Value	Recoded Value
Difficult	3
Easy	5
Extremely Difficult	1
Extremely Easy	7
Somewhat Easy	4
Very Difficult	2
Very Easy	6
*	

Source data columns TSQM9EasyToUse, TSQM9EasyToPlan
Recoded data columns Coded TSQM9EasyToUse - Coded TSQM9EasyToPlan

Code

Summary

Original Value	Recoded Value	Number of Rows
Convenient	5	21
Extremely Convenient	7	24
Extremely Inconvenient	1	2
Inconvenient	3	3
Somewhat Convenient	4	17
Very Convenient	6	23
Very Inconvenient	2	2

```
                          *        3

Source data column   TSQM9ConvenientToTake
Recoded data column  Coded TSQM9ConvenientToTake
```

Code

```
Summary

                     Recoded   Number
      Original Value   Value  of Rows
  A Little Confident       2        5
 Extremely Confident       5       37
Not at All Confident       1        1
  Somewhat Confident       3       17
      Very Confident       4       34
                           *        1


Source data column   TSQM9ConfidentMedGood
Recoded data column  Coded TSQM9ConfidentMedGood
```

Code

```
Summary

                    Recoded   Number
    Original Value    Value  of Rows
  A Little Certain        2        6
 Extremely Certain        5       30
Not at All Certain        1        4
  Somewhat Certain        3       19
      Very Certain        4       35
                          *        1

Source data column   TSQM9CertainGoodOutweighBad
Recoded data column  Coded TSQM9CertainGoodOutweighB
```

C.3 REGRESSION TABLES

Results of Regression for ASK-12 Survey and Participant Sites

ASK-12 Inconvenience				
Term	Coef	SEcoef	T value	P-value
Site 1 vs 3	0.437	0.813	0.54	0.592
Site 1 vs 4	0.220	0.544	0.41	0.686
Site 3 vs 4	-0.216	0.909	-0.24	0.812
ASK-12 Treatment Beliefs				
Term	Coef	SEcoef	T value	P-value
Site 1 vs 3	1.449	0.794	1.83	0.070
Site 1 vs 4	0.785	0.535	1.47	0.145
Site 3 vs 4	-0.664	0.888	-0.75	0.456
ASK-12 Behavior				
Term	Coef	SEcoef	T value	P-value
Site 1 vs 3	-0.40	1.03	-0.39	0.698
Site 1 vs 4	-0.193	0.693	-0.72	0.087
Site 3 vs 4	0.079	1.15	0.69	0.492

Results of Regression for Additional Barriers Survey and Participant Sites

HU Side Effects				
Term	Coef	SEcoef	T value	P-value
Site 1 vs 3	0.326	0.939	0.35	0.729
Site 1 vs 4	-0.532	0.619	-0.86	0.391
Site 3 vs 4	-0.86	1.05	-0.82	0.414
HU Difficulty				
Term	Coef	SEcoef	T value	P-value
Site 1 vs 3	0.033	0.836	0.04	0.969
Site 1 vs 4	0.577	0.559	1.03	0.304
Site 3 vs 4	0.544	0.934	0.58	0.561
HU Transportation				
Term	Coef	SEcoef	T value	P-value
Site 1 vs 3	-0.283	0.230	-1.23	0.220
Site 1 vs 4	0.023	0.154	0.15	0.880
Site 3 vs 4	0.307	0.257	1.19	0.235
HU Follow Up				
Term	Coef	SEcoef	T value	P-value
Site 1 vs 3	-0.893	0.432	-2.06	0.041
Site 1 vs 4	-0.096	0.289	-0.33	0.740
Site 3 vs 4	0.797	0.483	1.65	0.101

Results of Regression for TSQM-9 Survey and Participant types

TSQM-9 Effectiveness				
Term	Coef	SEcoef	T value	P-value
Adult and Caregiver	0.0401	0.0371	-0.108	0.282
Pediatric and Caregiver	0.0093	0.0286	0.33	0.745
Adult and Pediatric	0.0093	0.0384	-0.80	0.425
TSQM-9 Convenience				
Term	Coef	SEcoef	T value	P-value
Adult and Caregiver	0.0201	0.0396	0.51	0.612
Pediatric and Caregiver	0.0110	0.0308	0.36	0.721
Adult and Pediatric	0.0091	0.0410	0.22	0.825
TSQM-9 Global Satisfaction				
Term	Coef	SEcoef	T value	P-value
Adult and Caregiver	0.0009	0.0391	0.02	0.982
Pediatric and Caregiver	0.0162	0.0303	0.53	0.594
Adult and Pediatric	-0.0153	0.0405	-0.38	0.706

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