An Algorithm for Using Hydroxyurea in Sickle Cell Disease

Joy Elliott Curry

College of Nursing, East Carolina University

Doctor of Nursing Practice Program

Dr. Dianne Marshburn

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Abstract

Sickle Cell Disease (SCD) is an inherited blood disorder that affects many African Americans globally. This disease is characterized by acute complications from chronic anemia, episodes of painful acute on chronic vaso-occlusive pain syndrome, and organ damage. Despite optimizing Hydroxyurea (HU), these events can still occur. The purpose of the DNP project was to implement an algorithm to standardize HU for specific genotypes, particularly hemoglobin SS and hemoglobin Sβ-0-thalassemia. The project aimed to increase HU prescribing and improve educational opportunities for this disease-modifying therapy to achieve the benchmark of at least 80% prescribing. The Plan-Do-Study-Act methodology was used to test change and evaluate HU prescribing. Findings from the project indicated an increase in prescribing with the use of the algorithm. The algorithm provided an evidence-based guideline for decision-making based on eligible hemoglobinopathies. Standardizing this algorithm enabled providers to increase HU prescribing and provide educational leaflets on HU to patients which, in turn, increased the interests of the participants to engage in self-management. HU is an effective way of improving the patients' outcomes for preventing complications with SCD.

Keywords: sickle cell disease, hydroxyurea, algorithm, hemoglobin SS, and hemoglobin Sβ-0-thalassemia

Table of Contents

Section I. Introduction

Background

Sickle Cell Disease (SCD) represents a blood disease inherited from an autosomal recessive pattern (Keikhaei et al., 2015). According to the author, compared to healthy individuals, patients with SCD experienced significant declines in their health-related quality of life (HRQOL) across their life span due to the disease and its complications. Badawy et al. (2017) indicate that SCD is an inherited red blood cell disorder seen in 100,000 African Americans, namely in 1 out every 365 births. The disease is characterized by "chronic anemia, painful crises, organ damage, reduced quality of life (QOL), high health care costs, and shortened life span" (Smaldone et al., 2016, p. 2).

When addressing SCD, particular attention should be paid to Hydroxyurea (HU), a disease-modifying medication recognized as a standard of care used to prevent symptomatology in patients with SCD. This medicine is beneficial in both adults and children with decreasing the symptomologies and clinical manifestations of the disease. Hydroxyurea is an oral medication that is dosed once daily. The only approved therapeutic drug for sickle cell disease is noted to reduce symptoms, morbidity, and mortality and improve the individual's quality of life (Smaldone et al., 2016).

The Food and Drug Administration approves this medication for treating SCD. Hydroxyurea therapy emerged as a treatment for SCD that has evolved over thirty years ago, which benefits have been shown by increasing the fetal hemoglobin concentrations in adults with sickle cell disease (Smith et al., 2019). HU has several clinical benefits associated with decreasing vaso-occlusive sickle cell pain crises, decreasing acute chest syndrome, preserving organ function, and preventing organ damage to target organs such as the liver, heart, brain, and

kidneys. HU is an efficacious disease-modifying medication that is widely available and can be inexpensive. Ware (2015) noted that "the National Heart Lung and Blood Institute (NHLBI) issued evidence-based guidelines for SCD with an entire chapter devoted to HU therapy" (p. 436).

Organizational Needs Statement

The Hematology Adult Comprehensive Sickle Cell Clinic, affiliated with a nonprofit healthcare system in central North Carolina, has identified the need to improve HU prescribing in specific genotypes. The clinic will be proposing an algorithm for standardizing HU in specific genotypes, particularly hemoglobin SS and hemoglobin Sβ-0-thalassemia. The clinic will partner with several organizations initiating a quality improvement project for HU. Other organizations will propose their quality improvement (QI) initiative for HU by providing feedback for HU adherence. The partnering organization will connect with namely the Education and Mentoring to Bring Access to Care (EMBRACE) SCD Network to provide the best resources for patients with sickle cell disease. The partnership includes investigators from eight other states in Southeastern USA, with clinics implementing standards of care to improve HU prescribing. Institutions will collaborate in sharing individualized plans with clinicians in ways to improve HU prescribing using evidence-based guidelines.

EMBRACE is a collaborative network committed to increasing the number of providers adhering to the National, Heart, Lung, and Blood Institute (NHLBI) guidelines for providing exceptional care to patients with sickle cell disease, initiatives for increasing the pool of providers offering grounded evidence-based SCD care by disseminating technology to support providers, and implementing strategies for improving access to quality care in patients with SCD in a medical home. [Regional Project Manager] EMBRACE Project-Sickle Cell Disease,

personal communication, July 17, 2020). The proposed DNP project will be a quality initiative in collaboration with EMBRACE to implement an algorithm in the clinic to standardize the use of HU. The benchmark for the clinic is to achieve the goal of prescribing HU at least 80% or more significantly in the adult population with specific genotypes [project champion], personal communication, May 29, 2020). This effort would substantially prevent morbidity, mortality, and improve the quality of life of patients with SCD.

Currently, the clinic serves approximately 450 SCD adult patients, with at least two-thirds of the patients with genotypes of hemoglobin SS and hemoglobin Sβ-0-thalassemia [Associate Professor of Adult Comprehensive Sickle Cell Clinic] personal communication, July 6, 2020). A recent chart audit indicated the providers were prescribing HU at 60% [Associate Professor] of Adult Comprehensive Sickle Cell Clinic personal communication, July 6, 2020). In collaboration with the eight states, the organization recognizes the importance of this initiative for improving hydroxyurea prescribing by establishing measurable goals for improving the communities' healthcare in patients with SCD. The goal is to implement a standardized algorithm for HU prescribing of specific genotypes that include educating the staff, patient, family, and multidisciplinary clinicians about HU.

Presently, the clinic has not achieved the benchmark of at least 80% of eligible patients receiving HU prescriptions. A process to identify patients who meet the criteria to receive HU will be essential for improving the care of patients with SCD. This allows providers and clinicians the opportunity to discuss HU with specific patients of identified genotypes. According to Ware (2015), the NHLBI's first treatment recommendation, based on the consensus panel of expertise, includes educating all patients and families about HU therapy.

According to Healthy People (HP) 2020, major objectives include "increasing the proportion of persons with hemoglobinopathies who receive early continuous screening for complications, increases the proportion of persons with a diagnosis of hemoglobinopathies who receive disease-modifying therapies, and increase the proportion of community-based organizations that provide outreach and awareness campaigns for hemoglobinopathies" (Office of Disease and Health Promotion, 2015, para.4). The Healthy People 2030 proposed "a leading health indicator to increase the proportion of Medicare beneficiaries with SCD who receive disease-modifying therapies" (Office of Disease and Health Promotion, 2018, para. 4). The indicators will help educate the community, patients, and staff concerning the clinical benefits of HU prescribing. This supports the initiative to implement an algorithm with standardizing HU in practice. The indicators align with the clinic's goals to increase prescribing and achieving the benchmark of 80%.

Swarthout and Bishop (2017) noted that a recently developed framework aimed to improve health system performance deserves careful regard. From their perspective, the Triple Aim framework is likely "to improve health-systems performance by focusing on improving the individual patient experience, improving health outcomes for populations of patients, and reducing per capita cost of healthcare" (p. 1405). The need for this project aligns with the Triple Aim by initiating an algorithm that provides guidelines for standardizing HU prescribing that includes quality of care, improves patients' outcomes, and experiences of SCD. In addition, the use of HU decreases clinical manifestations of SCD by reducing the capital costs of care related to admissions or readmissions.

Problem Statement

Luzzatto and Makani (2019) noted that "HU is recognized in the national and international guidelines as the standard of care for patients with SCD" (p. 187). HU is noted to decrease effects on pain reduction, prolong survival, improve quality of life, and prevent organ damage with preserving the quality of life of individuals with SCD. Currently, there is no standardized algorithm for prescribing HU for patients with SCD at the clinic. The current prescribing HU rate is approximately 60%, below the clinic goal of 80% [Associate Professor] of Adult Comprehensive Sickle Cell Clinic, personal communication, July 6, 2020). The projected measurable goal is that 80% of adults with SCD of specified genotypes will receive HU [Project Champion] personal communication, May 29, 2020)

Purpose Statement

The purpose of the proposed Doctor of Nursing Practice (DNP) project is to develop and implement an algorithm to standardize HU in the Hematology Adult Comprehensive Sickle Cell Clinic. In addition, this project will provide an opportunity to address any barriers to prescribing and evaluate strategies in achieving the benchmark of 80%. This will be a collaborative effort with the clinic partnering with EMBRACE in providing evidenced-based care for improving HU prescribing in SCD patients [Regional Project Manager] EMBRACE Project-Sickle Cell Disease, personal communication, July 17, 2020).

Section II: Evidence

Literature Review

The literature review was conducted using the search engines, namely, Google Scholar, PubMed, and Cumulative Index to Nursing and Allied Health (CINAHL). The search terms used in Google Scholar included sickle cell disease, sickle cell anemia, adults, Hydroxyurea, medication adherence, hematological improvement, novel therapies, anemia, and hydroxycarbamide (another abbreviated name for HU). The MeSH terms used included the following ones: *MH "Hydroxyurea", OR TI (hydroxyurea), OR AB (hydroxyurea), "Hydroxyurea" (MeSH) OR hydroxyurea (tiab).* The PubMed search yielded 49 articles, CINAHL 72, and Google scholar 31 articles. The articles were reviewed looking for sickle cell disease (SCD), hydroxyurea, and adult populations with SCD. Once the additional limitations of inclusion and exclusion criteria were applied, this narrowed the search significantly.

Articles of interest, with publications dating from 1997-2020, were retrieved with 2 from Google Scholar, 12 from PubMed, and 6 from CINAHL (see Appendix A). The articles reviewed included the last five years, published and written in English. Literature were synthesized by using Melnyk & Fineout (2019) levels of evidence. The levels of evidence encompassed Levels VI and above (see Appendix B). The inclusion and eligibility criteria for the articles included persons aged 16 years or older, with sickle cell disease of specific genotypes hemoglobin SS and hemoglobin Sβ-0-thalassemia documented by the past medical history of hemoglobin electrophoresis, currently not on HU. The exclusion criteria included adults without a current diagnosis of SCD or those considered pediatric patients with SCD. Articles not meeting the inclusion criteria were removed from the literature of review. There were 16 articles retained.

Current State of Knowledge

The most recent published report provides a summary for improving the quality of care for individuals with SCD with evidence-based recommendations to guide practice for the treatment of adults with sickle cell disease (National Heart Lung and Blood Institute [NHLBI], 2014). Green et al. (2017) state that offering HU, a sole FDA-approved treatment, is the standard of care for eligible patients with SCD. In addition, the author states that HU provides anti-sickling properties that prevent the clinical manifestations that include vaso-occlusive crises and acute chest syndrome.

According to Luzzatto and Makani (2019), HU is recognized in national and international guidelines as the standard of care in patients with SCD. HU is considered one of the novel therapies currently being used to treat SCD. HU has the efficacy for alleviation, prevention, or even reversal of chronic damage of organs and effects on long-term mortality in individuals with SCD (Smaldone et al., 2016). The author noted that HU and its clinical benefits are pointed out for improving laboratory parameters, reduce clinical complications, and improving survival rates.

The American Society of Hematology strongly recommends HU for people with hemoglobin SS and hemoglobin Sβ-0-thalassemia. This treatment recommendation set high standards for specialists caring for patients with SCD. The literature review supported NHLBI guidelines of an algorithm as a guide for standardizing HU nationally in the specified genotypes.

Current Approaches to Solving Improving Hydroxyurea Prescribing

There were several approaches for addressing HU prescribing in the clinic. According to Badawy et al. (2018) patient-centered eHealth interventions with telemedicine, e-chats, and mobile messages can be used to enhance patient-centered care with decision making. Improving patient engagement is one important outcome that eHealth interventions improved the patients'

self-engagement in their healthcare. Interventions of eHealth were used in the clinic for discussing HU with patients by telemedicine since ideally, we reside in a world that utilizes technology regularly. This provided an intervention for reaching out to participants, of specific genotypes with education about HU (see Appendix C). The strategy incorporates text messaging, mobile APPs, and web-based apps. The interventions of web-based applications improved the patients' knowledge about HU and provided feedback about the medication.

Hankins et al. (2020) asserted that Mobile health (mHealth) apps could potentially provide benefits for the increasing adherence to HU and facilitation of prescriptions among medical providers. The existing body of research notes that support for mHealth provides interventions for improving treatment adherence with various chronic diseases, including SCD. The author mentions that mHealth can aide physicians in decision-making and facilitate consultations with other providers and experts in their areas of expertise. This would serve as an intervention for the clinic to help optimize the HU prescribing of providers.

The clinic used coaching from expert clinicians explaining the clinical benefits of HU with tracking prescribing of the providers. This strategy would inform the patients about HU and its clinical usefulness**.** According to Green et al. (2017) community healthcare workers are great adjunct staff for supporting the coordination of self-management responsibility to support participants' daily habit of HU adherence. The self-management interventions could educate patients about HU and provide a direct connection for patients to follow up with using technical resources with messaging or emailing providers about their HU adherence. The eligible participants receive literature on HU.

Evidence to Support the Algorithm

The evidence-based algorithm guided the team on decision-making regarding HU of eligible hemoglobinopathies with hemoglobin SS and hemoglobin Sβ-0-thalassemia (see Appendix D). Bakshi et al. (2017) discussed two approaches of disease-modifying therapies for SCD: either the collaborative approach (CO) or proponent approach (PA). The methods include: 1) CO, which is characterized by the need to emphasize and discuss all possible options to ensure that the family is making informed decisions, and 2) PA, by advocating a pre-determined treatment plan providing the patients/families' options which were characterized by determining the treatment plan providing patient/families' options with convincing them to accept the treatment of choice.

An algorithm for HU prescribing served as a guide for initiating HU. Since HU is recognized by the NHLBI standards of care for SCD nationally, this medication will be offered to the specified genotypes during their clinic visits. Green et al. (2017) state "that achieving the personal best, which is the maximizing of HU to the maximum tolerated dose, is the ideal option if tolerated by patients" (p. 2). Ware (2015) noted that HU has proven efficacy in numerous clinical trials as a disease-modifying medication used in SCD. HU should be offered to prevent irreversible complications in SCD. The author reported that HU is not a cure, but it significantly reduces the mortality of sickle cell anemia (SCA). The algorithm will be the intervention used in the clinic to initiate HU prescribing and education for eligible patients.

The algorithm will be used for dose escalation to guide clinicians in meeting the maximum tolerated dose of HU prescribing. This initiative will introduce HU safely and effectively in genotypes at risk for severe irreversible complications of SCD. Strouse (2016) noted that hydroxyurea reduced hospital admissions, acute visits for pain, and acute chest syndrome by half

in randomized clinical trials. The author suggests that multiple observational studies demonstrated improved morbidity and mortality in children and adults with sickle cell anemia of hemoglobin SS and hemoglobin Sβ-0-thalassemia genotypes treated with HU. The best intervention would be establishing an algorithm for HU (see Appendix D).

Evidenced-Based Practice Framework

Theoretical Framework

The Transtheoretical Model (TTM) has been identified as the theoretical framework in guiding this project. The stages of change theory within the TTM include: 1) pre-contemplation, 2) contemplation, 3) preparation, 4) action, and 5) maintenance (Raihan & Cogburn, 2020). The pre-contemplation is the first stage of identifying a need for the protocol and awareness of HU prescribing. Contemplation is an awareness of the clinic not meeting the benchmark of at least 80%. Preparation is identifying the problem and developing steps towards implementing a protocol with guidelines for HU. This is where change will occur. Finally, the maintenance step includes an ongoing implementation and evaluation of the algorithm for 12 weeks to determine if HU prescribing increases amongst the clinicians.

According to Prochaska and Velicer (1997), the transtheoretical model gravitates towards the stages of change to integrate processes and principles of evolution from different intervention theories. The preconception is thinking about HU and the clinical benefits of prescribing to the specific genotypes. Contemplation is the stage in which the clinicians are aware of the benefits of HU prescribing and intending on implementing the algorithm in the next 12 weeks. The preparation stage is when providers are ready for prescribing hydroxyurea with a plan of action to increase their monthly prescribing in individuals with specified genotypes of hemoglobin SS and hemoglobin Sβ-0-thalassemia. Finally, the maintenance phase

would be evaluating the sustainability of prescribing hydroxyurea of clinicians over a period. This will ensure that there's no relapse in prescribing.

Operational Framework

The Plan, Do, Study, Act (PDSA) cycle, was the operational framework used to test, change, and evaluate the process of improvement with HU. According to Knudsen et al. (2019), the PDSA cycles are widely used for quality improvement (QI) strategies in various healthcare systems. The PDSA cycles was a continuum of three cycles during the implementation phase. The PDSA served as the cornerstone predictor to guide the steps of the project, and adjustment were integrated at each cycle. The prediction was that using the HU algorithm to standardize HU prescribing in clinical practices would increase HU prescriptions in the clinic. The project aimed to show the impact of using an algorithm for prescribing HU that is noted to prevent severe irreversible complications in SCD. The act was initiation the algorithm to improve HU prescribing. The operational framework was used for the QI project to implement change.

Plan. Data was collected using clinical notes, snapshots, and laboratory assays of the eligible participants at the clinic. The project's objective were to determine if providing an algorithm to providers and educational leaflets improved HU prescribing. The project lead collaborated with the team members about the process for implementing the projects' PDSA Cycles 1, 2, and 3.

Do. This stage of implementation was the testing of the algorithm, initially in the first cycle to be followed additionally by the subsequent second, and third cycles, noticing the effects of HU prescribing of the providers in the setting of the COVID-19 pandemic.
This encompasses plotting the data weekly on the spreadsheets. Additionally, the activity of plotting data on the run chart to track the changes in weekly prescribing.

Study. Data analysis was collected and analyzed over 12 weeks. The initial goal was to reach the 80% or more benchmark for HU prescribing and providing educational leaflets to patients. However, some of the week's activities were limited due to restrictions of visits during the pandemic.

Act. The PDSA's framework final stage determined if modifications were needed before the last cycle based on what was learned from the previous cycles. The cycles provide iterative testing to improve or change the QI project. This process is evaluated on a continuum to assess the effectiveness of interventions used and modified during the cycles.

The proposed Doctor of Nursing Practice (DNP) project aimed to implement an algorithm through the collaborative effort of providers within the clinic. The clinic project team members were assigned to specific tasks with educating patients. The goal was to identify all individuals with specified genotypes of hemoglobin SS and hemoglobin Sβ-0-thalassemia for hydroxyurea prescribing. In addition, the team had informal bi-weekly meetings to discuss the QI project addressing any questions or concerns with implementation.

Ethical Considerations & Protection of Human Subjects

The project lead collaborated with the project champion at the comprehensive sickle cell clinic in addressing any ethical issues. The participants were treated fairly with equality, protecting their characteristics of race, gender, disability, religion or belief, and sexual orientation. Individuals were treated with dignity and respect, and their information was protected with privacy during this process.

In addressing the ethical considerations, the organization required specific training through Collaborative Institutional Training Initiative (CITI) reviewed Group 2 Social/Behavioral Research Investigators and Key Personnel. These were completed in preparation for the formal approval process (CITI, 2017). CITI is required for all persons

involved with human subjects and identifiable data to be used in the QI project or research. All efforts were made to ensure respect for dignity, anonymity, do no harm, and confidentiality maintained. This activity is part of the university requirement prior to the submission of document necessary for the Institutional Board Review (IRB).

Institutional Review Board Approval

A clear definition of the scope of the problem was identified and submitted to the Nursing Research Council for approval at the institution. A letter of organizational support was obtained from the project's site. The IRB of the academic center reviewed the QI project and deemed the project as non-human subject research. In addition, the university quality IRB review process was also completed, with no further formal IRB review required. However, there was additional training necessary to protect the subjects from Health Insurance Portability and Accountability Act (HIPAA)

Section III. Project Design

Project Site and Population

The quality improvement project was conducted in an Adult Comprehensive Sickle Cell Clinic. The project lead collaborated with the project site champion at the academic setting affiliated with a nonprofit healthcare system in central North Carolina. The project aimed to implement an algorithm for standardizing Hydroxyurea (HU) at the clinic. The clinic serves approximately 450 individuals with various genotypes [Associate Professor] of Adult Comprehensive Sickle Cell Clinic personal communicator, July 17, 2020). The population for the project comprised of individuals with specific genotypes, particularly hemoglobin SS and hemoglobin Sβ-0-thalassemia. Patients traveled from various surrounding counties, mainly from rural areas, for the hematological expertise care, which transportation can present as a barrier for many.

Description of the Setting

The setting for this DNP project is the Adult Comprehensive Sickle Cell Clinic, a hospital-based outpatient clinic located in central North Carolina. The hematologists at this clinic are skilled and equipped to diagnose and treat various sickle cell disease genotypes. The patient population is virtually African Americans. SCD occurs worldwide but is more prevalent in African Americans (Keikhaei et al., 2015). Sixty percent of patients at the clinic are either insured by Medicaid or Medicare or other individuals by private insurances [Project Champion] personal communicator, August 17, 2020).

Clinicians of the practice consist of three nurse practitioners, four medical doctors, five nurses, medical office assistants, triage nurses, office clerical staff members, clinical social

workers, clinical educators, psychiatrists, and other multidisciplinary teams that provide excellent care for patients with SCD. The clinics operating hours are Mondays through Fridays from 8 am to 5 pm, with most clinicians seeing patients with SCD and other hemoglobinopathies two to three times weekly. In addition, hematologists are available to provide 24 hours on-call, including weekdays, weekends, and holidays.

Description of the Population

The clinic staff consisting of three physicians, one advanced practice practitioner (APP), and the four clinical nurses will be the target group for the project. All who currently work full-time in the clinic. The project team leader will educate the providers, clinical research specialists, and the nurses. In addition, the clinical staff nurses, clinical research specialists, and providers will inform the patients about hydroxyurea. The clinic sees approximately 30-40 patients weekly, with most patients being seen every three months during their interval follow-up appointments.

The population of patients served at the clinic includes adults aged 18 years and older of various genders. The population comprises of patients with SCD, mainly genotypes, hemoglobin SS and hemoglobin Sβ-0-thalassemia. The characteristic of SCD is characterized by "chronic anemia, painful crisis, organ damage, reduced quality of life, high health care costs, and shortened life span" (Smaldone et al., 2016, p.1). Compared to healthy individuals, patients with SCD experienced significant declines in their quality of life across their lifespan due to the disease's complications (Keikhaei et al., 2015). The population consists 50% of hematological etiologies in the practice of the specified genotypes being evaluated [Project Champion] personal communicator, August 17, 2020).

Project Team

The project team consisted of the project leader (Doctor of Nursing Practice (DNP) student), project champion, faculty mentor, nurses, clinical research specialist, and administrative staff. The project leader's role in collaboration with the project champion included planning, implementing, and evaluating the project. The project champion was instrumental in guiding the plans carried out by the project leader. The faculty mentor also provided guidance and feedback during the monthly project update meetings on the implementation and process.

The nurses and clinical research specialists played an active role in educating the patients about HU. The administrative staff checked in the patients and made return appointments. In addition, the project lead worked closely in collaboration with the clinical research specialist with uploading HU videos, HU educational pamphlets, and importing data in REDCap. Education was provided in the English language, using Apple iPads for reviewing HU videos and leaflets on HU. In addition, the nurses collected questionnaires on HU after the visits and educated the patients on downloading the websites for the YouTube video sharing on their smartphones or computers.

Project Goals and Outcome Measures

The DNP project goal was to identify the prescribing practices of providers with using the algorithm for standardizing HU. The quality improvement project evaluated whether providing clinicians an algorithm and the patients with educational leaflets increased the prescriptions for HU amongst the physicians and APP caring for SCD patients of specific genotypes. The project was evaluated over 12 weeks, using the algorithm initiative to improve

HU prescribing by the physicians and APP. The project's measurable outcome was to increase HU prescribing to at least 80%. The outcomes were obtained by evaluating the weekly prescribing of hydroxyurea.

Description of the Methods and Measurements

The Plan-Do-Study-Act (PDSA) cycles were chosen to implement the DNP quality improvement (QI) project. The project was designed to promote provider HU prescribing based on evidence-based practice guidelines for standardizing HU. Providers used an algorithm adapted from Up to Date and evidence-based guidelines from the National Heart Lung and Blood Institute (NHLBI) addressing sickle cell patients with hemoglobin SS and hemoglobin Sβ-0-thalassemia. In addition, the algorithm provided recommendations for providers to address other genotypes based on their complications and disease severity.

PDSA cycles allowed the opportunity to test change and observe the plan by collecting and reviewing of specific data. The project consisted of three cycle reviews at one month, two months, and three months. Run charts were used to visualize weekly HU percentages of all the providers (see Appendix E). An excel spreadsheet was used to collect provider education and prescriptions for hydroxyurea with providers identified as A, B, or C (see Appendix F). A questionnaire was obtained from the patients at the conclusion of their visit. (see Appendix G). The summary from the questionnaire provided feedback that included: demographics, HU education, and HU prescribing (see Appendix H).

Discussion of the Data Collection Process

Data analysis from the project was collected from vital documents: Maestro Care snapshots, physician's and APPs notes, clinical records, medication administration records

(MAR), and questionnaires. In addition, the project team lead in collaboration with the clinical research specialists met weekly with a combination of in-person and virtual visits to review patients' charts using the Maestro Care snapshot. The activities provided an overview/summary of the patients' profiles. The sections identified the patients with hemoglobin SS and hemoglobin Sβ-0-thalassemia.

The clinical records provided practical information that identified the practicing provider of the eligible patients. The MARs were reviewed to determine if the patients were currently prescribed HU. The project lead reviewed the initiation of HU of the providers during the clinical visit and documented the findings on the excel spreadsheet. The patients completed the questionnaire while in the clinic, with the team members importing the data into the Research Electronic Data Capture (REDCap). REDCap is a web-based application that supports data capture for research studies (Kragelund et al., 2018). The research specialist, in collaboration with the project lead, built the data sets in REDCap. The software was supported by the organization and was used to evaluate the feedback from the surveys. The software provided descriptive data related to the participant's demographic characteristics of gender, genotype, general SCD questions related to laboratory assays, education, and hydroxyurea prescriptions.

The outcome measures included data collected weekly by the project lead in collaboration with the clinical research specialist. In addition, the project included weekly chart reviews at the start of implementation and throughout the 12 weeks. The project team lead entered the data from the spreadsheets weekly. The tools were used to evaluate the prescriber encounters for patients who met specific criteria for HU education and HU prescribing on specified days as identified by Provider A, B, and C. A run chart was used to display the weekly percentages for HU prescribing of the clinicians.

Implementation Plan

The implementation phase of this project, began with the project team lead collaborating with the project champion and meeting with the providers, clinical research specialist, and the team members to provide an overview of the project (see Appendix I). The project lead reviewed the algorithm with the providers and offered educational leaflets on hydroxyurea. Additionally, the team reviewed the videos and educational modules on HU. The project team leader met weekly or bi-weekly with the project champion and weekly with the project team members. Furthermore, the project leader met with the team members to address any questions or concerns about HU or the project goals.

During implementation, the staff provided the participants with HU pamphlets, questionnaires, and iPad to review videos on HU. PDSA cycle reviews were conducted monthly by the project lead in collaboration with the project champion. The chart reviews were conducted using the snapshot and the providers' clinical notes for identifying eligible patients. The data was reviewed weekly on eligible patients for HU, prescriptions for HU, and education provided on HU. This process included importing the data into the Microsoft Excel spreadsheets for data analysis and creating run charts to trend weekly prescribing that reflected the improvement that took place over a period of time.

Furthermore, based on the weekly reviews and informal weekly meetings with the project team, barriers to the project were addressed for HU prescribing and education by providing constructive feedback. A new PDSA cycle was started each month to evaluate and set priorities for small change. There was a total of three cycles at the conclusion of the implementation phase. At the conclusion of the three PDSA cycles, data were analyzed from the excel spreadsheets and

displayed in run charts. The data will be presented using both the excel spreadsheet and run chart for identifying hydroxyurea prescribing of the providers.

Timeline

The project implementation occurred over three months (see Appendix I). The initiation of the DNP project began in November 2020 with the initial submission of the Nursing Research/Project Organizational Feasibility form along with the project summary submitted to the healthcare organization. The proposed project was submitted in November 2020 to the Institutional Review Board (IRB), and the organization deemed the project a QI initiative process development project. The project's planning was implemented on February 1, 2021 and concluded on April 23, 2021.

There were weekly run charts plotting the progression of HU prescribing and education provided by the clinicians for the participants. In addition, the excel spreadsheet were used to track the daily prescribing and weekly percentages of the providers. The monthly reviews marked the start of a new PDSA cycle with subsequent cycles of 2 and 3. The completed final data analysis of the project was in May 2021. Data analysis retrieved from the flow chart and excel spreadsheets reflected results over the 12 weeks and a review of the three PDSA cycles of the project. Dissemination of the project findings to the project site occurred on July 13, 2021. The project was formally closed with a poster presentation at the College of Nursing and the DNP paper submitted into the ScholarShip repository in July 2021.

Section IV. Results and Findings

The project's primary goal was to improve Hydroxyurea (HU) prescribing of the providers for eligible participants with hemoglobin SS and hemoglobin Sβ-0-thalassemia. Implementation included using an evidence-based algorithm for providers and educational leaflets to improve HU prescribing of the clinicians. The process was measured by tracking HU prescribing and education by providers using a tabulated Excel spreadsheet and run charts.

Results

One hundred and one (101) eligible patients met the criteria for adults 18 years of age and older, with sickle cell disease (SCD) genotypes hemoglobin SS or hemoglobin Sβ-0-thalassemia as determined by hemoglobin electrophoresis and snapshots in Maestro Care. Of the 101 patients seen, all 101 (100%) received educational handouts and videos sharing links, and 81 (80%) were prescribed hydroxyurea. The algorithm provided a quick reference for the providers to identify the patients assigned to specific genotypes. The providers met the benchmark of 80% HU prescribing, except for weeks that accounted for providers on vacations, hospital rounding, and limited in-person visits in response to the COVID-19 pandemic.

During the 12-week implementation period, 20 individuals were not prescribed HU. Of the 20, five (25%) were pregnant. In the second trimester, the therapy can be safely given based on the hematologist's preference and depending on the patients' disease severity [Professor of Obstetrics & Gynecology], personal communication, February 21, 2021). Therefore, the individuals declined the therapy with consideration of restarting hydroxyurea once they delivered. Seven (35%) of the 20 declined additional disease-modifying treatments. The remaining eight (40%) of the 20 were treated via chronic blood transfusions or red blood cell exchanges, an alternative disease-modifying therapy. Generally, in the setting of chronic blood

transfusions or red blood exchanges, HU is normally not clinically indicated since the patients are already receiving a disease-modifying therapy that would increase their hemoglobin [Associate Professor of Adult Comprehensive Sickle Cell Clinic] personal communication, February 1, 2021. Treatments involve receiving blood products to improve the patient's hemoglobin are often individualized by the provider's preferences for preventing the severity of their disease and alleviating additional irreversible complications of sickle cell disease.

Data were extracted weekly from the Microsoft Excel spreadsheet, which included weekly prescribing of the providers and the number of eligible patients at the adult comprehensive sickle cell clinic. There were 59 (58%) females and 42 (42%) males who met the criteria (see details in Appendix H). Of the 101 eligible patients, 80% were prescribed HU, and 20% did not receive the medication.

The results were examined during three PDSA reviews: Weeks 1-4, Weeks 5-8, and Weeks 9-12. During weeks 1-4, 30 (85%) out of 35 patients were prescribed HU and provided educational leaflets. In weeks 5-8, 28 (76%) out of 37 patients were prescribed HU and provided education. In the final weeks 9-12, 23 (79%) out of 29 patients received HU prescriptions and education.

In weeks 5-8 (76%) of patients were prescribed HU, and the prescribing ranged from 60%-100%. The goal of 80% HU prescribing was not met during weeks 7-9. It was noted during this time, several providers were either on vacations or hospital rounding, which could have contributed to the decline in HU prescribing (see Appendix E and F).

During weeks 9-12, 23 (79%) out of 29 patients were prescribed hydroxyurea, ranging from 50% to 81% prescribing by providers (see Appendix E and F). A decrease in patients seen

was noted with limited provider availability due to hospital rounding and vacations. Data analysis was for weekly prescribing of all providers instead of individualized prescribing.

Using the PDSA review process, changes were implemented based on the staff and project champions' input related to weekly prescribing of all providers during cycle one. Furthermore, changes to the subsequent cycles (Cycles 2 and 3) included using smart phrase links for providing education based on feedback from the project lead, clinical research specialists, and project team members at the conclusion of the visits. The smart phrase links provided sharing of literature from the links readily available to the patients using technological resources.

Discussion of Major Findings

During the project's implementation phase, 101 patients met the inclusion criteria, 101 were educated, and 81 received prescriptions. This project achieved the original goal 80% hydroxyurea prescribing during the implementation phase, with 9 out of 12 weeks meeting the goal. Although the percentages decreased during weeks 7, 8, and 9; the clinicians met the overall goal of 80%. Prior to implementing the project, providers were prescribing hydroxyurea at 60%. Findings from the data analysis supported the intended outcomes of meeting the benchmark of 80% of hydroxyurea prescribing using the algorithm and providing education on HU. This was an improvement from 60% in HU prescribing prior to implementation

The COVID-19 pandemic has significantly impacted hydroxyurea prescribing and educational opportunities for the providers. While it may have been challenging, the pandemic affected the outcome through social distancing requirements, reduced office visits and impacted educational opportunities for the providers. Before the pandemic, the providers' weekly panels included at least 12 or more potential patients who were seen and eligible for HU. During the

project implementation, often visits were conducted by telemedicine that included telephone or video visits which, limited the in-person visits. Furthermore, the pandemic redirected resources and limited in-person visits, which may have affected the project's intent to provide additional eligible individuals with educational handouts on HU. Telemedicine visits led to fewer clinic visits that contributed to the decrease between the expected number of patients and the actual number seen.

Section V. Interpretation and Implications

Costs and Resource Management

The financial costs associated with conducting the quality improvement (QI) project at the organization were approximately $2,670.00 (see Appendix J). Expenses related to the project included: educational brochures, tablets, and supplies. If the project were expanded over five days versus three days or involved additional providers, the cost would increase. Further costs associated with the project include other expenses for purchasing extra tablets, educational leaflets, and the costs for the 15-sheet brochures to be provided to all eligible patients. The administrative and advertising fees could potentially cost the organization an additional $3,400.00.

The non-financial costs included the Quick response (QR) codes. QR codes were created online that link simple texts to websites, email, text messages, or phone calls that provide access to a PDF or specific application to be used on smartphones (Karia et al., 2019). QR codes provided a cost-effective approach for administrative expenses by using QR codes through the project site's website to provide educational leaflets on hydroxyurea (HU). Additionally, the project lead created a link using smart phrases, also known as "dot phrases," in the electronic medical record, EPIC, to send links to the patients to retrieve educational material. This would ideally reduce the expenditures by at least $2,200.00. This would be a cost savings by replacing some of the printed educational materials with visual technology. The smart phrases are links that were created that provided no costs to the project site's organization.

Each semester required a minimum of 125 hours for the project lead to plan, develop, implement, and disseminate the project. During this time, the project lead collaborated with the project champion, clinical research specialists, multidisciplinary staff, and colleagues with

project planning and implementation. The cost associated with the project lead time could be absorbed in the future by the organization through the roles of the advanced practice providers (APPs). The clinical nurse specialist and clinical educator who are advanced practice practitioners can ensure that evidence-based care for the sickle cell population will be continued by partnering with the organization entitled Education and Mentoring to Bring Access to Care (EMBRACE) network.

The project benefits include optimizing patients with sickle cell disease in the outpatient setting through prescribing hydroxyurea. The cost of inpatient visits, emergency room visits, hospital admissions, and readmissions outweighs the cost of outpatient care. By prescribing hydroxyurea to eligible patients with sickle cell disease, it allows providers to optimize patient-centered care in the outpatient setting to reduce the burdens of SCD. The medicine is effectively known for decreasing sickle cell pain crises, acute chest syndrome, reducing the need for blood transfusions, organ failure, and reduces morbidity and mortality. The annual cost related to SCD-care expenditures can be lowered inpatient, if providers optimize hydroxyurea prescribing of the targeted population outpatient.

Implications of the Findings

The project benefits in providing an algorithm for HU prescribing and educational leaflets were many. For starters, the project demonstrated an increase in prescribing by the providers. This initially increases the established line of communication between the patients and the health care team during the clinic visits. Patients were engaged by asking questions about the disease-modifying medication. Engaging patients in decision-making can lead to compliance with the identified therapy and potentially decrease irreversible complications and disease severity.

The QI project benefited the site by providing education to all the staff, including providers and patients on HU. The staff were provided educational leaflets and links to YouTube videos. The project included weekly meetings, and as a result, staff indicated that the education provided improved their knowledge about hydroxyurea. The providers were supported in prescribing hydroxyurea through the use of the algorithm.

The project members showed a genuine interest in educating the patients about HU. There was an increased interest in HU after providing the patients with videos and educational leaflets that convey knowledge differently. The clinicians provided ongoing feedback and addressed concerns of uncertainty for patients during their clinic visits. The sites' percentages for prescribing and providing educational leaflets was 80% or greater for 9 of the12 weeks.

Implications for Patients

The project plan impacts health and wellness by educating the patients, providers, and ancillary staff on HU in specified genotypes; this promoted patient engagement, self-management, and adherence to hydroxyurea. Educating patients on hydroxyurea can lead to reducing and preventing chronic complications of SCD. Furthermore, HU prescribing by providers prevented further chronic disease burdens and improved the quality of life for patients taking hydroxyurea. Ultimately, providing education enhances patients' involvement with shared decision-making in their healthcare with engaging in self-management. Hydroxyurea prescribing and providing education fosters adherence to the medication regimen.

According to Meier (2018), hydroxyurea is well tolerated disease-modifying therapy effective in reducing the number of sickle cell-related complications in all ages of people with hemoglobin SS and hemoglobin Sβ-0-thalassemia that experience episodic moderate-severe painful crises. The author states, the benefits of prescribing hydroxyurea include reducing

neutrophils and platelet counts that ameliorate the abnormal cell adhesion-inflammation pathways and correct the nitric oxide deficiency associated with sickle cell and hemolysis. With the increasing use of this medication widespread, it is hoped to increase the survival of persons living with sickle cell disease.

According to Nardo-Marino et al. (2020), HU remains the novel disease-modifying therapy and option in individuals with SCD. The author also notes that medication is emphasized as being safe and feasible in treating SCD. Of the novel therapies, HU appears to remain the only drug that improves the natural history of SCD (Nardo-Marino et al., 2020).

The average cost to patients for 12 months of hydroxyurea ranges from $59.00-$110.83, depending on the retail pharmacy (Shah et al., 2020). Most of the patients seen in the practice site have insurance, including Medicaid, Medicare, or some private insurance, which covers the costs of hydroxyurea with little to no copay. Prescription cards can be provided to help with the fee for those who are self-pay or have higher copays. Patients may be eligible for patient assistance if they cannot afford the out-of-pocket costs. Hydroxyurea is noted to decrease the number and severity of acute pain crises when taking once-daily as prescribed, which the most frequent reason for individuals seeking emergent care**.** Prescribing hydroxyurea reduces painful crises, acute chest syndrome, acute complications, unnecessary blood transfusions, and hospitalizations significantly.

Implications for Nursing Practice

The projects demonstrated the value of educating the providers and multidisciplinary staff on the benefits of HU. The practice implications are associated with implementing an algorithm for standardizing HU evolved in optimizing care in the outpatient setting, which reduces the cost for inpatient care. This supports the importance for nurses to take a leadership role in educating patients, providers, and multidisciplinary staff on HU prescribing guidelines.

The project demonstrated that the essential role of using electronic medical records for evaluating the clinical process of documentation for HU prescribing of providers is vital in identifying patients who were eligible for HU prescribing. The QI project confirmed the integral role of interprofessional collaboration among the healthcare team was to improve the patients' overall care. The project team learned that fostering interpersonal partnership with the team members, with the intent to educate the participants about HU, improves the overall care of the patients.

The nurses have the knowledge, responsibility, and expertise to provide patient care. Nurses in adult comprehensive sickle cell clinics can teach the patients about hydroxyurea and its clinical importance for preventing complications. The clinical leadership role can be influenced by providers with nurses explaining the use of the algorithm for prescribing hydroxyurea. The clinical leadership will enhance the skills of the sickle cell champions by having them educate the providers and multidisciplinary staff about the disease-modifying medication.

QI projects such as creating an HU prescribing algorithm allows advanced practice nurses to develop initiatives based on best practices to improve patient-centered care. The American Association of College of Nursing (AACN) DNP Essentials I through VIII are the fundamental outcomes competencies and core measures for all advanced practice roles, which are essential guidelines for graduates of the Doctor of Nursing (DNP) program (AACN, 2019). The DNP Essentials can be applied to QI initiatives in planning, implementing, and evaluating scholarly projects to improve health care outcomes based on evidence-based practice guidelines and recommendations (see Appendix K). This QI project applied best practices implementing evidence-based practice guidelines using an algorithm to standardize HU prescribing.

Impact for Healthcare Systems

The project demonstrates the use of an algorithm for HU prescribing to individuals with hemoglobin SS and hemoglobin Sβ-0-thalassemia. The organization can improve its healthcare quality and reduce the burdens associated with sickle cell disease with prescribing hydroxyurea. The project demonstrated this by achieving the goal of 80% majority of the weeks for HU prescribing. This was evidenced by treating patients' outpatient versus inpatient to optimize their care in the outpatient setting.

One objective of the project was aligned with the Triple Aim by focusing on improving the populations' health quality and reducing costs to the healthcare system. The clinic can decrease the costs by optimizing care through outpatient with prescribing HU. Increased hydroxyurea prescribing minimizes the burden of the disease, prevents or reduces hospital admissions, specialist visits, and emergency department visits.

Providing an algorithm to standardize HU management is an effective way to improve the patients' outcomes and prevent complications. The project implemented evidence-based practices to reduce healthcare costs by optimizing individualized care in an outpatient setting through prescribing HU to eligible sickle cell disease patients. This can lead to saving costs associated with blood transfusions. The individuals usually receive a minimum of 2 units of packed red blood cells which cost, $6,441.00. In addition, other patients may require red blood cell exchange, which costs $4,996.00 per session [Patient Financial Coordinator] personal communication, April 1, 2021). Therapeutic blood transfusions are provided monthly or more often and used to address acute events that include strokes, acute chest syndrome, and symptomatic anemia, which can be costly.

Sustainability

The practice identified ways to continue the initiative with the current staffing model with the use of advanced practice providers. This will be a continuum of the advanced practice providers' current roles and responsibilities. The costs associated with the staff and provider's time and other resources are feasible with the current plan. This can be supported beyond the project implementation with modifications made to the budget associated with the costs of educational leaflets and tablets. Staff members were identified who remain genuinely interested in educating the adult population on HU. The organization would benefit from designating sickle cell champions at the site to provide ongoing education on hydroxyurea and an algorithm for the ancillary staff and providers. The cost associated with the sickle cell champion advocating for patients with sickle cell disease and the use of hydroxyurea is far less than the rising costs of emergency department visits or hospitalizations.

A recommendation is for the project site to replace HU educational leaflets with QR codes using enhanced technology to support teaching and patient education, while reducing printed materials costs. The use of technology is a way that provides secure links for providing educational leaflets on HU to the patients. QR codes uses a quick response barcode to store data on specific topics for the user to access information instantly. This was supported by the Information Technological (IT) department at no additional fees to the organization.

In addition, the project will continue the site's established association with the EMBRACE sickle cell network. The relationship is built on a collaborating agreement with other sites and specialists interested in taking care of individuals with SCD through increased hydroxyurea prescribing. The site will continue to use the standardized algorithm to guide HU prescribing in specific genotypes. The algorithm will be incorporated into practice in rural areas

and specialized areas that take care of individuals with SCD. This cost-effective intervention educates clinicians about HU, which optimizes care for individuals with SCD.

Dissemination Plan

The project findings will be formally presented at the organization's health care institution on July 23, 2021. The projects data findings will be presented at a staff meeting. A poster of the quality initiative will be printed and displayed at the site for the patients, staff, and community. This will provide an opportunity for the clinic's audience to visualize the quality improvement initiative. This project site targets the patient population with SCD advocating for hydroxyurea.

The project was presented at the University College of Nursing on July 13, 2021. The final DNP paper was submitted to the university ScholarShip repository for public access on July 22, 2021. Additionally, presentations will be presented to the organization's Nursing Research Council, Education and Mentoring to Bring Access to Care (EMBRACE) SCD Network, sickle cell champion meetings, local churches, seminars, and local and state conferences upon requests. In addition, virtual presentations to Extension for Community Healthcare Outcomes Project (ECHO), which is a group that provides virtual meetings delivering best-practice care to various communities addressing health care disparities. The project lead plans to submit an abstract before the deadline to a potential journal of interest. Journals being considered to include the American Journal of Hematology and The American Journal of Nursing.

Section VI. Conclusion

Limitations and Facilitators

The project's limitations included limited time to implement a quality improvement (QI) project over 12 weeks with only three Plan-Do-Study-Act (PDSA) cycles in the setting during the COVID-19 pandemic. The coronavirus disease has affected healthcare systems globally. The limitations included the limited in-person visits with face-face interactions by the patients secondary to the COVID-19 pandemic with restrictions of social distancing. This resulted in a small sample size of 101 individuals who met eligibility criteria at the clinic.

Another limitation was time spent with the patients on telephone call visits by the team members filling out the questionnaire on individuals who left before completing the form. There were several missed return calls from the patients, and it was challenging to reach the patients. Often, the telephone number provided were not in service or incorrectly supplied.

The project champion provided support to the project lead with guidance and suggestions making necessary changes in project planning and data collection analysis. The collaborating partnerships with project members and administrative support were the significant facilitators of the project in implementing changes during challenges related to the pandemic. The primary team members included the project champion and research specialists, whose genuine interest in collaboration made a tremendous impact on the project's success. The team members and clinical research specialists' support helped with gathering the pertinent data for the project. With available technology, the project lead was creative in creating smart phrases that provided links for patients to review HU literature during clinic visits and uploaded to the after-visit summaries. The project lead and team members were open to using smart phrases and created a website for the QR codes that provided patients with educational leaflets on HU.

Recommendations for Others

The current DNP project would be beneficial and should be replicated in medical settings that include primary care, family practice, or internal medicine practices. Standardizing the prescribing of HU based on evidence practice guidelines can impact patient outcomes in a practice setting serving the sickle cell population. The algorithm included starting at 15-20 mg/kg dosing and titrating to the patients' maximized tolerated dose. Often, this medication is primarily prescribed by hematology specialists but can be prescribed by others with the support of the algorithm. With the help of a hematologist or authorized prescriber, this project could benefit the clinicians in rural areas and even globally by optimizing the care of individuals with SCD. The project lead recommends providing continuing education courses to health care professionals in primary care, family medicine, internal medicine, multidisciplinary staff, and rural areas about HU that include quarterly and annual updates.

A recommendation is for the algorithm be placed electronically in medical records as a guide to be used by inpatient providers for prescribing hydroxyurea. The algorithm guides the initial step in providing hydroxyurea to reduce the complications and severity of the disease. In addition, to build on the project by incorporating educational material electronically in the patient's portal for easier access to HU literature. This will help with initiating hydroxyurea and increase the interest of patients while being hospitalized or in outpatient settings.

Recommendations for Further Study

This DNP project could be replicated by providing additional evidence-based studies that address adherence to hydroxyurea. Additionally, studies assessing and evaluating providers' behaviors in optimizing hydroxyurea to reach the maximum tolerated dose in individuals. Future studies could provide updates on the current clinical benefits of HU since the last updated literature

from the National Heart, Lung, and Blood Institute (NHLBI) evidence-based guidelines were published in 2014 (Ware, 2015). In addition, clinical trials evaluating the success of HU prescribing in other countries and strategies for improving adherence in individuals globally are needed.

It would be beneficial to know if providing an algorithm to standardize HU in practices would increase the prescribing of clinicians locally and nationally. Due to the clinical benefits associated with hydroxyurea therapy, additional studies are needed to emphasize the benefits of the medication. Further studies are recommended on how the limited visits during the pandemic impacted HU prescribing and education provided to the patients. Since the COVID-19 pandemic started almost a year ago before the project implementation, it seems unlikely that COVID-19 not only affected prescribing for several weeks, but also the number of office visits.

Final Thoughts

The project started with the prediction of prescribing hydroxyurea to achieve the goal of 80%. Educational session for the team members were adjacent to providing an algorithm to the providers, which enhanced their knowledge about hydroxyurea. Data analysis was collected on specific genotypes hemoglobin SS and hemoglobin Sβ-0-thalassemia throughout the implementation, which identified providers achieved the goal of 80% hydroxyurea prescribing from pre-implementation of 60%. Continuing this initiative offers partnerships with other clinicians such as the EMBRACE network for increasing the awareness of hydroxyurea prescribing for patients with SCD. The project team members have enhanced the patient's education and knowledge about HU by promoting self-management with implementing the project. The project provides a foundation for improving care in patients with sickle cell disease.

The project aligned with the Triple Aim, by providing a medication that reduces capital costs, provides patient-centered care, and reduces the economic burdens of the disease.

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Appendix A

Search Log

Date of Search	Database	Key Word Searches	Limits	# of Citations Found/Kept	Rationale for Inclusion/Exclusions (include rationale for excluding articles as well as for inclusion)
7/18/2020	CINHAL	Sickle cell anemia, sickle cell disease adults, hydroxyurea, medication adherence, hydroxycarbamide, adults 16 years older	5 year period English language, full text, peer reviewed	49 found/kept 6	Included articles related to adult populations with sickle cell disease excluded articles for pediatric populations
7/19/2020	PubMed	Sickle cell anemia, sickle cell disease, adults, hydroxyurea, protocol, algorithm, hematological improvement.	5 year, English language, full text, peer reviewed	72 found/kept 12	Included articles related to adult populations with sickle cell disease, excluded articles for pediatric populations
7/23/2020	Google Scholar	Sickle cell anemia, sickle cell disease, hydroxyurea, novel therapies, algorithm	5 year, English language, full text	31 found/kept 6	Included articles related to hydroxyurea and sickle cell disease, excluded pediatric populations. Excluded articles related opinions

Appendix B

Literature Matrix

Authors	Year Pub	Article Title	Journal	Purpose and take home message	Design/Analysis/ Level of Evidence	IV DV or Themes concepts and categories	Comments/critique of the article/methods GAPS
Badawy, S.M., Thompson. A.A., Lia, J.S., Penedo, F. J., Rychlik, K., & Liem. R. L.	2017	Adherence to hydroxyurea, health related quality of life domains, and patients' perceptions of sickle cell disease and hydroxyurea: A cross-sectional study in adolescents and young adults	*Journal of Health and Quality of Life Outcomes*	To determine if self-efficacy contributes the engaging in education	Level V Descriptive Inferential Statistics	Sickle cell disease, Hydroxyurea, adherence, Health related quality of life, Patient reported outcomes, perceptions, and beliefs.	The authors suggested that assessment patients adherence and perceptions of Hydroxyurea (HU) should be assessed using other interventions. This would allow the clinicians to answers questions in regards to adherence or non-adherence. Approaches that included web or mobile based platforms would provide frequent assessments for address individuals' adherence in various settings. Limitations: The limitations included: the study being a single institution with convenience samples of patients with sickle cell disease (SCD), which could potentially limit the results, the cross sectional study limited the authors' ability to examine change amongst the perceptions of the patients and lastly, the limitation of specific ages 12-22. Usefulness: The study identified the strategies for influencing HU adherence in pediatric and adults patients with SCD perceptions about HU. Synthesis: The cohort found the patients with more SCD complications had more utilizations of ED and hospital visits their perceptions for HU was low. The patients with more negative perceptions, would be the individuals with lower perceptions about HU. In summary, the study should be used in various institutions to compare and contrast the domain scores to see if there is clinical l significance with medication non-adherence and examine others perceptions.
Badawy. S.M., Cronin, R.M., Hankins. J., Crosby. L., DeBaun. M., Thompson, A.A., & Shah. N.	2018	Patient-Centered eHealth interventions for children; adolescents, and adults with sickle cell disease: Systematic review	Journal of Medical Internet Research	To evaluate if providing technological tools would enhance patients self-management of their sickle cell disease.	Level I Systematic Review	Technological tools, Self-management of patients with Sickle Cell Disease	The articles identified that eHealth included: texting, mobile APPs, web-based APPS, mobile directed observed therapy contributed all provided patient centered technological resources that enhanced the participants' interests in their disease modifying medications. The strategies used and knowledge about their medications, and enhanced their self-management skills in managing their chronic illness with sickle cell disease (SCD). This provided a series of multimodal interventions with variable options of providing eHealth for their chronic disease. The systematic review identified several positive outcomes with using eHealth which showed improvement of SCD with the use of technology. Limitations: the search was planned and criteria was comprehensive but the possibility of missing additional relevant articles could not be excluded. The strongest available evidence was peer-reviewed, there could be a population bias. The study size was variable in ages, and the definition of adherence and preventive behaviors and other outcomes varied which resulted in limitations to the study.

Bakshi, N., Sinha, C. B., Ross, D., Khemani, K., Loewenstein, G., & Krishnamurti, L.	2017	Proponent or collaborative: Physician perspectives and approaches to disease modifying therapies in sickle cell disease	*Public Library of Science*	This collaborative decision making allows the MD to elicit their perceptions about disease modifying medication to help	Level VI Qualitative Study	MD's and patients perceptions for decisions about disease-modifying therapies	There were two approaches to addressing the disease-modifying agents 1) collaborative approach (CA) the need to discuss options with informed decisions and 2) proponent approach (PA) which advocated for predetermined treatment plans. The PA was advocated by the MD as the best option used by the MD and the CA focused on more than one treatment option. The author noted that MD presented HU as an option with SCD patients with clinical symptomology disease with severity. The article suggested that patient were hesitant to use the HU because of its classification as chemotherapy drug. The article suggests that there is a strong correlation with trust in partnering with providers in decision-making. The findings were limited to specialization of the participants with expert opinions, It would be ideal to expand the study to primary care and internal medicine providers who are not usually experts of SCD.
Bokolo. A	2020	Use of telemedicine and virtual care for remote treatment in response to COVID-19	*Journal of Medical Systems*	To determine if COVID-19 has changed the way providers provide care.	Level V Descriptive Statics	Telemedicine, Virtual Care, and Remote Treatment	Telemedicine is essential as integrated in the health care systems for delivery of care to patients in response to the COVID-19 pandemic. Telemedicine supports long distance medical care to patients. This entails provided health education to providers and patients, provider trainings, and meeting with multidisciplinary staff. Although, this provided rapid access to health care there is also concerns about privacy or if telemedicine meets the standards of care with providing physical examinations via technology. Having high quality networking may present as a barrier to many. Telemedicine is beneficial by providing safe and accessible care to patients. In summary, the study provided ways to guide medical practitioners in ways to employ virtual technology to increase any resilience in the future.

Authors	Year Pub	Article Title	Journal	Purpose and take home message	Design/Analysis/ Level of Evidence	IV DV or Themes concepts and categories	Comments/critique of the article/methods GAPS
Creary,, S., Chisolm, D.J., & O'Brien, S.H.	2016	Enhance-Electronic hydroxyurea adherence: a protocol to increase hydroxyurea adherence in patients with sickle cell disease	*Journal of Medical Internet Research*	To look at the impact of Mobile Directly Observed Therapy improved adherence of HU.	Level III Randomized Control Trial	Hydroxyurea, adherence, interventions, sickle cell disease	The primary outcome of this study was to measure HU adherence. The study showed significant statistical outcomes with using mobile technologies as an intervention to improve adherence for HU. Mobile Directly Observed (DOT) interventions would serve as a way to keep the patient actively involved in self-management with their chronic disease. The study demonstrated that Mobile technology is not only applicable for addressing adherence for SCD. The use of virtual technology provides a wide range of strategies for examining self-management skills and HU adherence.
Green, N.S., Manwani, D., Matos, S., Hicks, A, Soto, L., Castillo, Y., Ireland, K., Stennett,	2017	Randomized feasibility trial to improve hydroxyurea adherence in youth ages 10-18 years through community health care workers: The habit study	*Pediatric Blood & Cancer*	Discuss interventions to improve Hydroxyurea	Level II Randomized Control	Hydroxyurea, medication adherence, self-management, sickle cell disease	The initiative of the HABIT with the community health workers (CHWs) provided support through coaching and providing educational materials to patients with close follow-up to improve hydroxyurea adherence. The youth valued the intervention of the workers and were satisfied with the support provided for self-management. The limitations included the modest sample size and limited statically power that would be needed to examine the statistical significance. The HU doses were not standardized. In summary the trial demonstrated feasibility and acceptance of using CHWs in facilities to help improve HU adherence. The acceptability of the intervention was statistically significant within the sickle cell disease population.

Hankins, J. S., S., Shah, N., DiMartino, L., Brambilla, D., Fernandez, M.E., Gibson, R, W., Gordeuk, V.R., Lottenberg , R., Kutlar, A., Melvin,	2020	Integration of mobile health into sickle cell disease care to increase hydroxyurea utilization: Protocol for an efficacy and implementation study	JMIR Research Protocol	To use technology by proving mobile APPS for improving hydroxyurea (HU) adherence in patients with sickle cell disease and improve prescribing behaviors of providers.	Level III Nonrandomized , Closed Cohort Trail	Digital Medicine Health Innovative Mobile phones mHealth	Hydroxyurea has proven to be efficacious in treating sickle cell disease. The goal was to increase hydroxyurea utilization by providing mHealth for providers and patients in order to 1) improve prescribing of providers and 2) to use mHealth technology to provide medication adherence and self-efficacy among the patient, which in turn improves self- management skill for this chronic disease. The goal was to support the gap between ages 15 and 45 years, as noted the greatest gap in delivery of care. The logic was to foster hydroxyurea (Hu) utilizations among the patients and increase the interest of the providers behaviors for prescribing HU. Limitations: Proportion of days covered (PCD) which reflects the ideal setting as opposed to the use of electronic bottles, or video recorded dose ingestion which the author notes to directly observe adherence of medication administration. The study does not include randomized mHealth strategies. As noted, the study is currently participants and anticipate to be completed in 2021. It would be interesting to preclude additional findings once the study is completed.

Karia, C, T., Hughes, A., & Carr, S.	2019	Uses of quick response codes in healthcare education: A scoping review	BMC Medical Education	Examine the use of quick response codes for health care education	Level V Review of Literature	Quick codes and Technology	QR codes in health care is notably recognized in delivering health care with providing educational opportunities by using cost-effective technology. QR codes provides advantages and opportunities by using this enhanced technology aimed to provide a wealth of knowledge that can be easily linked by a simple text, website, email, or text message. This novel strategy fosters a variety of visual learning that can be used in various healthcare settings. QR codes can increase engagement with medical providers, educators, and patients. Limitations included: the majority of articles included the use of qualitative students perception instead of quantifiable data, which could limit the data analysis.
Keikhaei, B., Yousef, H., & Bahadoram , M.	2015	Hydroxyurea: Clinical and hematological effects in patients with sickle cell disease	Global Journal of Health Sciences	The discussion of clinical effects of hydroxyurea in the treatment for SCD	Level IV Cohort-Study	Hydroxyurea and Sickle Cell Disease and hematological improvement	The results of the study showed that hydroxyurea decreases anemia which is one of the reasons that patients receive transfusions. Hydroxyurea also, reduces several clinical manifestations that include but not all inclusive, decrease pain crises or severity of the pain, acute chest syndrome, reduces the number of admissions, reduces transfusions, and the number of visits to the specialists. In addition, patients with SCD that use HU therapy have a decreased rate of transfusions. Some individuals were completely free of transfusions by using HU. There was a statistically significance with decreased rate of hospitalizations from 93% to 31.5%. It was evident that HU a once-daily medication has several clinical benefits for patients with SCD. Limitations: were identified by the small sample size of 48 individuals, short duration of the study from 2013-2014, that limited the ability to summarize the survey. In addition, recommendations for longer follow-up with a larger sample size would be needed to validate the findings regarding HU as the sole disease-modifying medication for SCD.

	Year Pub	Article Title	Journal	Purpose and take home message	Design/Analysis/ Level of Evidence	IV DV or Themes concepts and categories	Comments/critique of the article/methods GAPS
Kragelund, S. H., Kjarsgaard, M., JensenFangel, S., Leth, R.A., & Ank, N.	2017	Research electronic data capture (REDCap) used and audit tool with a built-in database	Journal of Biomedical Informatics	To examine the use of a built-in database called REDCap	Level V Review of Literature	Audit Tool and REDCap	REDCap software meets the legality requirements for storing private information with security. This information can be shared by other researchers who have access to the software and authorized for sharing the data. This web-based software can be securely used by researches to protect their data sets in the future. Limitations: Entering data manually can create human error, which could alternatively been corrected by using visualization of the data. Additionally the time spent with manual data collection by the two experts in the cases may not be feasible due to time constraints.
Luzatto, L., & Makani, J.	2019	Hydroxyurea-An essential medicine for sickle cell disease in Africa	*The New England Journal of Medicine*	Hydroxyurea for the management	Level V Review of Literature	Hydroxyurea for Sickle Cell Disease in Africa	Hydroxyurea is recognized globally as the standards of care for individuals with sickle cell disease. If hydroxyurea is widely available the results of trails identified that all patients should receive HU. Patients with sickle cell disease (SCD) in Africa should have this medication equally available to their patient population to decrease the morbidity and mortality of the disease.
Meier, R. E.	2018	Treatment options for sickle cell disease	*Pediatric Clinic of North America*	Hydroxyurea is effective in reducing complications of sickle cell disease	Level IV Cohort Study	Treatment Therapies and Sickle Cell Disease	Therapies for sickle cell disease focuses primarily on prevention of HbS production and reducing the amount of HbS circulating in the blood stream. Hydroxyurea is noted for reducing complications in all ages of individuals with specific genotypes. Increased HbF prevents the sickling and hemolysis which is the main reason patient encounter sickle cell pain crises and other complications. By taking this once daily medication will increase the fetal hemoglobin HbF, which increases the life span of the red blood cell, which in turn can prevent complications of SCD. Transfusions reduces the concentration of the HbS, l-glutamine may be used as an option to decrease pain crises, and the curative option the stem cell transplantation. All of the therapies may have risks, but hydroxyurea is noted as a safe option for treating SCD.
Nardio-Marino, A., Brouse, V., & Rees, D.	2020	Emerging therapies in sickle cell disease	British Journal of Hematology	To examine therapies for treating Sickle Cell Disease that includes: hydroxyurea and gene	Level V Review of Literature	Sickle Cell Disease and Therapies	Emerging therapies in sickle cell disease (SCD), noted, to date hydroxyurea remains the novel therapy and main treatment for SCD. This drug is noted to have a greater than 30 years history and remains the primary disease-modifying option for the disease. HU has been identified as reducing complications of the disease, and improvement of quality of life, and survival. The author goes on to state that the other therapies may be used that include: Voxelotor, curative therapies which include the bone marrow transplant and gene therapy in the last decade are all options that can be used in treating SCD. However, the therapies may be limited to individuals related its costs. Hydroxyurea remains to be cost-effective and affordable by many.
Nazon, C., Sabo, A.N., Becker, G., Lessinger, J.M., Kemmel, V., & Paillard, C.	2019	Optimizing hydroxyurea treatment for sickle cell disease patients: The pharmacokinetic approach	Journal of Clinical Medicine	Providers need to stop under prescribing hydroxyurea and embrace in optimizing	Level III Interventional Trail	Sickle Cell Disease and Sickle Cell Anemia (SCA), and Hydroxyurea.	Examined the pharmacokinetic parameters of nine children using the PK analysis, The GC/MS was noted to show specificity and sensitivity that was required for the therapeutic follow-up on HU. 9 of the 9 children achieved therapeutic goal. In addition 4 of the 9 were deemed as being non-compliant to the treatment regimen. The use of laboratory parameters, pill counts, and log books necessitate as reliable methods for evaluating HU adherence. Limitations: The small sample size of 9.

Shah , N., Bhor, M., Xie, L., Paulose, J., & Yuce, H.	2020	Medical resources use and costs of treating sickle cell disease related vaso-occlusive crisis episodes: A retrospective claims study	Journal of Health Economics and Outcomes Research	The discussion of the economic burden among people with sickle cell disease	Level II	Economic Burdens, Sickle Cell Disease, and Vaso-occlusive crisis	The burdens of SCD primarily the vaso-occlusive pain crisis has been the driver of health care costs. Vasoocclusive crises remain the hallmark of the disease as the author notes that attributes to the significant economic burdens of the disease. HU has been known for its clinical benefits of reducing complications of the disease. Limitations: The study relied on mainly descriptive analysis of outcomes which limits the trends of results from direct observations or randomized clinical trials. There may have been discrepancies in the study that captured non-sickle cell patients related to the coding of visits during hospitalizations of patients with > 1 SCD diagnosis. The data set ranged from 2009-2013 and the current clinical complications have likely changed since the study. The conclusion is that additional studies need to explore broader populations to help clinicians reduce vaso-occlusive crisis and address ways for reducing burdens of SCD.
Smaldone, A., Findley, S., Bakken, S., Matiz, L. A., Rosenthal, S. L., Jia, H., Matos, S., Manwani, D., & Green, N.	2016	Study protocol for a randomized controlled trial to assess of an open label intervention to improve hydroxyurea adherence in youth with sickle cell disease	Contemporary Clinical Trials	Strategies by using community health care workers to improve health care with individuals with sickle cell disease	Level III Randomized Control Trial	Sickle Cell Disease, Hydroxyurea and Community Health workers	Clinical trials support HU treatments and benefits long-term with the safety regulations. The growing body of evidence showed that community health workers (CHW) helped with improving self-management skill of the individuals with this chronic disease namely sickle cell disease. CHWs intervention can be feasible as a proposed to help with hydroxyurea adherence long-term. This strategy can be used to reach patients in rural and other communities that have barriers for access to care. Limitations: Included the time frame limited to 6 months period for developing interpersonal relationships with the CHWs. The time frame also revealed the impact of being able to access the HU intervention and following up in with adherence. The project would benefit by having a larger sample size and in a multi-site setting.

Authors	Year Pub	Article Title	Journal	Purpose and take home message	Design/Analysis/ Level of Evidence	IV DV or Themes concepts and categories	Comments/critique of the article/methods GAPS
Smith, A., Bodas, P., Sidebotham, L., & Weilnau, J.	2019	Improving uptake of hydroxyurea in patients with sickle cell disease: A retrospective study of a clinic-based change in consenting practices	Journal of National Medical Association	If patients were provided informed consents this would improve their acceptance of the medication.	Level II Retrospective Study	Hydroxyurea and Consenting Practices	The study identified that using an informed consent for hydroxyurea treatment contributed to the statistical significance of increasing prescriptions. This helped the patients with making informed decision with explaining any side effects of the medication. Limitations included: there was no way to confirm if whether persons were eligible for HU ever offered this medication prior to the study. The contributions of consenting decisions of the patients and families was unknown. The study was not conducted in a controlled research setting. This was a clinic-based retrospective study with no controlled research setting.
Strouse, J. J.	2016	Hydroxyurea for sickle cell disease: Now is the time!	*Southern Medical Journal*	Providing providers and families with educational materials on HU would increase their knowledge	Level V Review of Literature	N/A	Randomized clinical trials noted by the author, that by using hydroxyurea in patients with sickle cell disease, it reduced their admissions, acute visits for pain, and acute chest syndrome by 50%. The concern is providers may be a significant barrier for prescribing HU. The survey identified several barriers that included: Concerns of providers' lack of knowledge about HU, patients' compliance with obtaining laboratory markers as clinically indicated, patients' perceptions about side effects, possibility of reduced fertility for males, and having providers that have expert knowledge about HU.

Ware, R. E.	2015	Optimizing hydroxyurea therapy for sickle cell anemia	*American Society of Hematology*	Discuss the use of HU therapy in the treatment of	Level V Review of Literature	Hydroxyurea Therapy and Sickle Cell Disease	The National Heart, Lung, and Blood Institute (NHLBI) has issued evidence-based guidelines and recommendations for hydroxyurea devoted to treatment for patients with sickle cell disease. There is strong recommendation for maximizing the safety and benefits of HU. Hydroxyurea should be offered nationally and routinely to eligible patients and is considered the standard of care for patients with SCD.

Appendix C

Hydroxyurea: Educational Leaflets

Hydroxyurea: A Medicine to Improve Your Health

What is Sickle Cell Disease (SCD)?

Sickle cell disease is a genetic disorder that affects the shape of the red blood cells. The job of the red blood cells is to take oxygen all over our body. When the shape of the cell is abnormal, it can block the blood vessels. This can cause pain and injury to our organs. There are many types of SCD but sickle cell anemia including HbSS and HbS-βnull thalassemia is the most serious kind.

What is Hydroxyurea?

Hydroxyurea is a medicine that can reduce the number of times and level of pain you have because of SCD. It has been found to work in patients who are nine months and older.

How Does it Work?

Our red blood cells are made of hemoglobin which helps us carry oxygen. The hemoglobin in people with SCD does not carry oxygen as well as it should and causes the cells to have a sickle shape. Hydroxyurea causes people to make more fetal hemoglobin, which carries oxygen very well and does not cause the sickle shape.

Who Should Take Hydroxyurea?

Anyone with one of the serious forms of sickle cell disease such as HbSS or HbS-βnull thalassemia should speak with their doctor about whether Hydroxyurea would help them. Others with different types of sickle cell disease, like hemoglobin SC disease (HbSC), should think about it if they have frequent problems.

I'M AN ADULT WITH SCD. HOW WILL HYDROXYUREA HELP ME?

Hydroxyurea may help lower your level of pain, decrease the number of times you have to go to the hospital, and even decrease the number of transfusions needed to keep you healthy. It has allowed many adults to lead a positive life by being more productive and enjoying better health.

I'M A PARENT OF A CHILD WITH SCD. IS HYDROXYUREA USEFUL FOR MY CHILD?

Hydroxyurea use in children has been studied for many years. Children who use Hydroxyurea have significantly fewer problems, including pain and hand-foot syndrome, when compared to children who do not use it. **It is important that Hydroxyurea be considered before health problems develop.**

Is This Drug Safe?

During the 30 years Hydroxyurea has been studied for treatment of sickle cell disease, many people have no serious side effects. However, it does not work well in everyone. A few people get headaches, nausea, vomiting, rash, or hair loss when they use Hydroxyurea. Sometimes, it can also reduce the number of white blood cells or platelets. For these reasons, it is important to speak with your doctor, and to be followed carefully when taking Hydroxyurea. When your body's reaction is closely watched, changes can be made in the dosage to find out what will work best for you. Generally, for most people with SCD, the benefits of taking Hydroxyurea are greater than the risks.

Hydroxyurea for Sickle Cell Disease

Treatment Information from the American Society of Hematology

About the American Society of Hematology

For more than 50 years, the American Society of Hematology (ASH) has been committed to helping hematologists conquer blood diseases. With more than 17,000 members from nearly 100 countries, ASH is the world's largest professional society of hematologists. We're dedicated to furthering the understanding, diagnosis, treatment, and prevention of disorders affecting the blood. To learn about how ASH is working towards conquering sickle cell disease, visit www.hematology.org/scd.

Table of Contents

About This Booklet

This booklet has been prepared by the American Society of Hematology and provides general information about hydroxyurea, which is one of the few FDA-approved therapies to treat sickle cell disease. This booklet is purely an informational resource. It does not provide medical advice and is not intended to substitute for consultation with a medical professional. People with sickle cell disease should talk to their doctor before making any changes to their treatment.

Introduction

If you have sickle cell disease, you know the impact it can have on your life. Sickle cell disease can cause periods of intense pain (called "pain crises") and other problems. You may even end up in the emergency room or the hospital.

But here's some good news: a medicine called hydroxyurea ("hi-drox-ee-ure-EE-a") can help adults and children with sickle cell disease. This medicine can help you have fewer pain crises — and even live longer. Hydroxyurea has helped many people and it could help you.

The American Society of Hematology developed this booklet to educate people with sickle cell disease about this important treatment option. We encourage you to talk with your doctor about your personal treatment plan and whether hydroxyurea could help. The decision to take hydroxyurea is up to you.

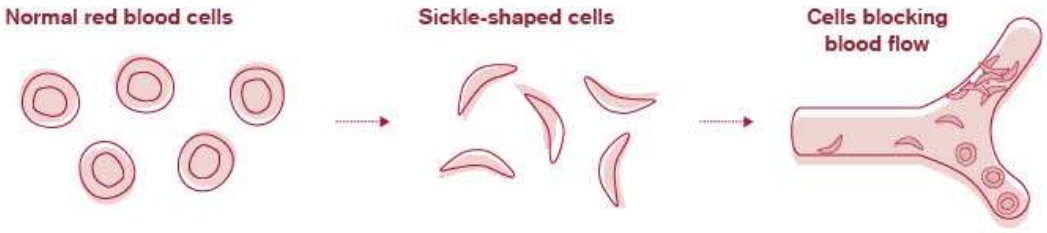
Sickle Cell Disease Basics

What is sickle cell disease?

Sickle cell disease is a blood disease that causes problems with red blood cells.

Normally, red blood cells are round and flexible, which allows them to move easily through your blood vessels. Red blood cells contain a protein called hemoglobin that carries oxygen throughout your body.

People with sickle cell disease don't have regular hemoglobin in their red blood cells. Their hemoglobin can give their red blood cells a curved shape, like a banana or a sickle (a farming tool with a curved edge). These sickle cells are hard and sticky, which means they can block the flow of blood in your body and cause serious problems.



What problems can sickle cell disease cause?

Sickle cell disease can cause:

- **Anemia** – when you have fewer red blood cells to carry oxygen in your body, which can make you feel tired.
- **Pain crisis** — pain in your chest, stomach, or bones. This happens when sickle cells block your blood vessels.
- **Acute chest syndrome** — a lung problem that happens when sickle cells block the blood vessels in your lungs. This can be life threatening and you will need to go to the hospital.
- **Organ damage** — harm to important organs like your brain, heart, lungs, kidneys, and eyes. This can lead to serious problems like kidney failure or vision loss.

Sickle cell disease can even shorten your life — but hydroxyurea can help you live longer. That's why it's important to consider taking it.

Hydroxyurea Facts

Hydroxyurea is a medicine that doctors have used to treat people with sickle cell disease since the 1980s. The Food and Drug Administration (FDA) approved it for treating adults with sickle cell disease in 1998. In 2017, the FDA approved it to treat children with sickle cell disease.

Hydroxyurea is also used to treat cancer. But doctors use a lower dose (amount) to treat sickle cell disease than to treat cancer.

Hydroxyurea can help people with sickle cell disease live longer.

How can hydroxyurea help with sickle cell disease?

Hydroxyurea reduces the problems that sickle cell disease causes. People with sickle cell disease who take hydroxyurea have fewer:

- Pain crises
- Episodes of acute chest syndrome
- Blood transfusions
- Hospital stays

Hydroxyurea can also prevent or slow down damage to your organs.

Cole's Story*

"This was my first activity without pain in years."

Before Cole started taking hydroxyurea, she had frequent pain crises. For a while, she was in the hospital every few weeks. She wasn't able to keep a job.

Then Cole's doctor recommended hydroxyurea. After she started taking it, Cole began to feel better. She even walked a 5K race just a few months later without going into crisis or having any pain. She was able to start working again — and she has gone more than 4 years without a major pain crisis.

*The stories in this booklet are from real people who shared their experiences with ASH.

How does hydroxyurea work?

Hydroxyurea makes your red blood cells bigger. It helps them stay rounder and more flexible — and makes them less likely to turn into a sickle shape.

The medicine does this by increasing a special kind of hemoglobin called hemoglobin F. Hemoglobin F is also called fetal hemoglobin because newborn babies have it. When you have higher levels of hemoglobin F, your red blood cells are less likely to cause problems.

Who should take hydroxyurea?

If you have any form of sickle cell disease, hydroxyurea could help you. This is true even if your symptoms aren't severe.

Different types of sickle cell disease respond to hydroxyurea differently. If you aren't sure which type of sickle cell disease you have, ask your doctor — and say that you'd like to know how hydroxyurea could help you.

- Experts strongly recommend hydroxyurea for people with **sickle cell disease type SS** or **type sickle beta zero (Sβ0) thalassemia** ("thal-uh-SEE-me-uh"). Hydroxyurea is proven to help people with both of these forms of sickle cell disease.
- If you have **sickle cell disease type SC** or **type sickle beta plus (Sβ+) thalassemia**, talk to your doctor. Hydroxyurea can help, but scientists have done less research on what hydroxyurea can do for people with these types of sickle cell disease.

Hydroxyurea can even help people who rarely have obvious problems caused by sickle cell disease.

What are the types of sickle cell disease?

There are many different forms of sickle cell disease:

- Sickle cell anemia, which includes sickle cell disease type SS and type sickle beta zero (Sβ0) thalassemia
- Sickle cell disease type SC
- Sickle cell disease type sickle beta plus (Sβ+) thalassemia
- Sickle cell disease type SD, SE, and other sickle cell disease variants

The Research on Hydroxyurea

Research shows that hydroxyurea is safe and helpful for people with sickle cell disease.

The Multicenter Study of Hydroxyurea

In 1992, scientists started a study of 299 people to see if hydroxyurea could help adults with these kinds of sickle cell disease:

- Sickle cell disease type SS
- Sickle cell disease type sickle beta zero (Sβ0) thalassemia

To do this, they randomly put people in the study into 2 groups. One group got hydroxyurea. The other group got a placebo (a pill that has no medicine). The people in the study didn't know which pill they were taking.

What did the study show?

The people who took hydroxyurea had fewer problems caused by their sickle cell disease.

They had half as many pain crises.

- The people who took the placebo had **nearly 5** pain crises in a year.
- The people who took hydroxyurea had about half as many — **fewer than 3** pain crises a year.

They had fewer hospital stays.

- People who took the placebo had **more than 2** hospital stays a year due to pain crises.
- People who took hydroxyurea had **only 1** hospital stay a year because of a pain crisis.

They got acute chest syndrome less often.

- **35** out of every 100 people who took the placebo got acute chest syndrome.
- Only **16** out of every 100 people who took hydroxyurea got acute chest syndrome — that's about half as many.

35 of 100 people got acute chest syndrome with the placebo

16 of 100 people got acute chest syndrome with hydroxyurea

They needed fewer blood transfusions.

- **50** out of every 100 people who took the placebo got transfusions.
- Just **32** out of every 100 people who took hydroxyurea got transfusions.

50 of 100 people got transfusions with the placebo

32 of 100 people got transfusions with hydroxyurea

They didn't have more side effects.

The researchers also looked at side effects and found that people taking hydroxyurea didn't have any more side effects than people taking the placebo.

Source: Charache, S., Terrin, M. L., Moore, R. D., Dover, G. J., Barton, F. B., Eckert, S. V., McMahon, R. P., and Bonds, D. R. (1995). Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia, The New England Journal of Medicine, 332(20), 1317-1322. http://doi.org/10.1056/NEJM199505183322001

What have other studies shown?

Many other studies have shown that hydroxyurea helps people with sickle cell disease — even children. One study showed that hydroxyurea is helpful and safe for children as young as 9 months old.

Safety and Side Effects

Is it safe to take hydroxyurea for many years?

Yes. Many people with sickle cell disease have taken hydroxyurea safely for over 20 years. Even young children can take it.

Does hydroxyurea cause cancer?

No. There's no evidence that hydroxyurea causes cancer in people with sickle cell disease. It's been used safely since the 1980s.

Nana's Story*

"Hydroxyurea has given me the opportunity to be in control of my health and life."

Nana started taking hydroxyurea when she was just 12 years old. She'd already been in the hospital many times. After Nana started taking hydroxyurea, she was in the hospital less and less. She even got near perfect attendance at school — and went on to study psychology at the University of Virginia.

*The stories in this booklet are from real people who shared their experiences with ASH.

What side effects can hydroxyurea cause?

All medicines can have side effects. Some people who take hydroxyurea may experience these side effects:

- Thinning hair or mild hair loss
- Fingernail beds that turn darker
- Nausea (feeling sick to your stomach)

Very rarely, hydroxyurea can cause more serious side effects. But most people with sickle cell disease who take hydroxyurea don't have any serious side effects.

If you have any new symptoms after you start taking hydroxyurea, tell your doctor — you may be able to take a lower dose.

Most people with sickle cell disease who take hydroxyurea have few or no side effects. Most side effects are mild.

Will I be able to start a family?

If you're thinking about having a baby, be sure to talk to your doctor about the pros and cons of taking hydroxyurea. Experts are still learning about how hydroxyurea affects your ability to have a healthy baby. Taking it during pregnancy is a personal choice that your doctor can help you make.

Many men and women who have taken hydroxyurea have had healthy babies.

Women

- If you are pregnant or planning to get pregnant, talk to your doctor to make a plan.
- Hydroxyurea may increase the risk of birth defects, but we don't know for sure yet.
- Some women choose to stop taking hydroxyurea early in their pregnancy and then start it again during the third trimester (after 29 weeks).

Men

- Hydroxyurea can lower your sperm count, which may already be low due to sickle cell disease.
- Painful erections are a complication of sickle cell disease that can cause permanent damage to the penis. Hydroxyurea may make these painful erections less likely.

Nikita's Story*

"My baby is perfectly healthy and doing just fine."

Nikita started taking hydroxyurea after she got sick during a business trip, and it helped her a lot. After taking it for over 5 years, Nikita got pregnant.

She talked to her doctor about continuing to take hydroxyurea, and together they decided the best choice for her and the baby was to stop taking it during her pregnancy. After she gave birth to a healthy baby boy, Nikita started taking hydroxyurea again. Now, both she and her son are doing well.

*The stories in this booklet are from real people who shared their experiences with ASH.

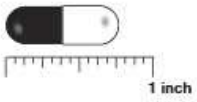
Taking Hydroxyurea

What do I need to know about taking hydroxyurea?

- Most people take hydroxyurea pills once a day. Your doctor will prescribe the dose he or she thinks is right for you. Sometimes you may need to take a different number of pills on certain days.
- Hydroxyurea is safe to take with most other medicines — but it's always a good idea to check with your doctor or pharmacist before starting a new medicine.
- Hydroxyurea pills are capsules that are about three-quarters (3/4) of an inch long.

Hydroxyurea isn't very expensive, and most health insurance plans cover it.

Actual size of sample hydroxyurea pill



Checking your blood count

You'll need to get your blood cell counts checked regularly when you take hydroxyurea. When you first start taking it, you may need to get your blood counts checked every month.

Ask your doctor about your blood count numbers to see how they change. The changes in your blood counts can be a good sign that the hydroxyurea is working!

When taking hydroxyurea, getting regular blood counts helps your doctor see how the medicine is working.

These tests will check for:

- **Hemoglobin**, the protein that carries oxygen in red blood cells. Hydroxyurea works by making your hemoglobin level **go up**.
- The **size of your red blood cells** (measured as "mean cell volume," or MCV). Hydroxyurea works by making your red blood cells **bigger**.
- **Neutrophils**, a type of white blood cell. Hydroxyurea makes the number of neutrophils **go down**. This is okay as long as your white blood cell count doesn't get too low.

Your doctor might change your dose based on your blood cell counts. For example, if the neutrophils in your blood don't go down, your doctor might increase your dose.

Your doctor will also check to see if some types of blood cells get too low. If this is the case, your doctor might ask you to stop taking hydroxyurea for a while.

What if I miss a dose?

- Hydroxyurea will only work if you take it every day.
- Missing a dose is not dangerous and will not reverse the benefits of the drug.

Remember to take it every day

It can be hard to remember to take hydroxyurea every day. Here are some tips to help you remember:

Mark your calendar every day after you take it.

Get a pill box with a section for each day of the week. Fill it on the same day every week.

Set an alarm on your cell phone that goes off every day.

Ask friends or family members to help remind you.

Ndiogou's Story*

"Talk to your doctor about giving it a try."

Ndiogou started taking hydroxyurea when he was 21 years old and noticed the difference a few months later. At first, he had a lot less pain. Eventually, it went away completely.

Sickle cell disease hadn't stopped Ndiogou from playing sports or taking part in other activities, and taking hydroxyurea made life easier for him.

*The stories in this booklet are from real people who shared their experiences with ASH.

What if I take hydroxyurea and it doesn't seem to help?

- Don't be discouraged! Hydroxyurea takes time to work. Try to stick with it for at least a year. It may take that long for your doctor to figure out the right dose for you.
- If you're having side effects, don't stop taking hydroxyurea — talk to your doctor first. Some side effects will go away after you take it for a while.

Adrienne's Story*

"It took a while to start working, but I feel much better now."

For a while, Adrienne was very sick and her blood counts were always low. Her doctor prescribed hydroxyurea for her sickle cell disease, but she stopped taking it after 4 months because she was worried about side effects.

When her doctor explained how hydroxyurea could help her over time, Adrienne decided to try it again. She started to feel better after about 6 months. Now she's able to be more active and she's been in the hospital a lot less, too!

*The stories in this booklet are from real people who shared their experiences with ASH.

The Next Step

Hydroxyurea can help people with sickle cell disease have fewer pain crises and better health. If you have sickle cell disease, it could help you. We hope this booklet has answered some of your questions about this treatment option.

Think hydroxyurea might be right for you? Start the conversation with your doctor.

Notes


AMERICAN SOCIETY OF HEMATOLOGY

ASK ME ABOUT HYDROXYUREA (HU)

FYI: What are the Benefits of Hydroxyurea

Hydroxyurea, also called HU is > 30 years old since **1980s**: drug available in prescription only which is approved to treat sickle cell disease.

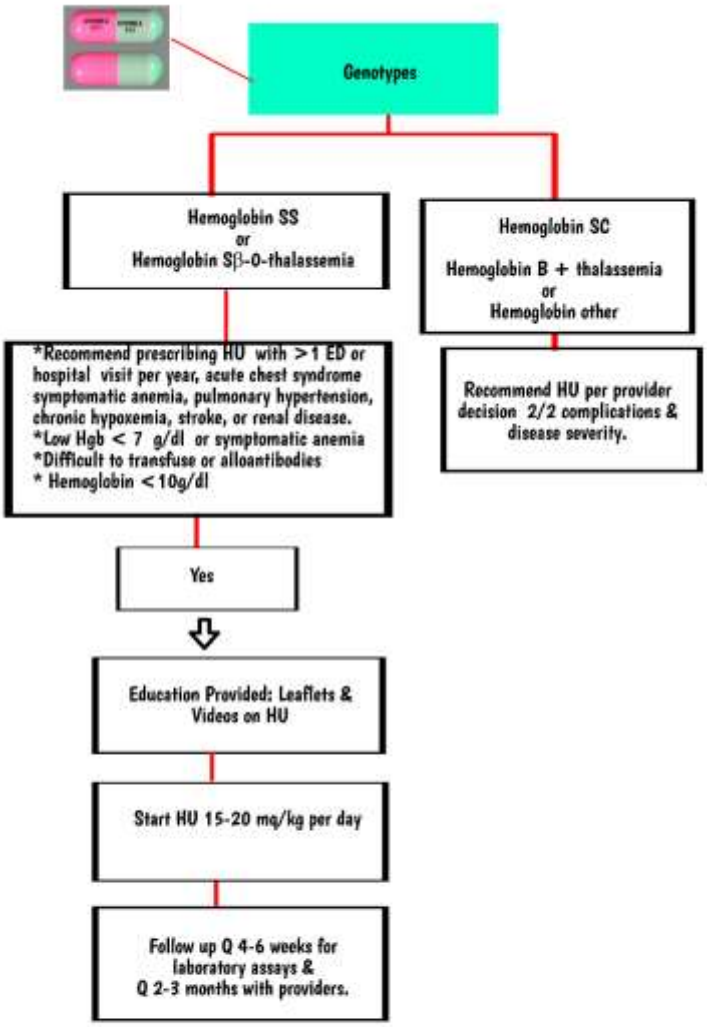
What are the benefits of HU?

- **Decrease frequency, severity, and duration of painful crisis or episodic events of vaso-occlusive crises** (HU treated in patients have ½ as many painful crises, with longer periods b/t crises and less hospitalizations (30% or 1 in 3 prevented visits with HU).
- **Prevent acute chest syndrome (ACS) and reoccurrence of ACS**
- **Prevent avascular necrosis (AVN) of the hip, shoulder or other major joints** which causes pain and the need to have joint placements.
- **Prevent organ damage and death**, (prevent harm to important organs like your brain, heart, lungs, kidneys, and eyes, which can lead to problems of kidney failure or vision loss). Over a 9 year period, studies noted patients had ½ the chances of survival (40% lowered rate for dying).
- **Reduce need for Blood Transfusions** Prevented need for 6/10 transfusions (58% < transfusions needed in HU-treated patients.
- **In Summary HU may help lower your level of pain, decrease the number of transfusions, prevent ACS, organ damage, mortality, and keep you healthy.**

Please ask your providers if you have any additional question(s) about HU.

Appendix D

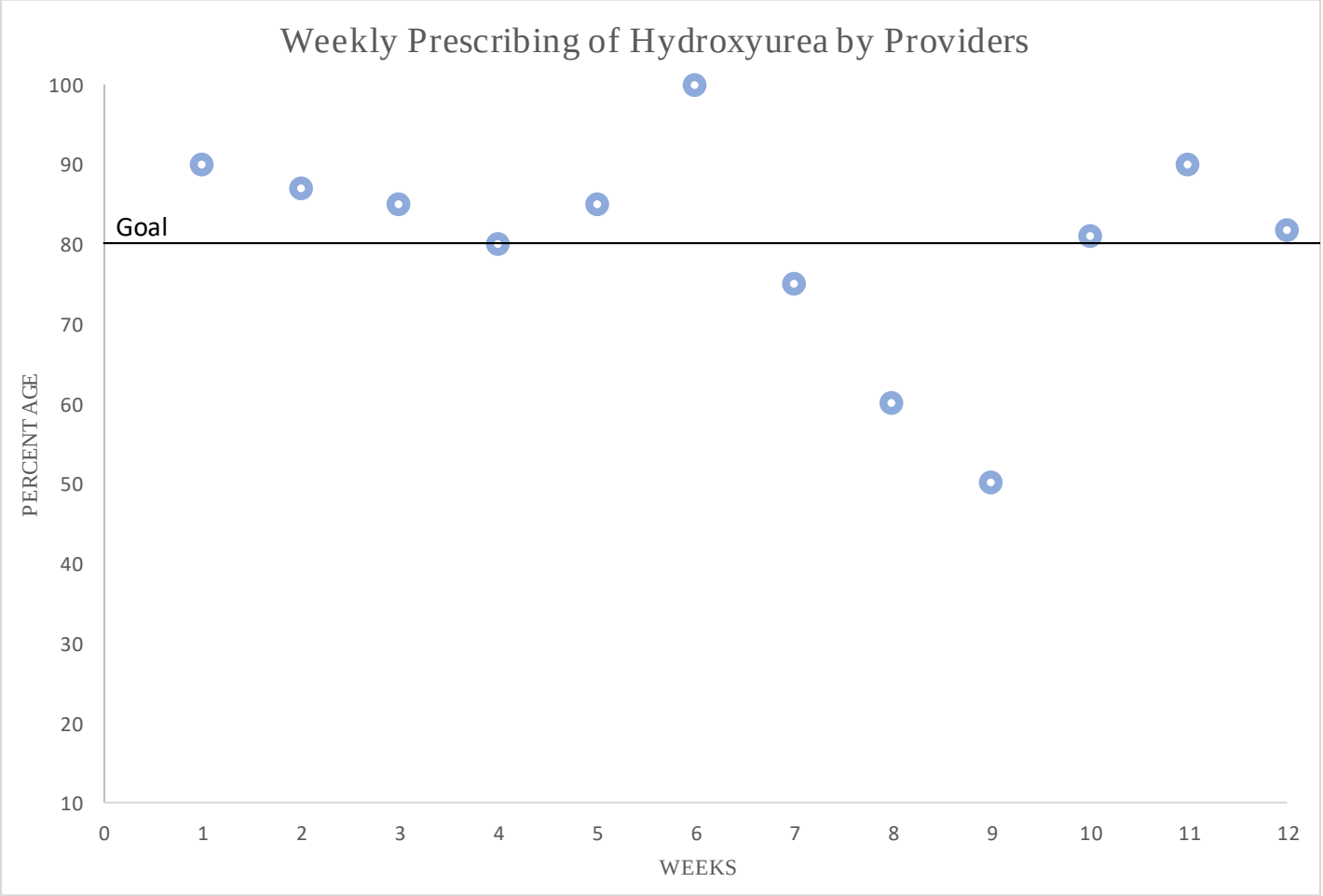
Algorithm: For Standardizing Hydroxyurea in Sickle Cell Disease



Exclusions: Allergy to HU, pregnant, planning pregnancy, breastfeeding, fathering a child, or prior use for at least six months at therapeutic doses without clinical benefits and good adherence.

Appendix E

Weekly Run Chart of Hydroxyurea by Providers



Note: The run chart trends HU prescribing within the 12 weeks with the projected goal of 80%.

Appendix F

Excel Spreadsheet for Hydroxyurea

Week Number	Provider A Education/RX for HU	Provider B Education/RX for HU	Provider C Education/RX for HU	%
1	2/2 (100%)	4/5 (80%)	3/3 (100%)	90%
2	3/4 (75%)	2/2 (100%)	2/2 (100%)	88%
3	Vacation	4/4 (100%)	2/3 (67%)	86%
4	4/5 (80%)	Vacation	4/5 (80%)	80%
5	3/4 (75%)	2/2 (100%)	1/1 (100%)	86%
6	3/3 (100%)	Hospital Rounding	1/1 (100%)	100%
7	5/5 (100%)	5/9 (56%)	2/2 (100%)	75%
8	3/4 (75%)	2/4 (50%)	1/2 (50%)	60%
9	Vacation	Hospital Rounding	1/2 (50%)	50%
10	5/5 (100%)	3/4 (75%)	1/2 (50%)	81%
11	4/5 (80%)	Hospital Rounding	Vacation	80%
12	4/5 (80%)	3/4 (75%)	2/2 (100%)	81%

Note: The excel spreadsheet tracks the weekly percentages of the providers

Appendix G

Hydroxyurea Questionnaire

1. Identify age of patient (Adults):
   - ☐ 18-25
   - ☐ 26-33
   - ☐ 34-41
   - ☐ 42-49
   - ☐ 50-57
   - ☐ 58-65
   - ☐ 66 >

2. Gender of patient:
   - ☐ Male
   - ☐ Female

3. Identify visit type:
   - ☐ Initial visit (new establishment)
   - ☐ Clinic follow-up visit
   - ☐ Hospital follow-up

4. Were laboratory assays done in preparation for the visit
   - ☐ Yes
   - ☐ No

   If yes were they collected?
   - ☐ On site
   - ☐ external lab

5. Was Hydroxyurea discussed and educational material provided
   - ☐ Yes
   - ☐ No

6. Did the patient review the videos on HU?
   - ☐ Yes
   - ☐ No

7. Did the patient have a prescription or receive a new prescription for Hydroxyurea (HU)?
   - ☐ Yes
   - ☐ No

   If not, why not?

   - ☐ Pt already has a valid script
   - ☐ Contraindicated documented allergy
   - ☐ Patient refused Reason:_____
   - ☐ Patient deferred to next visit
   - ☐ Medically contraindicated (pregnant, planning pregnancy, breastfeeding, other)

Please return to Joy E. Curry at joy.curry@duke.edu or in person

Appendix H

Demographics Characteristics

Patients Ages	
18-25	41 (41%)
26-33	23 (23%)
34-41	20 (20%)
42-49	12 (12%)
50-57	4 (4%)
58-65	0 (0%)
66>	1 (1%)
Gender of Patients	
Males	42 (42%)
Females	59 (59%)
Type of Visits	
Initial Visits	4 (4%)
Follow-up Visits	95 (94%)
Hospital Follow-up Visits	2 (2%)

Appendix I

Implementation Timeline

DNP 1 May/ July 2020 (Project Proposal)	DNP II August/ November 2020 (Tools & Education)	DNP III Jan/April 2021 (Project Implementation)	DNP Project IV May/ July 2021 (Final Preparation)
1. Literature Review 2. Identification of Problem 3. Identification of Project Partner and Project Team 4. Algorithm for Hydroxyurea (HU)	1. Doctor of Nursing Practice Proposal 2. Institutional Review Board (IRB) application 3. Letter of Support from Institution 4. Proposal to Nursing Research Council 5. Leaflets and Education on HU 6. Provided buttons Ask Me About HU 7. One pager summary to build case for project 8. Project Approval granted	1. Implementing begins 2/1/2021 2. Project Team Members began to educate the participants with specific genotypes, Hemoglobin SS and Hemoglobin S**β**-0-thalassemia 3. Tablets with HU Videos provided to patients to review during clinic visit 4. Plan-Do-Study-Act (PDSA) summarize three cycles 5. Every two weeks meet with Project Team and Project Champion by face-face interaction, emails, text messages, or Zoom to address questions or concerns in the interval. 6. Data collection weekly on M/W/Th 7. Evaluation of Implementation	1. Interpretation of data analysis from Research Electronic Data Capture (REDCap) 2. Evaluation of the impact of the problem and participants of HU prescribing 3. Final Approval of the Faculty member of the final paper. 4. Preparation for the poster presentation at ECU July 2021 5. Presentation at ECU in-person or virtually 6. Project submitted to scholarly repository

Appendix J

DNP Project's Budget

DNP Hydroxyurea (HU) Project's Budget Plan	Quantity	Projected Cost PER UNIT	Projected SUBTOTAL
Administrative Expenses			
Computer (Tablets)	2	$600.00	$1,200.00
Fax & Coping	100	$0.25	$25.00
Advertising			
Button: Ask Me About HU	50	$1.00	$50.00
Brochures: Hydroxyurea from the Amercian Society of Hematology-15 Sheet Package	100	$10.00	$1,000.00
HU: Educational Leaflets	100	$1.00	$100.00
Miscellaneous			
White Coat Clip Boards (Nurses)	5	$19.00	$95.00
Personalized HU Pens for Particpants	75	$2.00	$150.00
Personalized HU Pens for Staff	20	$2.50	$50.00
Total			$2,670.00

Appendix K

Doctor of Nursing Practice Essentials

	Description	Demonstration of Knowledge
Essential I ***Scientific Underpinning for Practice***	**Competency** – Analyzes and uses information to develop practice **Competency** -Integrates knowledge from humanities and science into context of nursing **Competency** -Translates research to improve practice **Competency** -Integrates research, theory, and practice to develop new approaches toward improved practice and outcomes	• A need for optimizing Hydroxyurea (HU) prescribing for individuals and standardizing HU in specific genotypes, particularly hemoglobin SS and hemoglobin Sβ-0-thalassemia. • Knowledge gained from the National, Heart, Lung, and Blood Institute (NHLBI) guidelines for optimizing evidence-based recommendations for prescribing and offering HU as the FDA-approval for greater than 30 years for eligible participants with sickle cell disease (SCD).
Essential II ***Organizational & Systems Leadership for Quality Improvement & Systems Thinking***	**Competency** –Develops and evaluates practice based on science and integrates policy and humanities **Competency** –Assumes and ensures accountability for quality care and patient safety **Competency** -Demonstrates critical and reflective thinking **Competency** -Advocates for improved quality, access, and cost of health care; monitors costs and budgets **Competency** -Develops and implements innovations incorporating principles of change **Competency** - Effectively communicates practice knowledge in writing and orally to improve quality **Competency** - Develops and evaluates strategies to manage ethical dilemmas in patient care and within health care delivery systems	• The initiative with providing an algorithm to guide clinicians with recommendations for HU based on specific criteria that outlines contraindications for HU prescribing. • The PDSA was introduced as the operational framework with 3 cycles, 4 weeks each testing change with HU prescribing of providers during the 12 weeks noting the

		success of reaching the 80% benchmark.
Essential III ***Clinical Scholarship & Analytical Methods for Evidence-Based Practice***	**Competency** - Critically analyzes literature to determine best practices **Competency** - Implements evaluation processes to measure process and patient outcomes **Competency** - Designs and implements quality improvement strategies to promote safety, efficiency, and equitable quality care for patients **Competency** - Applies knowledge to develop practice guidelines **Competency** - Uses informatics to identify, analyze, and predict best practice and patient outcomes **Competency** - Collaborate in research and disseminate findings	• The run chart used to plot the weekly prescribing of the providers. • The Excel spreadsheet tracking tool identified the weekly prescribing with analysis of the percentages by the providers individually ideally, but the DNP project partners decided to identify weekly prescribing of Providers identified as A, B & C in the setting of the COVID-19 pandemic. • 12 Weeks were analyzed.
Essential IV ***Information Systems – Technology & Patient Care Technology for the Improvement & Transformation of Health Care***	**Competency** - Design/select and utilize software to analyze practice and consumer information systems that can improve the delivery & quality of care **Competency** - Analyze and operationalize patient care technologies **Competency** - Evaluate technology regarding ethics, efficiency and accuracy **Competency** - Evaluates systems of care using health information technologies	• An algorithm was used to initiate prescribing based on specific evidence-based guidelines adopted from Up-to-Date and National, Heart, Lung, and Blood Institute (NHLBI) • Educational literature on hydroxyurea was provided by face-face interactions, smart phrases, and sharing YouTube video links. • Weekly Excel spreadsheets identified HU prescribing and education provided to the eligible participants. • QR codes were used to provide healthcare education on the clinical benefits of HU.
	Description	**Demonstration of Knowledge**
Essential V ***Health Care Policy of***	**Competency**- Analyzes health policy from the perspective of patients, nursing and other stakeholders	• The DNP project site used the algorithm, and smart phrases with

Advocacy in Health Care	**Competency** – Provides leadership in developing and implementing health policy **Competency** –Influences policymakers, formally and informally, in local and global settings **Competency** – Educates stakeholders regarding policy **Competency** – Advocates for nursing within the policy arena **Competency**- Participates in policy agendas that assist with finance, regulation and health care delivery **Competency** – Advocates for equitable and ethical health care	literature to provide information about the novel disease-modifying medication, HU. • Additionally, a website was created at the site to provide secured email links for the patients to use QR codes to retrieve education on HU. This advocates for providing literature to optimize the patients understanding of the therapy and supporting patient-centered care. • This new innovation of technology is a new way for patient to engage in self-management by learning about their chronic disease.
Essential VI ***Interprofessional Collaboration for Improving Patient & Population Health Outcomes***	**Competency**- Uses effective collaboration and communication to develop and implement practice, policy, standards of care, and scholarship **Competency** – Provide leadership to interprofessional care teams **Competency** – Consult intraprofessionally and interprofessionally to develop systems of care in complex settings	• The DNP project used the algorithm to prescribe this FDA-once daily dose that is recognized by national and international guidelines globally as standards in care for patients with SCD. • The project was led by the DNP student in collaboration with the project champion, project mentor, clinical specialist, and the project team members. • The collaboration with the team and interpersonal relationships with the patients addressed the

		approaches of optimizing the healthcare outpatient with prescribing HU to specific genotypes. • Interpersonal relationships and collaboration with Information Technology (IT) and their support with of telehealth and QR codes
Essential VII ***Clinical Prevention & Population Health for Improving the Nation's Health***	**Competency**- Integrates epidemiology, biostatistics, and data to facilitate individual and population health care delivery **Competency** – Synthesizes information & cultural competency to develop & use health promotion/disease prevention strategies to address gaps in care **Competency** – Evaluates and implements change strategies of models of health care delivery to improve quality and address diversity	• Health promotion and disease prevention focused on optimizing HU in individuals addressing the burden of the disease and discussing how optimizing HU could potentially prevent additional acute on chronic irreversible complications. • Literature was provided to help assist the individuals with understanding of this novel disease-modifying therapy. • The providers and project team members educated the patients about HU with patient-centered collaborations and decision-making with being an advocate for prescribing HU.

		• Improving patient's engagement with the eHealth interventions with technology of providing literature virtually has improved the patients' self-engagement. • The eHealth and technical advances will continue to be supported as with strategies interventions for improving the knowledge and acceptance of prescribing HU to its maximal tolerated dose.
Essential VIII ***Advanced Nursing Practice***	**Competency-** Melds diversity & cultural sensitivity to conduct systematic assessment of health parameters in varied settings **Competency** – Design, implement & evaluate nursing interventions to promote quality **Competency** – Develop & maintain patient relationships **Competency** –Demonstrate advanced clinical judgment and systematic thoughts to improve patient outcomes **Competency** – Mentor and support fellow nurses **Competency-** Provide support for individuals and systems experiencing change and transitions **Competency** –Use systems analysis to evaluate practice efficiency, care delivery, fiscal responsibility, ethical responsibility, and quality outcomes measures	• The DNP project Quality Improvement (QI) was measured by using educational advances with technology, algorithm that was guided by evidence-based practice, an Excel spreadsheet and run chart identified to evaluate gaps and weekly progress in prescribing. • The participants were protected and embraced based on their culture preferences. • Trusting relationships were established between patients and healthcare team

		members during the visits allowing participants to ask questions optimizing the care of SCD by reducing the burdens of ED visits, hospitalizations, and readmissions.