

**EFFECT OF STANDARD OF CARE CHANGES ON THE NO-SHOW RATE IN A
SICKLE CELL CLINIC**

by

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ABSTRACT

Background: Lack of appointment compliance is a problem that is consistent throughout outpatient clinics. Research has found that personal phone calls as opposed to automated systems can improve appointment compliance. Another barrier that has been identified is the frequency of appointments. For individuals with sickle cell disease, attending appointments is important for managing their medications and multi-disciplinary care. In this study, we seek to determine whether 2 standard of care changes have impacted the no show rate in a sickle cell clinic based at Children's Hospital of Pittsburgh of UPMC (CHP).

Methods: Clinical data were reviewed to assess the impact of these changes on the no-show rate before and after these changes were made. Statistical analysis was performed utilizing paired analysis and summary statistics. All patients who were followed in clinic at CHP both during a set time period before and after implementation and met inclusion criteria were included in the assessment.

Results: Changes to the appointment frequency for hydroxyurea patients and the personal reminder phone calls did not statistically significantly change the no-show rate with a p-value 0.6818 and 0.3421, respectively. There were 67 patients included in the hydroxyurea appointment frequency and 101 included in the phone call reminder portion.

Conclusions: Reducing the frequency of appointments in the subset of patients taking hydroxyurea and phone call reminders did not increase appointment compliance, but further research needs to be conducted to determine the full impact of these interventions. Methods to increase appointment compliance are especially important in the sickle cell disease population, as attending appointments is how medications and preventative and symptomatic care are managed. Further research needs to be done on barriers to access to understand why patients are not attending appointments before new implementations can be made.

Public Health Significance: Appointment compliance is important for keeping individuals healthy through preventative measures, following up with a chronic condition, and making the best use of health care resources.

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1.0 INTRODUCTION

Appointment compliance is beneficial to healthcare providers and hospital systems, but most importantly it is beneficial to the patients. Patients who are not attending their appointments are reducing the quality of care they can receive. For patients with sickle cell disease, appointment compliance is important to manage medications, check up on the patient and educate families, which are established preventative measures for sickle cell complications and painful crises.¹ There are approximately 100,000 people nationwide who are living with sickle cell disease, making it one of the most common inherited genetic diseases. Primarily African Americans are affected, and the disease affects about 1 in 365 African-American individuals.² There have been many significant improvements in the management of this condition, which has increased the lifespan from approximately 20 years to about 42-48 years of age for individuals with HbSS.³ Attending appointments, and in turn receiving the care that they need plays a critical role in the well-being of these patients.⁴

Standard of care changes initiated by the sickle cell team at the Pediatric Sickle Cell Clinic at Children's Hospital of Pittsburgh to increase appointment compliance have included personal reminder phone calls and increasing the interval between appointments for hydroxyurea follow-up. In other clinics, it proved effective to have personal phone calls as opposed to the automated system. Thus it was decided that personal calls would be conducted in addition to the automated system.^{5,6,7} The frequency of appointments has also been identified as a barrier for

individuals⁸; therefore, the clinic decided to increase the interval between appointments when medically feasible. Additional data for the use of hydroxyurea in the pediatric population has permitted the option of a longer interval between clinic visits for children with sickle cell disease on a stable dose of hydroxyurea with no evidence for toxicity. This provided an opportunity to change the frequency of clinic visits in a subset of patients on hydroxyurea. This study will provide the information necessary moving forward to see if in this particular clinic, the Pediatric Sickle Cell Clinic at Children's Hospital of Pittsburgh, could continue to benefit from these changes. Furthermore, this study should provide insight about possible further implementations to the standard of care practices that will optimize compliance with clinic appointments.

The goal of this study is to evaluate the effectiveness of changes to standard care to see if they increase appointment compliance in the Pediatric Sickle Cell Clinic. We hypothesize that multiple personalized reminders and reducing the frequency of appointments will increase the number of people attending clinic visits. This study will enable the research team to identify whether either of these two standard-of-care changes increases the percentage of families attending clinic and, furthermore, identify any additional barriers to appropriately adjust standard of care changes in the future.

To address the appointment no-show rate in the Pediatric Sickle Cell Clinic at Children's Hospital of Pittsburgh, the specific aims of this study are:

- Assess the impact of increasing time interval between appointments on the no-show rate in the Pediatric Sickle Cell Clinic for Hydroxyurea follow up patients.
- Assess the impact of reminding patients of their appointments on the no-show rate in the Pediatric Sickle Cell Clinic.

- Identify additional barriers that may reduce the no-show rate in the Pediatric Sickle Cell Clinic in the future.

This evaluation of the current practices in the Pediatric Sickle Cell Clinic will provide results that give information about how effective current practices are, but also give insight into some barriers to appointment compliance that could be addressed in future standard of care implementations. Study results will identify the efficacy of such practices and whether it makes sense to continue the practice moving forward. Increasing appointment compliance will not only help the patients receive the care they need and deserve, but will also help the healthcare professionals to see more patients. The cost of a no-show in a clinic can negatively impact the clinic by not using its resources as beneficially as possible.

2.0 LITERATURE REVIEW

2.1 OVERVIEW OF SICKLE CELL DISEASE

Sickle cell disease (SCD) is an inherited blood disorder, or hemoglobinopathy, that was first reported in 1910 by Dr. James Herrick who initially described the red blood cells as “peculiar elongated and sickle-shaped”⁹. The discovery of the condition was made in a student attending a professional school in Chicago who was from Grenada, West Indies and had struggled with anemia, presented with yellow sclera, and with a condition that was called muscular rheumatism.⁹

SCD is a condition that affects approximately 119,100 individuals in the United States and about 1 in 365 African Americans.² It is one of the most common single gene disorders worldwide.² The single gene mutation in HBB, Glu6Val, causes a normal hemoglobin (Hb A) to change to a sickled hemoglobin (Hb S). The altered hemoglobin is hard and sticky, which is what causes symptoms to present in those affected. Hb SS accounts for about 60-70% of sickle cell disease worldwide, however there are other common variants including Hb SC (16.1%), Hb S β +thalassemia and Hb S β ^o-thalassemia (3.2%).¹⁰ Other more rare variants exist such as Hb SD-Punjab, Hb, SO-Arab, and Hb SE.

Hallmarks of the disease include pain and vaso-occlusive crises, which include acute chest syndrome, infection, splenic sequestration, and cerebrovascular events.¹¹ The variability of these clinical manifestations is multifactorial including genetic variation, level of fetal hemoglobin, inflammation, oxidative stress, and hypoxia-induced angiogenesis.¹²

2.1.1 History

At the time of the original 1910 case report by Dr. James Herrick, no specific conclusions were drawn and no name was given to the condition.⁹ There was some time between Herrick's first description and the mid-twentieth century when serious developments were made in the understanding of sickle cell disease. It was not until 1949, when Linus Pauling et al. had described sickle cell anemia as the first molecular disease, that it was suggested that sickle cell disease was a disease caused by the crystallization of the hemoglobin molecule¹³.

Sickle cell disease had been described, and there were subsequent papers that attempted to identify the mechanism behind the disease. In 1949, electrophoresis revealed that sickle hemoglobin moved at a different rate than normal hemoglobin, which gave the indication that there was a molecular charge or shape difference.¹³ Electrophoresis was new at that time, so it wasn't until 1954, when it was more widely available, that it was discovered that there were different forms of sickle cell disease, specifically Hb SC, which opened the door for the detection of other sickle cell disease variants.¹⁴

One of the major findings occurred in 1958, when Ingram et al. used fingerprinting and tryptic digests to identify that there was a single amino acid change between the Hb A peptide and the Hb S peptide that resulted from the trypsin digestion. Both of these peptides contained the same nine amino acids, with the exception of the first glutamic acid of Hb A being changed in Hb S to a valine (E→V).^{15,16} This was an important discovery for the future of understanding the mechanism for sickle cell disease, because it had validated the previously explained two less carboxyl groups in Hb S than in Hb A.^{13,17} This discovery also opened the door for further research into the mechanisms that cause sickling of the red blood cells.

Although the condition was discovered in the early 1900s and additional discoveries were made in the mid-1900s about how the HbS hemoglobin was abnormal, it was not until the 1970s when sickle cell disease awareness became a public concern. In 1971, there were fifteen community sickle cell organizations that came together for a conference, forming the National Association for Sickle Cell Disease.¹⁸ This organization remains today, but was renamed in 1994 as the Sickle Cell Disease Association of America.¹⁸ Health organizations became involved and acted as advocates for research funding. In 1972, President Richard Nixon passed the National Sickle Cell Disease Control Act, which provided the establishment of voluntary sickle cell disease screening, education, information, testing, counseling, research, and treatment programs.¹⁹ Shortly after, between 1972-1973, the National Sickle Cell Disease Program was established and the National Heart and Lung Institute began funding comprehensive sickle cell centers, as well as creating a sickle cell branch.²⁰ The research, promoted by funding from the National Heart, Lung, and Blood Institute (NHLBI) provided mechanisms for supporting research and disseminating information that led to important advancements for the medical care, survival, and quality of life for individuals with sickle cell disease. These advancements included newborn screening, penicillin therapy, pneumococcal vaccines, splenic palpation in splenic sequestration, hydroxyurea therapy, and bone marrow transplantation.²¹

More recently, in 2006, another public health improvement for sickle cell disease occurred with the recommendation that sickle cell disease be added to all state newborn screening panels. However, many states were already screening for it by this time, based on the recommendation in 1987 following the landmark study that showed that penicillin therapy beginning shortly after birth prevented deaths in infants and young children with sickle cell disease.²² New York was the first state newborn screening program that made sickle cell disease a required condition, having done

so since April 1, 1975.²³ This has proved instrumental in early diagnoses and proper prevention of sickle cell related complications in the infant period.²⁴ Before this was the case, many parents were unaware of their child's condition and had to watch them suffer through infection, stroke, and frequently, death. It was possible for parents to be unaware of the condition because the symptoms of sickle cell disease are not present immediately after birth. The reason for no symptoms is because babies are typically born with fetal hemoglobin (HbF) as the primary hemoglobin, which persists at high levels until about the sixth month.²⁵ Although very small amounts of HbF persist into adulthood, levels are reduced to about 0.6%.²⁵ However, this can range between 0.3% to 4.4% in the normal adult population.²⁶ Fetal hemoglobin is important because the sickle cell change affects the beta chains, and HbF is formed from alpha and gamma chains rather than beta chains.

In 1988, a study was done on the effect of mortality of children with sickle cell disease. There were two groups in this study, one was a group whose disease status was detected in the newborn period containing 89 patients, the other was a group in which disease status was detected only after symptoms were present containing 64 patients. Mortality among the newborn screen group was 1.8% compared to 8% in the control group. That difference supports a significant change in life-threatening events for children with sickle cell disease.²⁷ The justification for adding sickle cell disease was due to studies showing the benefit of early penicillin prophylaxis and the benefits it had on the survival of young children with sickle cell disease.^{22,28} The guidelines for management in conjunction with those that should be added to the newborn screen has solidified the testing of sickle cell disease and other related hemoglobinopathies in the United States and is now being applied to many other regions of the world.^{29,30}

The newborn screen is done by collecting a blood sample from a heel prick shortly after the baby is born, ideally between 24 and 72 hours after birth. With that dried blood spot, isoelectric

focusing is used to determine the sickle cell disease status. HbS, HbC, HbE, HbO Arab and HbD are the most common variants, and these can be confirmed using DNA probes. In Pennsylvania, the results are reported to the primary care physician listed on the filter paper as well as regional sickle cell centers. That physician is provided with specific instructions on follow-up, referral planning, and further diagnostic procedures. The Pennsylvania Department of Health has an order of action recommendation, which includes first advising the Department or laboratory which Treatment Center/Specialist is being recommended, then contacting that Treatment Center/Specialist for a referral and additional information before contacting the family. After the information is gathered, the family is contacted to check in on the status of the newborn and refer the family to the Treatment Center/Specialist for confirmatory testing and management.³¹ For carriers, the Newborn Screening and Follow-Up Program does not have formal hemoglobin trait guidelines, but does recommend consideration of confirmatory testing and genetic counseling. There is no immediate clinical significance with most hemoglobin traits, but it may be worthwhile to go to the appropriate treatment center for follow-up testing, education, and counseling services.³²

2.1.2 Molecular Genetics

Sickle cell disease has some genotypic variation, and at the molecular level is associated with pathogenic variants in the HBB gene. Typically, in individuals who have sickle cell disease one of these pathogenic variants is Glu6Val which results in Hb S. About 60-70% of the time, individuals are homozygous for this variant resulting in Hb SS disease. In the other cases of sickle cell disease, individuals have one pathogenic Hb S, Glu6Val mutation and then another variant which might include Hb C (Glu6Lys mutation), Hb D (Glu121Gln mutation), Hb O (Glu121Lys

mutation), Hb E (Glu26Lys mutation), or a β -thalassemia pathogenic variant. These are the most common variants that lead to sickle cell disease, although others have been identified and reported. Sequence analysis is typically required to find these mutations; however, duplication/deletion analysis is important in identifying a missing thalassemia allele.

Sickle cell disease is inherited in an autosomal recessive pattern.³³ In a scenario where both parents are carriers (also referred to as having sickle cell trait (AS)), with each pregnancy there are three potential outcomes: 1 in 4 or 25% chance that the child has sickle cell disease (SS), 2 in 4 or 50% chance that the child has sickle cell trait (AS), and a 1 in 4 chance that the child has neither sickle cell trait nor disease (AA).

2.2 CARING FOR INDIVIDUALS WITH SICKLE CELL DISEASE

2.2.1 Providers

The primary provider for an individual with sickle cell disease is typically a hematologist who can help manage medications, prevention, and therapies. The hematologist can refer the individuals to appropriate specialists when the time comes. Some of those specialists might include a pulmonologist, dentist, ophthalmologist, and cardiologist, to name a few. It is also important that an individual with sickle cell disease sees a primary care physician regularly, just like any other individual for wellness visits.

Another specialist that could prove important for caring for an individual with sickle cell disease or sickle cell trait is a genetic counselor. A genetic counselor can help the child's parents confirm their carrier status, explain how the condition is inherited, explain the individual risks for

that couple, and then give information on options moving forward based on what the couple desires. If both parents were confirmed to be carriers, the genetic counselor can discuss prenatal testing options as well as assisted reproductive options such as preimplantation genetic diagnosis. The genetic counselor can provide psychosocial support for the family because taking care of a child with a chronic illness can be a large responsibility, and it is important to acknowledge that. For individuals who are identified as a carrier on the newborn screen, a genetic counselor can speak with the family to help them understand what this means for the child, and what information is important to discuss as the child ages.

2.2.2 Prevention, Management and Treatment

Prevention in sickle cell disease can fall into three categories: preventing the disease (primary prevention), preventing early complications of the disease (secondary prevention), and preventing further complications of the disease (tertiary prevention). The first of these, preventing the disease, requires that a parent knows the carrier status for both themselves and their partner. If this is information that a couple is interested in or concerned with, there is the option to speak with a genetic counselor, or other educated personnel at a sickle cell center.

Once a child is born with sickle cell disease, the main concern becomes preventing early complications of the disease. Management begins at a very young age for individuals with sickle cell disease beginning with prophylactic penicillin starting at the age of three months, the flu vaccine administered yearly after six months of age, a special 23-valent pneumococcal vaccine at age two and five, and a meningococcal vaccine.^{29,34} Additionally, they are supposed to follow the vaccine schedule outlined for all children.

The most common causes of death in children with sickle cell disease are infection and splenic sequestration crises, with about 66% of children with sickle cell disease younger than age six being more susceptible to *S.pneumoniae* and children with sickle cell disease older than age 6 being more susceptible to *E.coli* (30%).^{24,35} Prophylactic penicillin was introduced in 1986 after a study was done by the Prophylactic Penicillin Study Group that assessed the efficacy of penicillin prophylaxis in preventing bacterial infections in children with sickle cell disease. The study was a randomized, double blind study done over the course of two years in the United States. There were two groups, one of which received penicillin V potassium 125 mg twice daily, and the other, placebo group, received vitamin C 50 mg twice daily. Patients were monitored every three months with a physical examination and a complete blood count. Pill counting and urine samples were used to determine compliance. The study ended 8 months early due to an 84% reduction in *S. pneumoniae* infection and lack of deaths in the penicillin group.²² The mean age of death improved after 1978 since the implementation of the special pneumococcal vaccines and prophylactic penicillin. The deaths due to infection also revealed a change with 74% of deaths due to infection occurring in adults after 1985.²⁴ Fatality in individuals with sickle cell disease due to infection in the United States used to be around 35%²², whereas after the implementation of prophylactic penicillin that rate is now rare.

Splenic sequestration must be monitored in young children as well, as many may need further intervention. About 94% of children with sickle cell disease, specifically HbSS disease, experience vaso-occlusion within the spleen which leads to functional asplenia by the age of five.³⁶ As many as 11% of children with sickle cell disease may experience a stroke. These strokes occur due to partial or complete occlusion of the internal carotid artery, anterior or middle cerebral arteries, or vertebral artery.³⁶ Originally it was thought that this was due to the sickling of cells

within tiny blood vessels, but showing that the large arteries were responsible revealed that this was not the case.³⁶ Later, it was shown that this may be due to perfusion failure as well as intravascular sickling.³⁷ One of the measures put into place to help prevent these events are transcranial Doppler (TCD), which is a type of ultrasound that measures the blood flow velocity through the blood vessels of the brain by measuring the echoes of ultrasound waves moving through the brain. It is recommended that a TCD is done annually, starting at the age of 2 years, for children with HbSS disease. A child is monitored this way and a normal TCD velocity is less than 170 cm/sec. If the flow velocity is at an elevated level of 200 cm/sec or greater³⁸ the child is identified as being at higher risk for the development of a stroke.³⁹ The child is started on a preventative chronic transfusion program to reduce the level HbS to less than 35%, which lowers the risk of stroke by greater than 70%.³⁹ Over the years, the TCD has proved to be a useful and valuable tool for stroke detection of risk factors for stroke in individuals with sickle cell disease.³⁸⁻

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Much of management of sickle cell disease is focused on treatment of symptoms or complications of the disease. When symptoms occur, they are managed and prevention measures that are implemented are to prevent further complications. Prevention and management guidelines for sickle cell disease have been created by the National Heart, Lung, and Blood Institute. An expert panel consisting of doctors and physician assistants came together to review the available scientific evidence about sickle cell disease to assist primary care physicians in caring for patients with sickle cell disease. The guidelines suggest preventative screenings for many complications, including pneumococcal infection, renal disease, pulmonary hypertension, echocardiogram, hypertension, retinopathy, strokes, pulmonary disease, and genetic counseling.⁴

The management of sickle cell disease is very complex, and it is critical as the only current cure, or treatment, for sickle cell disease is a hematopoietic stem cell (“bone marrow”) transplant. The transplant requires a human lymphocyte antigen (HLA)-donor, typically a family member. Beyond needing an exact donor, there are added complications that include a 7% transplant-related mortality rate as well as a 9% graft failure rate, meaning the disease-free survival rate is about 85% with a perfect match sibling donor.⁴¹ Different studies revealed data that contributed to these overall findings. One of those studies analyzed 44 patients given allogeneic related cord blood transplant for thalassemia or SCD, 11 of which had SCD. None of the patients in this study died, and 90% of SCD patients had 2-year event-free survival. It was also found that the use of methotrexate for prophylaxis was associated with greater risk of treatment failure.⁴² In France, a study was done over the course of six years between 1988 and 2004 with 87 patients, ranging from ages 2 to 22 years. Of note, antithymocyte globulin (ATG) was introduced into the conditioning regimen in 1992; this change improved the graft rejection rate, decreasing from 22.6% before to 3% after including ATG. Overall survival in this study was 93.1%, and the event-free survival was 86.1%. Graft versus host disease was the main cause of transplantation-related mortality.⁴³ Another study revealed that allogeneic bone marrow transplantation leads to normal erythropoiesis, as well as has a positive impact on the growth and the stability of CNS imaging studies and pulmonary function. This study followed twenty six patients for at least two years after transplantation with engraftment, and for 22 of 26 of these patients, complications related to sickle cell disease had improved.⁴⁴

Sickled cells not only cause complications for individuals with sickle cell disease, but they also have a much shorter survival, lasting 10 to 20 days instead of the normal 120 days.²⁹ Folate levels are then much lower in those with sickle cell disease. Folic acid may be beneficial in the

treatment in hemolytic anemia, however there is less data to support folate deficiency and/or the need for folate supplementation in sickle cell disease. Some have suggested that folic acid be administered on an individualized basis, and that evidenced based medications like penicillin and hydroxyurea continue to be used.⁴⁵

The first and only medication approved by the FDA for the treatment of sickle cell disease is hydroxyurea. This medication has proved effective in reducing hospitalizations, pain crises, and acute chest syndrome. The efficacy and effectiveness of the drug have both proved beneficial for those individuals living with sickle cell disease. Hydroxyurea has been the most significant benefit for those with sickle cell disease, but also needs to be adjusted to the optimal dose and monitored closely for toxicity and side effects. There need to be more frequent visits to the hematologist to check on blood count and hemoglobin levels as part of that monitoring process. Since this medication has shown such improvement for patients, compliance is important, and the drug cannot be safely prescribed without regular visits to ensure appropriate dose and to minimize side effects.

2.3 HYDROXYUREA

2.3.1 History

The first synthesis of hydroxyurea was done in Germany by Dr. WFC Dressler and Dr. R. Stein in 1869.⁴⁶ Hydroxyurea was originally intended to be used for the treatment of malignant and benign growths, such as cancer. The safety of the drug was approved by the FDA in 1967 for the use of treating a variety of solid tumors, especially carcinomas in humans.⁴⁷ There were

various clinical trials over the years testing the efficacy of this drug for treating other conditions, such as myeloproliferative, neoplastic, and non-hematological diseases, as well as HIV.⁴⁷ However, it was not until February 1998 when it was approved by the FDA for use, that hydroxyurea was used for adults with sickle cell disease who experienced recurrent moderate to severe painful crises. It was not approved for use in pediatric patients with vaso-occlusive crises and acute chest syndrome until 2007, and this was only by the European Medicines Agency.⁴⁸ Then in 2008, the Agency for Healthcare Research and Quality published a comprehensive systematic review and the National Institutes of Health Consensus Development Conference was held, both in discussion of the use of hydroxyurea for treatment in individuals with sickle cell disease.^{49,50} Efficacy and effectiveness found in multiple studies was reviewed, showing that it was efficacious in children and adults with SCD, reducing pain crises and hospitalizations, as well as increasing the percentage of HbF, quality of life and possibly increased survival.

2.3.2 Drug use and efficacy

The original study by Charache, Terrin, Moore and Dover that proved the efficacy of hydroxyurea in sickle cell disease was run from January 1992 until June 1994 and was ended 10 months early due to the significant differences between the hydroxyurea and placebo group (1995). The study had 134 patients who completed follow-up, as the study ended early and not all of the 299 patients were able to complete the full two years of follow-up before the study ended. Individuals were only included in the study if they were 18 years or older and their sickle cell disease was Hb SS or sickle cell-beta⁰ thalassemia. Hydroxyurea was found to reduce annual rate of crises by 44%, increase median time interval to first crisis from 1.5 months to 3 months, and increase median time to second crisis from 4.6 months to 8.8 months.⁵¹ It is important to note that

at this time the efficacy had only been shown in adult patients with sickle cell disease. For children, the efficacy of hydroxyurea was shown as early as 1996, but has not yet been FDA approved for use in children in the United States. The efficacy of hydroxyurea was evaluated through the events requiring hospitalization, which showed that 73% of individuals were not experiencing severe enough painful events to be admitted to the hospital while on hydroxyurea. This study included 22 patients with the median age of 8, and found that there was no relevant toxicity due to hydroxyurea.⁵² Another study assessed thirteen hydroxyurea patients, between the ages of 10 and 17 years, with HbSS or HbS-beta⁰ thalassemia. This showed the efficacy through the increase in total hemoglobin (1.3gm/dl), MCV (15.5 fl), and level of Hb F (6.9% to 15.2%). Hospitalization was also decreased from 4.1 to 1.7 days per month, with all values being statistically significant.⁵³ Another study looking at 8 children with Hb SS from ages 2-5 years found that hospital admission rates decreased by 55% and total hospital days decreased by 60% while using hydroxyurea in children with SCD. Transfusions were also decreased by 75% in this group, and Hb F levels increased from 6.8% to 19.9%.⁵⁴ Taken together, these many different studies have shown a wide range of benefits for the use of hydroxyurea in sickle cell disease.

2.3.3 Short and long term effects

Hydroxyurea has shown improvements for patients with sickle cell disease, particularly reducing the morbidity due to complications associated with sickle cell disease⁵⁵. In the short-term usage, it increases the fetal hemoglobin (HbF) levels in adult patients while also decreasing the frequency of vaso-occlusive events.⁵⁵ Long term, the increased levels of HbF have shown improvements in both morbidity and mortality. One study reports hydroxyurea usage after 9 years of follow up being associated with a 40% reduction in mortality in adults.⁵⁵ This study included

233 patients with complete follow-up data who were recruited from 21 centers throughout the United States and Canada.⁵⁵ In another controlled clinical trial that had originally identified the safety and short-term efficacy for hydroxyurea in individuals with sickle cell disease, specifically HbSS, continued to follow patients for 17.5 years. At any point during this time, patients could start or stop hydroxyurea. The death rate amongst the cohort was high, 43.1%, however, 87.1% occurred in patients that did not take hydroxyurea or took it for less than five years. The largest cause of death (24%) in this cohort was pulmonary complications.⁵⁶

Children who were observed over the course of 5-10 years were found to have no severe side effects that were related to the hydroxyurea treatment.⁵⁷ The treatment was discontinued in some patients, but this was due to the failure of the treatment or compliance issues.⁵⁷ Some studies identified many positive long term effects for children with sickle cell disease taking hydroxyurea.⁵⁸⁻⁶⁰ After 4 years, some blood specific changes that were observed were increased hemoglobin concentration, percentage of HbF, and mean corpuscular volume. In addition, there were decreased reticulocytes, white blood cells, and platelets. Acute chest syndrome events were significantly reduced, and patients experienced better spleen function and improved growth rates. This was one of the first indications that hydroxyurea could possibly preserve organ function.⁵⁸ In a long-term study by Zimmerman et al. that followed 122 pediatric patients over the course of eight years, they demonstrated the long-term safety of hydroxyurea.⁵⁹ There were also no issues with growth during this period, even with increased levels of Hb F. The same increases were found in this study as the study discussed above.⁵⁹ The Belgian Registry reported that in following patients over the course of six years, there was continued response to hydroxyurea with no significant long-term effects noted. This cohort contained 32 patients between the ages of 8 months

and 19 years, with 25% of the patients not experiencing sickle cell related issues that required hospitalization.⁶⁰

Since hydroxyurea is now a widely-used drug for children with sickle cell disease, it was important to evaluate the toxicity of the drug to ensure long-term safety and look at negative effects. In both of the studies mentioned above, there was no long-term toxicity that was found.^{59,60} An additional study done in 2006 with 75 patients between the ages of 17 months and 19 years. It revealed information like the two listed above, that hydroxyurea did not reveal any long-term toxic effects.⁵⁷

Despite all this, not all children with sickle cell disease are taking hydroxyurea. Some parents are hesitant to give their child medication before they are symptomatic, and not all children are facing the same medical issues, and are doing well overall. Typically, those with HbSS sickle cell disease experience complications earlier on in life than those with other variants. Taking hydroxyurea requires that individuals be seen in clinic more regularly to make sure their dosage is correct, which may hinder individuals from taking this medication as well.

The research has shown the many positive benefits of taking hydroxyurea for individuals with sickle cell disease. It decreases the number of crises and hospitalizations, among many other benefits. With a medication that has proven so effective, it is important to encourage individuals to make it to their appointments, so that the medical providers can optimize the dose and monitor for toxicity, especially with dose adjustments needed for growing children. Promoting appointment compliance is crucial in keeping these children healthy by ensuring they are taking their medications and doing well.

2.4 APPOINTMENT COMPLIANCE

2.4.1 Clinical no-show rate

The no-show rate in outpatient clinics is a costly problem that most clinics face, and unfortunately it is something that may not be well recorded. When the no-show rate is recorded, it is important to take advantage of this information and work towards ways to improve the number of individuals attending clinic appointments. The cost of the no-shows includes resources and physician time not being used appropriately. At a hospital based in Alaska, the no-show appointment total in 2015 was 13,344 patients, costing the hospital an estimated \$2 million, ranging from about \$176-\$202 per missed appointment.⁶¹ It is important to note that this cost is likely much higher in a multidisciplinary clinic. In a family clinic in Palmetto Richland Memorial Hospital/University of South Carolina, no-shows and cancellations accounted for 31.1% of scheduled appointments, and cost the hospital anywhere between 3%-14% of annual income.⁶² At a large medical center that included 10 regional hospitals at the Michael E. DeBakey VA Medical Center in Houston, Texas, it was found that in 2008 the cost per patient that did not attend their appointment was \$196.⁶³ More importantly, it negatively impacts the quality of the care the patient might receive and thus the satisfaction with that care. In a focus group of physicians, it was found that patients who missed appointments were viewed negatively, and some physicians recommended charging patients for these missed appointments.⁶⁴ This creates tension between the doctor and the patient and could then impact how the patient perceives the interaction in the future.

It is essential for individuals with chronic conditions, like sickle cell disease, to be seen in an outpatient clinic on a regular basis to receive their medications, immunizations, TCD screens, check blood counts, and adjust the care as needed as an attempt to prevent crises and complications,

as well as emergency department visits.⁴ Without these appointments, individuals with sickle cell disease could be at an increased risk for life-threatening conditions, including pneumococcal sepsis and stroke. With the advancements that have been made and the clinics that make that care possible, the lifespan of those living with sickle cell disease has increased to somewhere between 42 and 48 years old for those with HbSS³, compared to the 1970s when the life expectancy was less than 20 years.⁶⁵

2.4.2 Efforts to improve the clinical no-show rate

As the clinical no-show rate is an issue that clinics all over the country have experienced, there is some research about methods that have shown to be effective^{6,63,66-68}. One of the ways that has been implemented to increase appointment compliance is reminder phone calls.^{6,63} It is common that clinics have an automated system in place for reminding patients about their appointments. However, a personal connection was thought to be more effective, so some patients were called by a staff member and other patients were called using the automated system. There was a significant difference between the two methods for reducing the no-show rate, with the staff reminder calls (n=3266) proving more effective, with a no-show rate of 13.6% compared to the automated system (n=3219) with a no-show rate of 17.3% (p<0.01). Both methods reduced the no-show rate, as was seen by the no-show rate of 23.1% in the control group where no call was made. This study showed that the staff and automated calls had more people either come to clinic or cancel their appointments than in the group where they were not called.⁶ Other studies have looked at similar situations and found that the reminder calls slightly reduced, but did not statistically significantly reduce the no-show rate amongst their patients, making it effective but not ideal.^{63,66} In a retrospective cohort study, they evaluated the no-show rate, effect of reminder calls, and cost

of no-shows. The study found that reminder calls only reduced the no-show rate from 16.3% to 15.8%($p = 0.03$), and that the average cost per no-show was about \$196 in 2008.⁶³ Another study also found a reduction in no-show rate from 26% to 19% ($p = 0.0065$). This study is interesting because it also found that telephone reminders allowed more people to cancel or reschedule their appointments instead of not showing. That being said, it found no significant difference in the show rate in clinic, staying at about 63%. This means that the no-show rate along with cancellations accounted for 37% of total appointments.⁶⁶ In making these phone calls, studies have shown that the ability to actually reach the patient leads to a significantly higher rate of people keeping their appointment as opposed to those who were unable to be contacted, either due to no answer or lack of a phone.⁶⁹ Moving forward, knowing the target population and access to a telephone are important factors to keep in mind. Most people have phones, but the numbers may change, there may be temporary loss of service, and some families do not have phones.

2.4.3 Barriers

Implementing different systems to encourage appointment compliance is incredibly important, and to find the best solution it is necessary to find out why people are not attending appointments in the first place. Since there has not been a consistent method that has proved effective, studies have been conducted to discover these patient-perceived barriers. In one study patients consistently identified three different themes: emotional barriers, disrespect of beliefs and time, and distrust and lack of understanding of the scheduling system.⁵ Emotional barriers consisted of not wanting to hear bad news that is typically associated with going to the doctor, or the patient was not feeling ill at the time so there was the lack of urgency. The view of disrespect stems from the amount of waiting that takes place, either in the waiting room or in the examination

room. Patients feel as if their time is not taken into consideration. Lack of understanding in this case means that patients did not realize the cost of the no-show and how that impacted a clinic. It was perceived that the clinicians were happy about this because it was less work for them. Other common themes that came out of this study that was previously reported by other studies as well were transportation and child care issues.⁵ It is important to note that the population for this study was an adult population.

Perceived barriers in a pediatric sickle cell disease clinic have also been specifically studied, which is the most applicable study to be extrapolated for this project. The study population included 32 adolescent patients, aged 13-21 years from three sickle cell clinics in the Mid-west.⁸ The most common barriers that were reported were competing activities, feeling healthy and well, relationships with the provider, poor clinical experience, and forgetting. Semi-structured interviews revealed that appointment reminders seemed to be the most effective way to preventing the no-shows as well as flexible scheduling to accommodate competing activity issues. One way that was suggested for assisting with this was having evening appointment times. Interventions that could also impact appointment compliance are reminders, both in the form of phone calls and text messages. As far as addressing the issue of patients not attending clinic when they feel well, more education may be beneficial for informing individuals about why it is so important for their care and further wellness to regularly attend clinic visits.⁸

Although there is limited data with the sickle cell patient population, research has been done in other populations on barriers to appointment compliance. Forgetting is a common theme that is proposed for non-compliance. A randomized controlled trial of appointment reminders was done at Royal Children's Hospital in Melbourne, Australia, which sees patients ages 12-19 years. This study found that telephone reminder phone calls in the adolescent population reduced non-

attendance by 60%, from 20% to 7.9%. Participants were also surveyed and of those in the control group, 81% reported that reminder calls would be helpful, and in the reminder group, 77% reported that the calls were helpful.⁷⁰ In a diabetic nutritional care clinic, 293 patients undergoing outpatient treatment were surveyed and had their charts reviewed to determine non-attendance to clinic visits. The results of the study found that nonattendance was associated with many factors, including satisfaction with the provider and the utility of the appointment.⁷¹ Satisfaction with the provider is a theme that occurred in another study in San Jose, California. The study found that the patients' satisfaction was highly correlated with appointment compliance. Females and older adolescents were more commonly satisfied and thus had a higher appointment compliance.⁷²

In the sickle cell clinic at Children's Hospital of Pittsburgh of UPMC, providers started to observe that some changes might be necessary to provide the best care for the patients. Some families who were being seen for hydroxyurea follow-up informally expressed interest in having fewer clinic appointments and that they were coming to the clinic too often. This led to the implementation of having the frequency of appointments go from every month to every two months for patients who were on a stable dose of medication with no sign of toxicity and were considered safe to lengthen the time between monitored visits. Appointment compliance is something that all clinics aim to improve, and the sickle cell clinic wanted to be sure everything was being done to assist patients in coming to their appointments. Since patients commonly identify forgetting their appointment as a barrier, the standard of care changed to having a person call for appointment reminders in addition to the automated system. The hydroxyurea follow-up appointment frequency change in standard of care was initiated in September of 2015, and the personal phone call reminders began in September of 2016.

3.0 MANUSCRIPT

3.1 BACKGROUND

Sickle cell disease is a condition that is caused by sickling red blood cells and causes severe complications such as infection and severe painful crises. It affects approximately 100,000 individuals in the United States and about 1 in 365 African Americans.² While African Americans are primarily affected, it is of note that they are not the only population that is affected. Historically, the most common complication leading to death in sickle cell disease was infection, leading to fatality about 35% of the time. The efficacy of prophylactic penicillin was demonstrated in 1986, showing an 84% reduction in *S.pneumoniae* infection.²² It was this study that revealed that early intervention was important for survival for individuals with sickle cell disease, which eventually led to the nationwide addition of sickle cell disease to state newborn screening panels. With this policy implementation, more young children are being diagnosed with sickle cell disease, allowing them to be followed from an early age to prevent life-threatening complications.

For patients with sickle cell disease, it is imperative to be seen regularly for medications, checking blood counts, and adjusting care to prevent painful crises and complications.⁴ Management begins at a very young age for individuals with sickle cell disease beginning with prophylactic penicillin starting at the age of three months, the flu vaccine administered yearly after six months of age, a special 23-valent pneumococcal vaccine at age two and five, and a meningococcal vaccine.^{29,34} Further management guidelines for prevention have also been outlined by the National Heart, Lung, and Blood Institute.²⁹ Hydroxyurea is the most recent addition to the recommended management guidelines for individuals with SCD, showing many improvements in

reducing the morbidity due to complications associated with SCD^{55,58}, with limited toxicity^{57,59,60}. Follow up becomes even more critical for individuals taking this drug, as it is important that they maintain an effective yet healthy dose.

Lack of appointment compliance, or high no-show rates, is a problem that is consistent throughout outpatient clinics across the country and worldwide.^{6,63,66-68} Not all clinics have a good system for tracking this, but some have been able to track not only the no-show rate but the cost that comes along with that missed appointment. Research has shown that a single no-show can cost a healthcare system between \$175-\$200.⁶¹⁻⁶³

One common reason for missing appointments has been found to be forgetfulness.⁸ Many institutions have an automated reminder system in place; however, others have seen an improvement when using personal reminder phone calls.^{6,63} Both studies showed slight reduction in the no-show rate, and increased the number of patients who were calling to cancel and reschedule appointments. Patients cancelled more appointments than just not showing, but interestingly, it did not improve the show rate of about 63%.⁶³ A study by Parikh et al. found a significant difference between automated calls and personal phone calls.⁶ The no-show rate differed with automated calls having 23.1% no-shows and personal phone calls having 17.3% no-shows, and the study found that more individuals were canceling their appointments. In a separate study, patients reported that reminder phone calls were or would be helpful to encourage them to attend appointments.⁷⁰ Studies have also found that respect for the patients' time was important in encouraging appointment compliance, because sometimes patients feel that their time is not taken into consideration.⁵

The Pediatric Sickle Cell Program at the Children's Hospital of Pittsburgh of UPMC has a comprehensive multi-disciplinary team and serves about 250 patients from birth to age 22. In the

sickle cell clinic, providers started to observe that some changes might be necessary to provide the best care for the patients. For example, patients who were being seen for hydroxyurea follow-up expressed interest in having fewer clinic appointments and stated that they were coming to the hospital too often. This led to the implementation of having the frequency of appointments go from once every month to once every two months for patients who were doing well with the medication. Patients were identified as doing well on their medication when their blood counts remained consistent at a particular dosage. This change was implemented in September of 2015. The Pediatric Sickle Cell Program later decided to implement reminder phone calls because patients commonly identified forgetting their appointment as a barrier. In September of 2016, the standard of care in the clinic changed to include having a person call patients for appointment reminders both seven and two days prior to the appointment in addition to the reminders sent out by the automated system.

Although there has been some previous research into the barriers to care in young people with sickle cell disease⁸ and studies on the effectiveness of various strategies in reducing the clinic no-show rate, this study specifically looks at the separate impacts that fewer appointments and appointment reminder calls have on appointment compliance. In this study we aim to evaluate the effectiveness of these standard of care changes in the Pediatric Sickle Cell Program at Children's Hospital of Pittsburgh specifically designed to address to appointment no-show rate by measuring this rate during a set time period both before and after implementation of the changes.

3.2 METHODS

The participants for this study were chosen from the pediatric patients diagnosed with sickle cell disease who were cared for in the Pediatric Sickle Cell Program at Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center. The participant population included male and female patients ranging from ages 0 to 22 who were cared for in the sickle cell clinic. Patients of all types of SCD were included in the study.

3.2.1 Clinic Composition

The Pediatric Sickle Cell Program at Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center is staffed by a multidisciplinary team of medical specialists including a number of hematologists, physician assistants, social workers, nurses, genetic counselor and behavioral health specialists. The program was established in 1978, and identifies children with sickle cell disease as early as possible to provide management to best care for these individuals. The clinic has an annual patient volume of about 210 patients from birth to age 22. This particular clinic is included as one of the specialty treatment facilities for newborn screening, thus results are sent here and the multidisciplinary team works with families to provide appropriate follow up care through the clinic.

3.2.2 Policy Changes

The Pediatric Sickle Cell Program began calling patients to remind them of their appointments as part of a standard of care change that was implemented in September 2016. Under

this new office protocol patients were called by a sickle cell team member seven days prior to the time of their appointment and then called again two days prior to the appointment. The phone calls reminded the patient that they had an appointment, checked to ensure that the appointment date and time were still good for the patient, and gave the patient the number for scheduling and the opportunity to change the appointment if needed. The patient had the opportunity to cancel the appointment when they were called; however, they needed to make an additional call to scheduling in order to reschedule. If there was no answer and the patient's voicemail box was set up, there was a scripted voicemail left with the details of the appointment and the number where the patient could call to reschedule their appointment. When there were other patient issues that needed to be addressed, those were documented and addressed by the appropriate team member. Previously, patients were receiving calls regarding their appointment three days prior from an automated system, and this continued throughout the change as well.

The second standard of care change that was made in the Pediatric Sickle Cell Program was a change in appointment frequency for patients who were being followed for hydroxyurea management. These individuals previously were scheduled for an appointment to be seen every month. In September 2015, this requirement was changed to having an appointment scheduled every two months if the dose of medication was not changed and there were no concerns from the history, physical examination and laboratory studies. The patients who were seen both before and after this change were used to compare the no-show rate within this population before and after the policy change. This was done to determine if changes to the appointment frequency were effective in encouraging patients to attend their appointments.

3.2.3 Phone Call Participants

This participant population included patients who had at least one appointment in the Pediatric Sickle Cell Program over a 6-month period from September 2015 – February 2016 (prior to the implementation of additional reminder phone calls) and September 2016 – February 2017 (after the implementation of additional reminder phone calls). For inclusion in this portion of the study, participants needed to be called with an appointment reminder during the 6-month period from September 2016 – February 2017, and had to have appointments in the same time frame in the year prior. Individuals that were unable to be called during the phone call reminder time period were excluded from the study. The phone call reminder change was implemented in September 2016. The number of individuals included in this portion of the study is 101.

3.2.4 Hydroxyurea Participants

This participant population included patients who had at least one appointment in the Pediatric Sickle Cell Program over a 12-month period from July 2014 - June 2015 (before the change in appointment frequency) and January 2016 – December 2016 (after the change in appointment frequency). For inclusion in this part of the study, patients had to be taking hydroxyurea during both time frames stated above. Individuals who were not seen during both time frames or were not taking hydroxyurea during both time frames were excluded from the study. The change in frequency of appointments from every month to every other month occurred in September 2015. The number of individuals included in this portion of the study is 67.

3.2.5 Data Collection

The data were collected from the electronic medical record and coded. A no-show is counted when the patient does not show or cancels on the day of the appointment. Appointments that were cancelled prior to the day of the appointment were not included the dataset and did not count against the no-show rate. The data points that were collected included date of appointment, appointment status (cancelled, no-show, or completed), date of cancellation, sex, date of birth, and hydroxyurea status (for appointment frequency change).

3.2.6 Statistical Analysis

The data were collected from before and after these two standard-of-care changes were implemented. The appointment compliance before and after these changes were compared using paired analysis to determine statistical significance of the changes to the no-show rate. The data were not normally distributed so Wilcoxon signed rank test and a permutation test were done using Stata 2.0. Appointments that were cancelled before the day of the appointment were considered cancelled appointments as opposed to a no-show. These cancelled appointments were not included in the data, as cancelling prior to the appointment allows for someone to be rescheduled in the time slot. Descriptive statistics revealed the no-show rate, male to female ratio, and average age, and these were done in Microsoft Excel for Mac 2016. The data for each group of participants were considered separately. Patient names were coded and there was some overlapping patients between the groups. For those who had more than one appointment during the eligibility times, all appointments were included in this data set.

This study was approved by the University of Pittsburgh IRB.

3.3 RESULTS

The results of this study provide information about the efficacy of the standard of care changes that were implemented in the Pediatric Sickle Cell Disease Clinic at the Children's Hospital of Pittsburgh. The two changes that were being evaluated were a change in appointment frequency for hydroxyurea patients from every month to every two months, and an increase in personal phone call reminders to all patients.

3.3.1 Personal Phone Call Reminders

The individuals who were included needed to be seen both before and after the implementation of the additional phone call reminders, giving a total of 101 patients included in this analysis. The composition of this group included 46 females (46%) and 55 males (54%), ranging in age from 1 year to 21 years with an average age of 11.1 years (Table 1). The implementation of personalized phone calls started in September 2016, and the data were reported for this six month period and compared to the same six month period in the year prior. In the six months before the standard of care change was made, the overall no-show percentage was 28.5% (103/362 clinic visits). After the phone call reminders were implemented, the percent of no-show was 26.5% (76/287 clinic visits). The phone call reminders slightly reduced the no-show rate; however, it was not a statistically significant change (p-value = 0.3421) using a Wilcoxon signed

rank test. The 95% confidence interval for the median difference between the no-show percentages was from -12.5% to +5.8% (rate: -0.125 to +0.058). A decrease of 12.5% would be the equivalent of one fewer no-show per 8 appointments and an increased no-show percentage of 5.8% would equal approximately one more no show per 18 appointments. Since an improvement of one no-show per 8 appointments is likely to be considered clinically significant by most clinics, we do not have enough information from the number of patients in this study to determine the true effect and it is possible that a larger study would find a significant difference. Improved appointment compliance was seen for 35.6% (36/101) of patients after the implementation of the additional phone-call reminders, a decline in compliance was seen for 35.6% (36/101) of patients and 28.7% (29/101) remained the same. Of note, 22 out of 29 of those whose no-show rate remained the same were individuals who did not miss a single appointment (100% show percentage) in either time frame, with only 1 out of 29 being someone who missed all of their appointments (0% show).

3.3.2 Hydroxyurea Appointment Frequency

We studied 67 patients who were prescribed hydroxyurea during both periods of observation for this study. The patients' ages ranged from 2 to 22 years with the average age being 12.06 years. There were 33 (49%) females in this population as well as 35 (51%) males (Table 1). The hydroxyurea change in standard-of-care occurred in September 2015, so the data was collected regarding appointment compliance for June 2014 – July 2015 and January 2016-December 2016. Both of these time periods are a full calendar year that includes all seasons of the year. From June 2014-July 2015, there were 467 appointments scheduled for the participants (Before) and from January 2016-December 2016 there were 391 appointments (After). The percent of no-shows in the Before time period was 25.2% (118/467). In the following year the After no-show percentage

was 27.8% (108/391). The same 67 patients were included in both the before and after groups, and the Wilcoxon signed rank test revealed no significant difference between the two groups in the no-show rate (p value = 0.6818). The 95% confidence interval for the median difference was -11.9% to +7.4% (-0.119, 0.074). This means that the true effect could range from one fewer no-show out of 8.4 appointments to an extra no-show per 14.5 appointments. Similar to the Phone call study, an improvement of one no-show per 8 appointments is likely to be considered clinically significant by most clinics. Therefore, we do again not have enough information from the number of patients in this study to determine the true effect and it is possible that a larger study would find a significant difference.

The personal reminder phone call implementation happened during the second time period for the patients taking hydroxyurea. While the same individuals may not be in both the hydroxyurea and phone call group, we wanted to see if the addition of the personal reminder call had any effect on no-show rates. Interestingly in the hydroxyurea group before the phone call change was made in September 2016, the percent of no-shows was 28.5% (77/270) and after the phone call reminders the percent of no-show clinic visits was 25.6% (31/121).

Upon further evaluation, we found an improvement in compliance for 39.7% (27/68) patients, a decline in compliance in 39.7% (27/68), as well as 20.6% (14/68) patients whose compliance stayed the same. For patients who stayed the same, 10 out of 14 were individuals never missed an appointment (100% show), with 3 of these patients having 11 appointments in the first time range alone. None of these individuals missed all their appointments (0% show).

Table 1. Summary of Results

Reminder Phone Calls		Hydroxyurea Appointment Frequency	
101 individuals		67 individuals	
46% Female	54% Male	49% Female	51% Male
Age Range: 1-21 yrs. (Avg. 11.12)		Age Range: 2-22 yrs. (Avg. 12.06)	
Percent No-Show			
Before	After	Before	After
28.5%	26.5%	25.2%	27.8%
% Difference			
6.9%		9.3%	
p-value = 0.3421		p-value = 0.6818	

3.4 DISCUSSION

The standard of care changes made by the Pediatric Sickle Cell Program to improve appointment compliance provided information about these specific changes and how to effectively move forward.

This study assessed the effect of implementing reminder phone calls at 7 days and 2 days prior to the appointment on the clinic no-show rate. The no-show rate prior to implementing the personal reminder phone calls was 28.5%, and after implementation it was 26.5%, but this result is not statistically significant. In combination with prior research^{63,66}, this study shows that phone calls do not prove effective in reducing the no-show rate. The results of this study differ in the way the study was designed. There was always an automated system in place at our institution, whereas one previous study compared having no reminder calls to implementing both automated and personal phone calls at the same time as separate interventions. In the future, it might be essential

to consider other methods of communication. In a world that has become more technologically savvy, the implementation of a routine email or text messaging system could prove effective. Allowing a patient to cancel via text message might make for an easier scheduling process as well. Other ways that the phone call system could be changed to be more effective might be to do targeted calls for patients who have a higher no-show rate, while dropping the calls made to those who consistently have 100% compliance.

Based on the data from the change in appointment frequency for the patients taking hydroxyurea, it seems as if this is not enough to improve appointment compliance. The no-show rate prior to decreasing the appointment frequency for this group was 25.2% and after implementation, the no-show rate was 27.8%, but this was not statistically significantly different. Even though this intervention did not result in decreasing the number of no-show appointments, it may be that it does improve ease of access for some individuals, but this was not assessed as part of this current study. The number and frequency of clinic appointments was thought to be an issue, but in this limited assessment, the implemented changes were not shown to lead to significant change in no-show rates. While the results from this study do not show reason to continue with this policy, different results may be found if this was looked at for a longer period of time giving the opportunity for more individuals, or different individuals, to be included in the data.

Further analysis was done to see if a combination of both, a change in appointment frequency for hydroxyurea patients and personal phone call reminders, was useful in improving appointment compliance. There was a portion of these time frames that overlapped, and we were able to look at those no-show rates. There were some individuals that may have overlapped in these two groups, however in the hydroxyurea group before the personal phone call reminders the no-show rate was 28.5% and after it was 25.6%. These preliminary results do show a decrease in

the no-show rate, but further research would need to be done in order to determine whether these two interventions together make a statistically significant difference in the no-show rate.

There are a several limitations that exist in this study. One of the limitations includes the short time period over which appointment compliance was evaluated. To see significant changes, it may require studying these implementations over a longer period of time and/or with a larger number of patients. Many things can change over the course of years, including a difference in staffing, direction of the clinic, and policy implementations. For our clinic in particular, we certainly had many changes over the time period being studied. During this time there was a change in the medical director, which can influence the clinic and the patients. There was also construction being done to improve the clinic space which can change patient feelings toward coming to clinic. Some may feel that this is an additional barrier to coming to clinic and others may feel like this gives more urgency to actually attending their appointments. Patient factors can change over time as well including number of children needing transportation or childcare, means of transportation, changes in living conditions, and potentially guardianship, to name a few. The study looked at time periods with one year differences, and with that it means that the age of the child changes. The age of the child may be something that influences appointment compliance, and may warrant further research to tease apart these factors. The other factor hindering the efficacy of the standard of care changes is the prior rate of no-shows. The appointment compliance in the clinic, even before these changes, was 75% and 72%, in the hydroxyurea and phone call groups, respectively. This is a much higher show rate than has been previously reported in similar sickle cell clinics.^{63,66} This may indicate that this patient population already realizes the importance of regular care in the management of their condition, and appointment no show rates may be due to unanticipated reasons that would not be impacted by either of the changes implemented in this clinic. Since our

show rate was higher than those reported in the literature, it becomes harder to make significant changes to the improvement of the no-show rate. Both comparison groups only looked at individuals who were seen both before and after the change was made. It might be important to consider adding these individuals to the data as it does not include the new patients being seen in the clinic. There is, however, a strength in that there was a seasonal month-matched design.

Previous studies have looked at additional barriers to appointment compliance including feeling well, waiting times, transportation issues, child care issues, and competing activities.^{5,8} For this population, it seems as if forgetting may not be the issue, as the reminder calls were not effective in improving the no-show rate. These other barriers could be issues that are affecting our patient population as well. Transportation, for example, was not assessed, but in a metropolitan area it is not uncommon for individuals to rely on public transportation. Additionally, since many families are composed of more than one child, it is not unreasonable to think that lack of child care would be a barrier for families. Both were not assessed and could be considered for potential barriers. There was no information reported in this study on why patients were not attending their appointments, so this might be an important point of further research. While child care issues may be difficult to address, transportation barriers might be easily managed by offering transportation assistance during phone call reminders. The clinic currently provides transportation assistance to return home in the form of gas cards to families. It would be helpful to enhance this with the use of offering assistance through CSCF to get the patients to their appointments.

Since there seem to be many other barriers being reported in the literature, it would make sense to first ask the patients what prohibits them from coming to clinic appointments. One way to initiate the information-seeking process would be to survey the patients, and give them a chance to report what their perceived barriers are and what the clinic could do to assist them. It is important

to understand what the real cause for lack of appointment compliance is before any further changes can be made. Once the needs of the patient are understood, the clinic can move toward making changes that positively influence the patient population that they are serving.

Future research should focus on some other proposed or patient perceived barriers. It would be interesting to see if there were any differences in appointment compliance for those who are attending clinic from a distance. This would be useful in creating ways to make clinic more accessible through transportation funds or potentially through outreach clinics. The lessons that were learned from this study are that not all clinics are the same, and the population can differ. This leads to difficulty extrapolating other clinics barriers. It is important to look within for the answers because what is believed to be the barrier can be very different from what is actually the barrier. While there are many ways to move forward with further research surrounding this topic, it may be important to continue to look at the data that is already available. Some other factors to consider as sub-analyses to these data would be looking at differences based on factors such as age, sex, and distance from the clinic, to name a few. These are potentially factors that make a difference within the clinic and would therefore be important to consider for future research with this study in this clinic.

Overall this study provided the information that our clinic no-show rate probably did not benefit from a change in frequency of appointments or additional reminder phone calls. Based on the confidence intervals, it is possible that a longer or larger study may find a clinically significant improvement as these changes go forward. To further improve the standard of care and appointment compliance, different changes may need to be implemented. As this study emphasizes, it will be important to continue to track these changes in care to assess their impact in

the real clinic setting. These changes should be based on patient-perceived issues, to make sure the patients are benefitting as much as possible to encourage attendance to clinic visits

4.0 SIGNIFICANCE TO GENETIC COUNSELING AND PUBLIC HEALTH

Individual compliance to scheduled appointments is important across many fields throughout the healthcare system, including genetic counseling and public health. Genetic counselors and genetic counseling as a profession may be more directly impacted by patients not showing up for appointments than other public health professionals. As a profession, genetic counselors are in high demand and there are currently not enough people being educated quickly enough to fill all of the available positions.⁷³ That being said, it is important to understand how to help individuals keep their appointments, since time with genetic counselors is limited.

In order for the health of the public to be at its best, it is important for public health workers to be aware of appointment compliance for the individuals they are serving. There are still some public health departments that provide services for individuals so it is important for public health professionals to be aware of what works to encourage patients to adhere to appointments. Services that are provided include primary care, cancer screenings, and vaccinations amongst others. With the specific services they provide, there are often medical staff on site, and time and resources may be limited. Often, public health departments are providing services with a very low budget. Missed appointments, when there is limited time and resources, cause individuals with limited access to potentially miss some of these essential services. Public health departments cannot afford to have people missing appointments with frequency, otherwise their resources are depleted and fewer people are cared for. Thus, it is important that effective methods to encourage appointment compliance are also researched in the field of public health.

When patients do not attend their scheduled appointments, it is a cost concern for the hospital, can make it difficult for counselors to legitimize their time, and can act to extend already

long wait times for an appointment. The cost of a no-show for a hospital is estimated to be about \$200 per no-show, but this is for a general clinic appointment and not specific to a genetic counselor or other specialty provider.^{61,63} If patients are not attending, it may become even more difficult for hospitals to see the worth of genetic counselors who often measure their effectiveness via number of patients seen. Missed appointments add to this problem because alternate patients cannot be scheduled in an appointment slot of a person who no-shows. The cost of no-show appointments combined with sometimes limited access to genetic counselors can compound to make this issue an important one for genetic counselors and the hospitals or clinics that employ them.

Clinical genetic counselors typically operate in a health care setting with scheduled appointment times and often have significant appointment waitlists. Genetic counselors are in very high demand with many jobs available, and not enough educated professionals to fill these positions. As one might imagine, for a health care provider who is in such high demand, wait lists can exist and become backed up very quickly. There are many individuals who need to be seen by a genetic counselor, and those who are missing appointments take away the opportunity for someone else to be seen. Since there are not enough genetic counselors to see all patients who need to be seen, physicians have been encouraged to order testing themselves or put other providers in a position to do so^{74,75}, and no-show appointments could result in an increase in this conduct. While some doctors may have experience and the skill set to offer genetic testing with the proper information and counseling, many do not. Many physicians who order genetic tests have limited genetic knowledge; therefore, the patient is not receiving enough information or may even be receiving information that is not correct.⁷⁴

Genetic counselors have worked hard in some states to obtain licensure, but in other states that do not have licensure, it can be more difficult for counselors to bill for services, order tests, and be recognized as the experts in providing genetic counseling services. There are currently 19 states that have established licensure for genetic counselors, 3 states in rulemaking, and most of the other states are in progress towards obtaining licensure.⁷³ Licensure can help genetic counselors increase their value to a hospital. With licensure, genetic counselors are often better able to bill for their services and their time, and in some states they are even able to order their own genetic testing. The ability to bill for services is important because when this does not occur the hospital must cover the cost of the genetic counseling. This cost combined with the decreased efficiency and increased cost due to no-show appointments may become prohibitive to a hospital hiring new genetic counselors to meet patient needs.

Genetic counselors are important and can provide services to a broad spectrum of individuals in many areas including cancer genetics, prenatal genetics, pediatric and adult genetics, cardiogenetics, neurogenetics, and many more. Sickle cell disease is a part of a group of hematologic conditions, many of which are genetic, thus benefitting from the services a genetic counselor can provide. Genetic counselors can be a part of the comprehensive sickle cell programs that exist around the country where individuals identified on the newborn screen are referred. When an individual is identified with either sickle cell trait or disease, it is important to discuss inheritance, risks to other family members, management, reproductive options, and genetic testing. Genetic counselors are specially trained to provide this type of information to these individuals and their families, as well as provide that psychosocial counseling. Appointment compliance would be especially important for individuals affected with conditions found on the newborn screen since treatment is often recommended to start early. Since these patients generally need to

be seen in a set time span, no-show appointments may result in added stress on a clinic and its providers.

From a public health perspective, appointment compliance is important for several reasons. When looking at the three core functions of public health, appointment compliance is important in each of these three areas, assessment, policy development, and assurance. Under the function of assessment, the focus is monitoring health status and diagnosing health problems within the community. Individuals with sickle cell disease need to adhere to their appointments in order for their health to be appropriately monitored. Sickle cell disease is also included on the newborn screen as a way to identify individuals with this particular health condition who are then followed through clinic appointments for diagnosis confirmation. In addition, the diagnosis of their further health complications are identified through their clinic visits, and this can only be done when individuals are attending their appointments.

Policy development relies on understanding what methods are effective in reducing the number of individuals who are not attending clinic visits. This study directly relates to policy development because it provides an evaluation of policies that have been put in place at the clinic level. Evaluation is an important aspect of public health policies and interventions because it allows practitioners to assess whether the changes are working. In this study, the evaluation has thus far shown that the standard of care changes have not affected appointment compliance. This may inform future changes to the policies in order to best address appointment compliance in this population.

The core function of assurance is addressed by providing care to people, and this becomes more difficult if patients are not attending their appointments. The other main component of assurance is evaluating the accessibility of services, which is exactly the aim of the project.

Standard of care changes were evaluated to see the effectiveness in overcoming barriers to appointment compliance for individuals with sickle cell disease.

Attending appointments helps to keep people healthy, especially those individuals who are living with a chronic illness. Not only have no-show appointments been shown to be costly to hospitals and clinics, but hospitalizations and emergency department visits can increase the cost of healthcare spending, and these visits can increase without consistent care. The lifetime cost of care for an individual with SCD estimated to be \$460,151 in 2009⁷⁶, which is both a concern for public health and policy officials and a potentially significant burden on individuals and families experiencing this disease. Pain crises are one of the most common complications of sickle cell disease, and many individuals are admitted to the emergency department because of this. Emergency room providers may be unfamiliar with the details of sickle cell disease, which can result in delayed care or care that does not follow established guidelines.

The goal of public health as a whole is to ensure the health and well-being of all individuals collectively. When someone with a chronic illness is not attending regular visits, this can result in complications and can impact not only their health and quality of life, but also adversely affect family and friends around them. If a child with sickle cell disease is sick, they cannot attend school, and parents either need to find child care or take off work, and the financial and emotional burdens quickly add up.⁷⁷ These issues are better managed or prevented when individuals are regularly attending clinic visits.⁴ Since appointment compliance is so important, it is critical from a public health perspective to see what methods best encourage this behavior, and these implemented methods need to be evaluated in order to determine whether they are working and/or if other practices might be more useful to the patient population. Once barriers are identified, public health

programs could provide critical resources to help patients and their families overcome obstacles and successfully access the care they need for their health and well-being.

5.0 PUBLIC HEALTH ESSAY

5.1 BACKGROUND

Patients not attending their clinic appointments is an issue faced by healthcare systems across the country, and beyond. Patients cannot receive the care they require, and health professionals miss out on a chance to help other individuals when individuals do not adhere to scheduled appointments. There is also an associated cost to the healthcare system, both in the form of cost of the no-show, but also the cost of complications associated with lack of preventative care. In an attempt to increase appointment compliance, many institutions have implemented systems to encourage attendance, most commonly including reminder phone calls.^{6,63,66} Our clinic implemented a system of reminder phone calls and did not find a significant difference in the no-show rate. The study found that over a six month period with phone calls, the no-show rate did not change significantly from a six month period where personal reminder calls were not being done. In this study, reminder phone calls did not seem to significantly improve the no-show rate, suggesting that other barriers may be important.

In order to optimize future interventions aimed at increasing appointment compliance, it is important to gain an understanding of patients' perceived barriers. There have been a number of studies done in various clinics to better understand what some of these barriers might be. In a study where a population of children with sickle cell disease was specifically assessed, some common barriers were competing activities, feeling well, provider relationships, and forgetting their appointments.⁸ Suggestions on how to improve appointment compliance given these barriers consisted of appointment reminders and scheduling flexibility. In other clinics, not specific to the

sickle cell population, forgetting as well as satisfaction with the provider and utility of the appointment were identified.⁷⁰⁻⁷² Other barriers to care can include transportation, childcare, and prior work commitments that influence the ability to come to clinic. The literature has shown transportation to be a barrier that effects many people, including minority groups such as Hispanics and African Americans.⁷⁸⁻⁸⁰

Clinics can differ in their patient population, appointment policies, appointment reminder system, and a number of other factors. Based on these differences, it is important to evaluate the population being served by a specific clinic to see what the patients perceive as their barriers to appointment compliance. The Pediatric Sickle Cell Program is in an urban location in the Pittsburgh area. The clinic cares for patients 0-21 years old from all over western Pennsylvania. Since this clinic serves patients from all over the region, some patients are coming from an hour or more away. In order to assess perceived barriers to care in the patient population at the Pediatric Sickle Cell Program, we developed a survey for our patient population. The goal of this pilot study is to gain an understanding of what our population finds to be their most common reasons for missing an appointment and individuals' thoughts on appointment frequency, as well as giving patients the opportunity to identify specific changes that might improve their accessibility to the clinic. The results from this pilot study will be combined with future survey results to inform policy changes and the development of additional programs that address the barriers identified specifically by this population.

5.2 METHODS

5.2.1 Survey Rationale

The survey was implemented in the clinic to identify barriers to accessibility for the patients and their families as part of a new, larger research registry. Appointment compliance has been a focus in the clinic, and there have been efforts implemented to improve it. When new policies or protocols are made in a clinic, it is important to make sure they are effective and are addressing actual needs of the patient population. To ensure that further implementations are most likely to be effective, we felt we first need to go to the patients and their parents/guardians to see what their perceived barriers to attending appointments are. The survey was the tool that we felt was best to gather feedback on perceived barriers from patients.

5.2.2 Survey Design and Description

The survey consisted of four questions as well as space for the parent of the patient or patients over the age of 18 to provide any additional suggestions for us to make coming to appointments more accessible and beneficial to them. Three of the four questions gave patients the opportunity to check as many choices as they felt appropriate, as well as an “other” option where they could be more specific with responses. The fourth question was an open-ended question to allow participants to state what the most important reason for missing an appointment was. We wanted participants to be able to select all issues that applied to them and give additional input, because barriers to care is often a multi-faceted issue with multiple barriers often affecting access to services. We also thought it would be useful to know the most important of these barriers. The

options that were added to the survey for patients to select from were barriers that had been identified via a literature review and the experiences of the sickle cell team.

5.2.3 Research Registry

Patients or patients' parents were only eligible to take this survey after being consented to participate in our research registry. Individuals were given the opportunity to then fill out the barriers survey, however it was voluntary. The consent for the research registry takes place during the patients' regularly scheduled clinic visits. A member of the research team takes time at the end of the clinic appointment to talk with the patients and their parents/guardians about the research registry. Consent to the registry allows the research team to look at past, current, and future medical records in order to improve policies in the clinic and identify eligibility for future research studies. By participating, patients also consent to having specific demographic information shared between the research team and the Children's Sickle Cell Foundation, Inc. as the two work closely to provide the best care and support for families.

5.2.4 Study Population

The participants for this study were recruited from the Pediatric Sickle Cell Program at Children's Hospital of Pittsburgh between December 2016 and March 2017. Parents of patients under the age of 18 or patients over the age of 18 were asked to participate in this survey. All patients were individuals with sickle cell disease, including all types of sickle cell disease. The survey was administered after patients were consented to participate in the research registry in the Pediatric Sickle Cell Program. Both the research registry and the participant survey were approved

by the University of Pittsburgh IRB. The patient population included 11 patients between the ages of 3 and 16. There were no exclusions, and anyone attending a clinic appointment was included in the study population if they consented and chose to fill out a survey. Participation was completely voluntary.

5.2.5 Data Analysis

The data was collected from the paper surveys filled out by participants. The information was analyzed using descriptive statistics on Microsoft Excel for Mac 2016. Tables and charts were also generated using this software.

5.2.6 Pilot Study

The results from these surveys are being used as a pilot study to determine preliminary results about patient perceived barriers. The surveys were collected from December 2016 to March 2017, but research with this survey will continue beyond this survey. The goal is to continue to get people consented for the research registry, and receive more surveys about ways to improve the accessibility to clinic appointments.

5.3 RESULTS

The results of this pilot study showed that 91% (10/11) of participants did not think that they had too many clinic or hospital appointments (Table 2). The one participant who identified

having too many clinic appointments shared that they prioritized which appointments they attended by what they felt was most important.

Table 2. Survey Question 1

Do you think you have too many clinical or hospital appointments?	
Yes	1
No	10

Participants could identify barriers to their appointment adherence. When asked what the most common reason for missing an appointment was, 54% (6/11) of participants reported that the patient not feeling well or being in the hospital as the reason. Transportation was reported by 36% (4/11) of participants. Expense of transportation, which was a survey option, was identified by 27%, and another 9% filled in their own response of “transportation”. At least one participant stated that forgetting, weather conditions, and the inability to get off work each were the most common reasons for missing an appointment (Table 3).

Table 3. Survey Question 2

What are the most common reasons for missing an appointment?	
Not feeling well or in hospital or ER	6
Expense of transportation	3
Forgot	2
Poor weather	1
Unable to get off work	1
Transportation	1

Participants were also asked about ways that accessibility to the clinic could be improved in the future (Table 4). The most frequently chosen response was transportation assistance with 63% (7/11) reporting that this would be helpful in improving their ability to come to clinic. Reminder phone calls from Children’s Sickle Cell Foundation, Inc.(CSCF) or the sickle cell team and the coordination of appointments on the same day were reported by 18% (2/11) that each of these would improve the accessibility. Reminder phone calls – automated from the hospital and reminder text messages were also mentioned as ways to improve appointment compliance by at least one participant for each response.

Table 4. Survey Question 3

How do you feel that this could be improved?	
Transportation assistance	7
Reminder phone calls – from CSCF or sickle cell team	2
Having several clinic and testing (radiology or lab) visits coordinated on the same day	2
Reminder phone calls – automated from the hospital	1
Reminder text messages	1

5.4 DISCUSSION

Information from the results of this study confirmed some barriers found to be present based on prior research on this subject. In this study, 54% of participants identified that a common reason for missing a clinic appointment would be not feeling well or being admitted to the hospital

or ER. For individuals with sickle cell disease, it is not unreasonable to think that they would need to miss an appointment during an acute hospitalization, especially during seasons when certain illnesses are going around or they are experiencing crises. During the cold winter months, sickle cell patients are ill more frequently due to the cold causing decreased oxygen in the blood, as well as their susceptibility to illness and infection with many sicknesses occurring during this time.⁸¹ However, it might be important to determine whether this is due to not feeling well in particular or whether it is due to a hospitalization. If an individual is not feeling well, but not admitted to the hospital and still not attending their clinic appointment, then this is a concern. Individuals with sickle cell disease should consider coming to the clinic or hospital if there is a severe pain crisis and should always immediately seek medical care any time their temperature exceeds 101 degrees Fahrenheit.²⁹ There is concern that if individuals are not feeling well and still not going to the hospital, that there could be some gaps in patient understanding around this issue that then result in gaps in care. As part of the clinic appointment, it is important to emphasize the need to come to the hospital when the child is not feeling well. This is also an interesting finding because previous studies have found that patients feeling well has been a barrier for appointment compliance, but the opposite is true in this population, meaning that different interventions may need to be used in a clinic serving individuals with sickle cell disease as opposed to standard chronic illnesses or other indications.

Transportation was a theme observed when participants were asked about common reasons for missing appointments, and also ways to improve accessibility to clinic appointments. Only 36% of participants identified transportation as a reason for missing an appointment, almost double that number (63%) reported that transportation assistance would help to improve their ability to come to clinic. In the literature, various studies have been done on transportation as a barrier to

medical compliance. There have been studies showing that transportation affected 38% - 67% of the population, and found that minority groups such as Hispanics and African Americans were effected more.⁷⁸⁻⁸⁰ There are currently some methods in place through the social worker in the clinic to assist families with some of the burden of travelling home from the appointment. In Pennsylvania, particularly, there is a Medical Assistance Transportation Program (MATP) through the Department of Human Services. With this program, an application must be filled out, but all outpatient services are eligible for this service. MATP offers rides using vans as well as reimbursement for mileage or bus tickets. Similar services may be available in other states as well. This is an important resource to provide to patients who express the need for transportation assistance. Despite this service being available, patients are still identifying transportation as an issue, which may mean that this program is not fully meeting the needs of this patient population. Should this issue persist with the collection of additional surveys, the clinic might consider looking into additional programs to assist with transportation to the clinic for this patient population.

Other barriers were stated in the survey, but with less frequency. Recognizing that this is a pilot study, barriers reported even in low numbers should be considered. Some of those issues included forgetting, poor weather, and inability to get off work. Forgetting clinic appointments has been something that has been seen in the literature⁸; however, when studies are done on the efforts to address this barrier there have been mixed findings, including our study. Some studies found that telephone reminder calls do not significantly affect the no-show rate^{6,63} and others found that it has improved the no-show rate⁷⁰. Individuals with sickle cell disease react poorly to cold and poor weather, so many times parents like to protect them from exposure. Work commitments and issues with the weather have been reported in the literature as obstacles for some patients.⁸²

Suggested ways of improving appointment compliance included 18% of participants stating that they would like personal reminder phone calls from a member of the CSCF staff or sickle cell clinic staff and coordinating appointments to have multiple clinic visits on the same day. Prior studies have shown that individuals prefer a personal phone call to a call from the automated system.^{6,63,66} However, the literature has provided the knowledge that phone calls in general have not been significantly effective in reducing the no-show rate. There have been mixed findings in the literature on whether or not it is helpful in improving the no-show rate. A retrospective chart review study was done in our clinic to assess the effect of personal phone calls on the no-show rate, and the results showed that it did not make a statistically significant difference. It is important to note that individuals filling out this survey should have been getting the reminder calls, so it is interesting that some are still identifying this as something that would be helpful. This might indicate that some patients are not getting calls, do not have the ability to accept voicemails and/or are not listening to the voicemails. Interestingly, one patient identified wanting a reminder call from the hospital, which is something that is already routinely done in this hospital. In this case it would be important to address if the patient is receiving this call, because it could be a matter of the hospital having the wrong contact information. This is a situation that can be resolved easily by simply updating the patients' contact information. Reminder text messages were also mentioned by one participant, and recently this, too, has been implemented into the automated system.

Based on the identification of transportation being an issue in our population, it makes sense that individuals would find it more convenient to have those clinic appointments coordinated. Other reasons this might be convenient for patients is that it would require fewer missed days of school or work, as well as fewer days of additional childcare because the

appointments will be coordinated on the same day. Having many clinic appointments affects an entire family, and easing that burden helps the care of the individual. In the Pediatric Sickle Cell Disease clinic, our administrative assistant, who takes care of scheduling, and our social worker both work closely with the family and the care coordinators in the hospital to coordinate visits to the extent possible.

In this limited analysis, we did not find patients reporting some barriers that were reported in the literature, but because it has been shown to be an important barrier, it may be reported with additional study participants. Some of these barriers reported in the literature include the lack of child care, feeling well, expense of care, competing activities, utility of appointment, satisfaction, wait times, and travel time.^{5,8} Since patients with sickle cell disease can have a variety of medical providers, the number of appointments can add up quickly. Participants in this pilot study did not overwhelmingly seem to think that this was a barrier for them, with only one participant finding too many clinic appointments to be a barrier. Again, more participants in the study may provide a different result.

In the short time of our project, this pilot study can now be used to identify any barriers that can be managed with programs that already exist or provide a rationale to add a new intervention. There are some ways to provide transportation assistance to families in the clinic at this time. The registry also provides the link to the community based organization (CBO), Children's Sickle Cell Foundation, Inc. and with that link in place, the hospital and CBO can work together to best support the families and attendance in clinic. In the future, once a higher number of the patients in the clinic have been surveyed, those results will be important to implementing more broad and potentially more effective changes. Moving forward it might also be important to look at the structure of the survey itself. Some potential responses make analysis and interpretation

difficult. For example, the response to one question is “not feeling well or in the ED/hospital”. It is important to distinguish between these. Individuals need to come to clinic if they are not feeling well, but if they are in the hospital then their acute illness is already being addressed.

Limitations of this study include the small number of individuals who participated in the survey, as this is only a fraction of the number of patients who are routinely seen in this clinic. Participants who completed this survey were individuals who made it in to their appointments, and thus they may be experiencing fewer burdens than other patients who did not show up to clinic. This therefore does not account for data from individuals who are unable to make it to their clinic appointments. Patients are also self-selecting into this study, which may result in bias. Selection bias is important to consider in this study, and also as the study population grows. Anyone who comes to clinic is eligible, meaning there is no randomization in the data, and that the study participants may not adequately represent the desired population, which includes those who have failed to make it to clinic. The goal is to address barriers to coming to clinic, and if only those attending clinic are filling out the survey, it does not address the barriers of those not coming. Those who are not coming could be facing the most significant barriers, and they would be the ones that we would want to hear from the most. In this situation, it might be helpful in the future to do a survey over the phone or through a mailing. Confirmation bias could also arise in the future, as more and more individuals fill out the survey, the research team may look back at this pilot study and/or have their own beliefs about what is important. While focusing on confirming their beliefs, they might miss out on important themes that emerge. The framing effect could also be a bias that exists now and in the future. Different conclusions can be drawn from the same data when multiple people are analyzing it. In this study, where transportation came about, some might think

that individuals selected this, not because it is an actual issue, but because it would not hurt to have that assistance.

Future research should include the continuation of this survey as well as implementing and evaluating an intervention targeted for the most common barrier that arises. The study population in this study was small, so it is first important to continue gaining as much information as possible. Including as many patients as possible is critical to identifying a problem and solution that would impact the largest number of individuals. Once the barriers are found, they need to be addressed to the best ability of the clinic taking into consideration available resources. This can be done by implementing a clinic-wide intervention that aims to overcome a specific barrier. The effectiveness of this policy change would need to be evaluated as well to see the true impact it would have on the clinic.

Pediatric patients with sickle cell disease are vulnerable and it is important to address their barriers to access more than the average healthy individual. Having a chronic illness, specifically sickle cell disease, can cause many complications if not followed and treated preventatively and regularly. When individuals with sickle cell disease face issues that require them to be hospitalized many are effected. Parents are unable to go to work, children are unable to go to school, and other children in the family need to be cared for, just to name a few. Education for children is important and parents maintaining the affordability to care for that child are important to public health. If children are unable to attend school and parents are unable to attend work due to hospitalizations, this is an issue. Accessibility and equality of care are focused on in much of public health, and identifying patient perceived barriers aids in improving the quality of life of the public.

In conclusion, this survey data provides some insight that could very easily extrapolated to the rest of the clinic, and potentially other clinics serving patients with sickle cell disease and other

childhood genetic conditions as well. There was some consensus about barriers, and there seems to be some reasonable solutions to these issues. Moving forward, it would be beneficial to continue to survey individuals who are being cared for in the Pediatric Sickle Cell Program. In the meantime, Preliminary data can help to inform current practices to ensure the best quality of care. It will also be important to continue to measure the impact of any standard of care changes made as we move forward.

5.4.1 Public Health Significance

There are 10 essential public health services that fall under three public health core functions. The public health core functions include policy development, assurance, and assessment. Assessment services include monitoring health and diagnosing and investigating disease. Policy development encompasses informing, educating, empowering, and mobilizing community partnerships, and developing policies. The assurance core function involves evaluating, assuring competent workforce, linking to/providing care, and enforcing laws.

This pilot study touched on each of the three core functions of public health. As a clinic, we were investigating to identify our particular population's perceived barriers. Policy development includes using evidence to create new policies or edit existing policies at the clinic level. In doing so, participants were empowered to give their feedback for improvements, providing an evidence-based basis for change while also creating and solidifying community partnerships. Also, it helps with assessment because the registry will enable future research to be conducted to improve care for this population. As part of the registry, individuals' information can be shared between the research team and the Children's Sickle Cell Foundation, and getting the

patient on board to be a part of the relationship that already exists between the hospital and the CBO adds a critical unifier to the relationship. By connecting the families to that CBO, participants were linked to care. While the hospital provides the physical care, the CBO can offer the social and emotional support that makes for better all-around care. Assurance involves helping to ensure that patients are receiving recommended care for their diagnosis and addressing gaps in care. With this survey we were able to address the patient-perceived gaps to access in care by identifying the barriers that make it difficult for them to attend clinic appointments. By identifying barriers, it again helps policy development, but in addition to that it helps individuals make it to their clinic appointments, in turn allowing them to receive the recommended care for their diagnosis.

APPENDIX A: IRB APPROVALS



University of Pittsburgh Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
<http://www.irb.upitt.edu>

Memorandum

To: Cheryl Hillery, MD
From: IRB Office
Date: 3/16/2017
IRB#: [PRO17020086](#)
Subject: EFFECT OF STANDARD OF CARE CHANGES ON THE NO-SHOW RATE IN A SICKLE CELL CLINIC

The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:

45 CFR 46.110.(5)

The IRB has approved a waiver of informed consent/HIPAA authorization to access, record and use protected patient health information/patient medical record information.

This study has been approved under 45 CFR 46.404 for the inclusion of children.

The risk level designation is Minimal Risk.

Approval Date: 3/16/2017
Expiration Date: 3/15/2020

This study meets the criteria for an extended approval period of three years. **In the event that any type of federal funding is obtained during this interval, a modification must be submitted immediately so the IRB can reassess the approval period.**

For studies being conducted in UPMC facilities, no clinical activities 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.

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



University of Pittsburgh Institutional Review Board

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Memorandum

To: Cheryl Hillery ,
From: IRB Office
Date: 12/9/2016
IRB#: [PRO16070078](#)
Subject: Sickle Cell Research Registry

The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:

45 CFR 46.110.(5)

45 CFR 46.110.(7)

There are no items to display

This study has been approved under 45 CFR 46.404 for the inclusion of children. The IRB has determined that the written permission of one parent is sufficient.

The risk level designation is Minimal Risk.

Approval Date: 12/9/2016

Expiration Date: 12/8/2017

For studies being conducted in UPMC facilities, no clinical activities 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.

APPENDIX B: PUBLIC HEALTH BARRIERS SURVEY



Marty Ostrow Treatment Center
Children's Hospital Drive
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Pittsburgh, PA 15224
412-692-5055
Fax: 412-692-6675

This questionnaire is to help us better understand the challenges that may exist for coming to clinic visits.

www.chp.edu

What are the most common reasons for missing an appointment?

- Forgot
- Issues with child care
- Unable to get off of work
- Already received care (physical, labs, prescriptions) in the hospital or ER and didn't desire follow up in the clinic
- Expense of transportation
- Feeling well
- Not feeling well or in hospital or ER
- Expense of clinical care
- Competing activities or another appointment
- Don't find the appointment useful
- Satisfaction with care
- Clinic wait times
- Travel time
- Other, please specify _____

What is your most important reason for missing appointments?

Do you think you have too many clinical or hospital appointments?

- Yes
- No

If yes, can you please briefly describe how you choose which appointments to attend?

How do you feel that this could be improved?

- Transportation assistance
- Having several clinic and testing (radiology or lab) visits coordinated on the same day
- Reminder phone calls - automated from the hospital
- Reminder phone calls - from CSCF or sickle cell team
- Reminder text messages
- Other, please specify _____

Please list any other suggestions you may have for us to help make coming to appointments more accessible and beneficial to you.

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