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Trial design of comparing patient-specific versus weight-based protocols to treat vaso-occlusive episodes in sickle cell disease (COMPARE-VOE)

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ABSTRACT

Objectives: Painful vaso-occlusive episodes (VOE) are the most common reason for emergency department (ED) visits experienced by patients with sickle cell disease (SCD). The National Heart, Lung and Blood Institute (NHLBI) evidence-based recommendations for VOE treatment are based primarily on expert opinion. In this randomized controlled trial (RCT), we will compare changes in pain scores between patients randomized to a patient-specific analgesic protocol versus those randomized to a weight-based analgesic protocol, as recommended by the NHLBI guidelines.

Methods: We report the rationale and design of a multi-site, phase III, single-blinded, RCT to be conducted in six EDs in the United States. Eligible participants will be randomized after providing consent, anticipating 50% of those randomized would have an ED visit during the enrollment period. A total of 230 participants with one VOE ED visit provides sufficient power to detect a clinically significant difference in pain score reductions of 14 between groups with 0.05 type I error. Uniquely, this trial randomizes participants in a larger population than the study population, given the impossibility of consenting and randomizing participants during emergencies. The primary endpoint is the change in pain scores in the ED from time of placement in treatment area to time of disposition (hospitalization, discharged home, or assigned to observation status) or a maximum treatment duration of 6 hours. Additional outcomes include hospitalizations and ED visits seven days post enrollment, side effects, and safety assessments.

Conclusions: The COMPARE-VOE study design will provide high-level evidence to support the NHLBI VOE treatment guidelines.

1. Introduction

Sickle cell disease (SCD) is a genetic disorder and one of the most common hemoglobin disorders in the world [1]. It affects an estimated 90,000–100,000 Americans and ranked as the fifth most common principal diagnosis for Medicaid's super-utilizer hospital stays (4 or

Abbreviation: AE, Adverse Event; DSMB, Data Safety Monitoring Board; ED, Emergency Department; EHR, Electronic Health Record; Hgb, Hemoglobin; HR, Heart Rate; ITT, Intention To Treat; IV, Intravenous; KG, Kilogram; MG, Milligram; MM, Millimeter; NHLBI, National Heart, Lung, and Blood Institute; Q, Every; RA, Research Associate; RCT, Randomized Controlled Trial; RR, Respiratory Rate; SAE, Serious Adverse Event; SCD, Sickle Cell Disease; SpO2, Peripheral Saturation of Oxygen; VOC, Vaso-Occlusive Crisis; VOE, Vaso-Occlusive Episode.

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more hospital stays in 1 year) in 2012 [2]. SCD primarily affects vulnerable populations, occurring in 1 in 365 African American births and 1 in 16,305 Hispanic American births [3]. In SCD, genetically abnormal beta globin subunits of the hemoglobin molecule polymerize and cause morphologic deformity of erythrocytes under conditions of stress and de-oxygenation. These "sickled" erythrocytes adhere to blood vessel endothelium, causing occlusion that results in tissue ischemia, end-organ damage, and debilitating pain. Painful vaso-occlusive episodes (VOE), historically termed vaso-occlusive crises (VOC), are the most common manifestation of SCD experienced by patients and the most common reason for ED visits [4]. Pain from VOE occurs suddenly and is excruciating and unpredictable [5]. Patients with an increased frequency of VOE have higher morbidity and mortality rates [6].

In 2014, the National Heart, Lung, and Blood Institute (NHBLI) published evidence-based recommendations for the various complications of SCD; including 17 recommendations for treatment of VOE [5]. A key recommendation suggests the use of either a patient-specific analgesic protocol written by the patient's SCD provider, or a SCD-specific protocol for pain management. However, "SCD-specific" analgesic protocol was not defined, and there is a lack of standard or evidence-based analgesic protocols to treat VOE. Patients suffering from VOE experience inconsistent management while frequently facing bias [7–9]. In a recent cohort study, 81% of patients reported choosing to stay at home to manage their VOE, and of those, 83% reported that past negative ED experiences influenced this decision to stay home [7]. However, patients often require treatment in the ED to not only manage pain but also to immediately evaluate and treat other potentially serious complications.

A 2015 review of the NHLBI recommendations identified gaps in evidence and the need to compare the effectiveness of patient-specific and weight-based analgesic protocols for VOE was identified as a priority research area [10]. Subsequent to this review, a randomized pilot study was conducted and compared patient-specific versus a standard weight-based SCD protocol in a sample of 52 patients with a total of 106 ED visits (two EDs). Results demonstrated a significantly greater reduction in pain scores for patients assigned the patient-specific protocol [11]. While promising, it is not sufficient to definitively recommend the patient-specific protocol due to the sample size and limited generalizability of research conducted at only two sites. Therefore, it is necessary to conduct a phase III RCT to compare these two analgesic protocols with a large and heterogeneous sample from multiple ED sites.

This paper describes the design and protocol for COMPARE-VOE, a multi-site, phase III, single-blinded, RCT that will compare changes in pain scores as the primary outcome between patients randomized to a patient-specific analgesic protocol versus those randomized to the weight-based analgesic protocol.

2. Methods

The study protocol has been approved by the Western Institutional Review Board (IRB), which served as the central IRB. This study was also approved by Duke University IRB and each participating site IRB. All participants will provide informed written consent prior to randomization and participation. The trial is registered in Clinical Trials with the identifier NCT03933397.

2.1. Study synopsis and clinically significant difference

The COMPARE-VOE study is a Phase III, single-blinded RCT that will be conducted at six U.S. sites over an enrollment period of approximately 24 months. Potential participants will be screened using inclusion and exclusion criteria for randomization. Upon obtaining informed consent, participants are randomized to one of the two analgesic protocols using a 1:1 treatment allocation ($n = 460$). Upon presentation to the emergency department for VOE, the participant will be re-screened for inclusion, then enrolled in the study ($n = 230$). Data collection begins once the participant is placed in a treatment area. Data are collected every 30 minutes until the time of disposition or a maximum treatment duration of 6 hours. A synopsis of the COMPARE-VOE study is presented in Table 1, and the study flow is summarized in Fig. 1.

2.2. Study objectives and outcomes

The study aims to determine if the patient-specific analgesic protocol is superior to the weight-based analgesic protocol (control) in improving change in pain scores in patients with VOE randomized to these two protocols. The primary hypothesis for this study states:

Participants randomized to the patient-specific protocol will experience a greater statistically significant and clinically meaningful (14 or greater on a 100-point scale) reduction in pain intensity scores than those randomized to the weight-based protocol.

The primary outcome of the study is the change in pain scores in the ED from the time of placement in treatment area to the time of disposition (hospital admission, discharged home or assigned to observation status) or a maximum treatment duration of 6 hours, whichever comes first. The clinically meaningful difference of 14 was selected based on pilot study data [11] and extant literature on changes in pain scores for patient populations experiencing high pain levels upon ED presentation [12]. The study will also investigate differences between the two analgesic protocols in secondary outcomes of ED length of stay, hospitalization, seven-day return ED visits and hospitalizations. Additionally, side effects and safety will be monitored.

2.3. Inclusion/exclusion criteria

To be included in the intent-to-treat population for this study, participants must be 18 years old or more and have one of the following SCD genotypes: HbSS, HbSC, HbSß+, HbSß°. Exclusion criteria include patients with sickle cell trait genotype, patients with a treatment protocol that does not allow administration of opioids, patients with an existing ED protocol that includes oral opioids only, or patients prescribed buprenorphine-containing medication in the outpatient setting or methadone. An additional exclusion criterion of suspected or confirmed COVID-19 at the time of the ED visit was added after the onset of the SARS-CoV-2 pandemic. The selection criteria in Table 2 were designed to be inclusive and representative of the SCD population, including appropriate representation of women.

Table 1
Executive summary of COMPARE-VOE.

Title	A Comparison of Patient-specific vs. Weight-Based Protocols to Treat Vaso-Occlusive Episodes in Sickle Cell Disease (COMPARE-VOE)
ClinTrials Number	NCT03933397
Location	6 clinical sites (Emergency Departments) in the United States
Objectives	To compare the two analgesic protocols recommended by the NHLBI for treating VOE in the Emergency Department.
Primary Hypothesis	The patient-specific analgesic protocol is superior to the weight-based analgesic protocol.
Study Design	A Phase III single-blinded randomized study of approximately 460 participants to capture data on 230 participants with one ED visit in the study population.
Treatment Regimens	1:1 treatment allocation will be used. Participants will be randomized to receive analgesic management for VOE either via a weight-based SCD analgesic, or a patient-specific analgesic developed by their primary SCD outpatient provider.
Primary Endpoint	Change in pain scores in the ED from the time of placement in treatment area to the time of disposition (hospital admission, discharged home or assigned to observation status) or a maximum treatment duration of 6 h, whichever comes first
Secondary Endpoints	• ED length of stay • Hospitalization for pain control • Return ED visits, hospitalizations, or day hospital visits within seven days of index ED visit • Safety and side effects

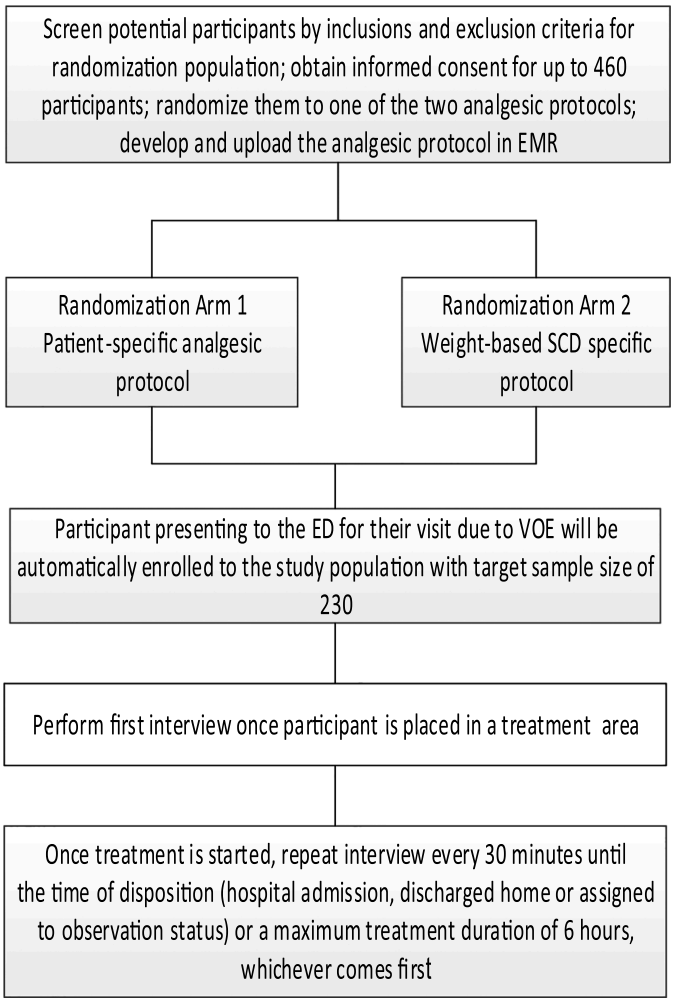

Fig. 1. Study Flow Chart.

Table 2
Inclusion Criteria for Randomization (consent) and Enrollment (ED visit).

Study Phase	Inclusion Criteria	Exclusion Criteria
Randomization	• 18 years of age • SCD patients with the following genotypes: o Hgb SS o Hgb SC o SB+ thalassemia o SB- thalassemia	Patients with • sickle cell trait • a treatment protocol that does not allow administration of opioids • an existing ED protocol that includes oral opioids only • prescribed buprenorphine-containing medication in the outpatient setting • prescribed methadone
Enrollment	• Patient is randomized • ED visit for VOE requiring parenteral opioid analgesia	• Patients presenting to the ED with other complications (e.g., acute chest pain, stroke, sepsis, priapism and other pulmonary complications) not clinically appropriate/stable for inclusion

2.4. Recruitment, randomization, and enrollment

The intent-to-treat population (ITT) for this study includes adult SCD patients with an ED visit due to VOE with pre-specified inclusion and exclusion criteria. In a typical RCT, participants in the ITT population are approached for informed consent first and if consented, they are randomized. Those randomized are usually considered as enrolled participants. In this study, it would be logistically impossible to consent and randomize participants during an ED visit due to severe pain experienced during a VOE, the inability to obtain an individualized pain plan from the SCD provider and have it available for the ED provider in the electronic health record. There is no reason to think the patients randomized are any different than those who eventually do, or do not, have an ED visit for VOE. The occurrence of VOE is totally unpredictable and not related to overall disease severity or genotype.

Therefore, we plan to screen, consent, and randomize participants in a larger population, called the randomization population. We plan to recruit this population during SCD clinical visits or hospitalizations. After patients have provided informed written consent, they will be randomized to either the weight-based analgesic protocol or a patient-specific analgesic protocol that will be developed by their hematologist/sickle cell team. Patients will also participate in a baseline interview and provide demographics and typical pain medication taken on a severe pain day. A 1:1 treatment allocation will be used with site as the stratification variable. A computer-generated permuted block randomization schedule with stratification by clinical site will be prepared by the unblinded Data Coordinating Center (DCC) statistician with a randomly chosen block size that will not be revealed to investigators. This scheme provides chronological balance during enrollment with respect to the number of patients allocated to each treatment arm, and thus balances the treatment groups with respect to possible changes in the mix of patients over time. For the sites, the randomization will be available through the password protected and customized web-based

electronic data capture (EDC) system. The EDC will be maintained by the Data Coordinating Center data management team. When randomized participants have an ED visit due to VOE for which their randomized protocol is utilized, they would be enrolled in the ITT population, called the enrollment population.

2.5. Description of analgesic protocols

All analgesic protocols will be written by the participant's SCD provider using a standardized method to determine the patient-specific dose or weight-based dosing (Table 3). During the baseline interview conducted after providing consent, patients provide typical analgesics taken over a 24-hour period when experiencing severe pain, including daily use of both long and short acting opioids. This information is provided to the SCD hematologist who then determines the appropriate ED dose based on the randomized protocol. The primary difference between the two analgesic protocols is the starting opioid dose. Other elements of both analgesic protocols reflect the NHLBI expert panel recommendations, including recommended route and re-dosing intervals. All protocols must be completed and uploaded to the electronic health record (EHR) within two weeks of randomization by an unblinded research study staff member, to be accessed if and when the patient has an ED visit for VOE. All protocols include the following statement to avoid over sedation: This protocol is intended to be used as a research protocol when research staff and monitoring are present. No additional sedating drugs or intravenous diphenhydramine should be co-administered with this protocol. Additional features of the two study arms are described in Table 3 and typical weight-based doses are provided in Table 4.

2.6. ED visit data collection

Upon presentation to the ED with VOE, an ED provider, blinded to treatment arm, will access the patient's randomized analgesic protocol (weight-based or patient-specific) from the EHR. Only the drug, dose, route and interval are indicated. The patient is also blinded to their randomized arm, but may still be told what drugs and doses they receive in the ED. Only one ED visit per patient is recorded for the primary and secondary outcomes of this study.

Table 3
Comparison of Patient-specific and Weight-based analgesic protocols.

	Patient-specific analgesic protocol	Weight-based analgesic protocol
Agent	To be determined (TBD) by SCD provider after randomization for use at a future ED visit (morphine sulfate or hydromorphone)	To be determined (TBD) by SCD provider after randomization for use at a future ED visit (morphine sulfate or hydromorphone)
Dose	TBD a priori by SCD provider, based upon current outpatient opioid therapy and past doses required to treat VOE during past ED visits or hospitalizations.	TBD a priori by SCD provider. Initial dose = weight-based hydromorphone 0.02 mg/kg morphine sulfate 0.1 mg/kg.
Route	Intravenous (IV) unless unable; sub-cutaneous when IV access is difficult.	Intravenous (IV) unless unable; sub-cutaneous when IV access is difficult.
Monitoring	Per routine standard of care Q30 min per research protocol / research assistant (sedation level, SpO2, BP, HR, RR).	Per routine standard of care Q30 min per research protocol / research assistant (sedation level, SpO2, BP, HR, RR).
Repeat Doses	TBD by SCD provider – Q20-30 minutes as required to treat unrelieved pain. No maximum dose set.	Q20-30 minutes for unrelieved pain. All additional doses, if required, may be provided at the same dose as the 1st dose, or no more than a one-time 25% increase above the original dose.
Intravenous hydration	Maintenance rate (unless dehydrated) when patients are unable to drink fluids adequately.	Maintenance rate (unless dehydrated) when patients are unable to drink fluids adequately.

Table 4
Weight-Based doses for morphine sulfate and hydromorphone.

Weight range (kg)	Morphine dose (mg)
<50	**4**
50–69.9	**6**
70–89.9	**8**
≥ 90	**10**
Weight range (kg)	**Hydromorphone dose (mg)**
<60	**1**
60–89.9	**1.5**
≥ 90	**2**

Patients will be interviewed by research assistants (RA), who are also blinded to the study participant's allocated study arm, to obtain pain intensity data for the primary outcome while in the ED. The interview will be conducted every 30 minutes until the patient is: 1) discharged home, 2) admitted to the hospital or assigned to observation status for continued pain management, or 3) after six hours of treatment (maximum data collection period), whichever comes first. RAs will ask participants to verbally rate their pain using the 0–100 verbal numeric rating scale [13], where 0 is no pain and 100 is the worst ever. If COVID-19 regulations allow the use of paper at a study site, a 0-100 mm VAS [12] pain score will also be collected from participants using the same qualitative anchors of pain intensity. If a patient is not in his/her room (e.g., in radiology), the RA will have 10 minutes to collect data after each 30-minute assessment. If the RA is unable to collect data for a 30-minute assessment, this assessment is marked as missing.

A sedation score based on the Pasero Opioid-Induced Sedation Scale will also be obtained at each assessment [14]. A provider will be notified should a participant have a sedation score of 3 or more to initiate closer respiratory status monitoring and opioid administration adjustments. In addition, potential side effect assessments will be obtained directly from the patient during the 30-minute interviews, including nausea, vomiting, and itching; these are expected adverse events (AE's). The participant completes the study as soon as the enrollment ED visit is recorded. Upon completion of the study, the patient's randomized analgesic protocol will be removed from the EHR.

2.7. EHR review of subsequent ED visits, hospitalizations and side effects

After the completion of the patient's enrollment ED visit, the RA will review the EHR periodically to obtain the number of ED visits and number of hospitalizations (including day hospital visits) seven days after the enrollment visit for collection of secondary outcomes. The RA will also periodically review the EHR to determine the number of missed ED visits between randomization and enrollment for each participant for tracking purposes. Should an ED visit be missed due to RA unavailability, the next ED visit will be recorded. A schedule of study visit assessments is provided in Table 6.

2.8. Safety

Safety outcomes will be assessed during the ED visit and again seven days after the enrollment ED visit via EHR review to assess for any side effects if the patient was admitted for up to seven days of hospitalization. The RA will review the medical record and assess whether the participant experienced any respiratory side effects including signs of respiratory distress, administration of naloxone, assistance with respiration and/or ventilation, participant transfer to ICU or suspected acute chest syndrome.

Due to the difficulty in ascertaining the diagnosis of acute chest syndrome, an adjudication process will be used to confirm the diagnosis of acute chest syndrome in any participant with this suspected diagnosis.

Reported acute chest syndrome (ACS) events in the EHR will be reviewed by an adjudication committee consisting of study site investigators specializing in hematology and emergency medicine within 15 days of event entry into the hospitalization data collection form. Each reported ACS event will be reviewed by two members of the committee. If they do not agree, a third member of the committee will review the event and the result of the majority decision will be recorded. Committee members will not review events from their site. The adjudication results will be entered into the ACS data collection form by the Clinical Coordinating Center within five business days of the completed adjudication.

Protocol-specific expected AEs occurring during the enrollment ED visit will be collected and reported to the Data Safety Monitoring Board (DSMB) biannually. Expected AEs for this protocol are listed in Table 5. Serious adverse events (SAE) will be collected from the time of first administration of pain protocol drug during the study ED visit through seven days post ED visit. Protocol-specific SAEs are described in Table 5. SAEs will be recorded and reported to the DSMB along with the study site principal investigator's assessment of relatedness, within 24 hours of knowledge of the event and reported to NHLBI.

2.9. Sample size and power

The primary null hypothesis of this study is equality of pain score reduction between the two analgesic protocols. A two-sample *t*-test is used to test this hypothesis. A sample size of 230 participants with ED visits provides 90% power to detect a clinically significant difference in pain score reduction of 14 between the two groups with 0.05 type I error, with the assumptions of the same standard deviation (SD) of 31 in pain score reduction in the two groups while accounting for 10% missing data rate on the change of pain score. The assumptions of SD and missing data rate are based on the data from the pilot study where the overall SD of the pain score reduction was 30 and the missing data rate was 8% [11]. Thus, assumption of SD = 31 and 10% missing data rate in pain score reduction is conservative. By varying the SD from 30 to 32 and missing data rate from 5% to 15%, the corresponding power ranges from 88% to 92%. Therefore, we have sufficient power with the target sample size of 230 for this trial.

The corresponding sample size for the randomization population depends on what percent of randomized participants would have an ED visit during the enrollment period. In the pilot study with 13 months of enrollment, 49% of the randomized participants had an ED visit [11]. Given the 24 month planned enrollment period in this trial, which is double that of the pilot study, it is conservative to assume that 50% of the randomized participants will have their first ED visit within the 24 months. Participants randomized earlier would have a longer lead time to present to the ED. Thus, a total sample size of 230 participants for the enrollment population and 460 participants for the randomization population are reasonable and conservative estimates. We plan to stop randomization as soon as we reach 230 enrolled participants.

Table 5
Summary of Protocol-Specific AEs and SAEs.

Protocol-specific Adverse Events (AEs)	• Nausea • Vomiting • Pruritus • SPO2 < 95% requiring supplemental use of oxygen via nasal cannula due to opioid therapy • Moderate or severe sedation • Drowsiness • Respiratory depression not requiring intubation or naloxone • Low blood pressure
Protocol-specific Serious Adverse Events (SAEs)	• Respiratory depression requiring naloxone administration given within 2 h of last administration of pain protocol drug • Events resulting in death • Events that are considered life-threatening complications • Events requiring admission to Intensive Care Unit (ICU) or intubation within 7 days of first administration of pain protocol drug during the enrollment ED visit.

Table 6
Schedule of Assessments.

	Screening/ Enrollment Randomization	ED Visit	Day 7 Post ED Visit
Informed Consent (Site study staff)	X		
Inclusion/exclusion criteria confirmed	X	X	
Pain evaluation questions		X*	
ED medication administration; Recording on names of drugs, doses and timing of administration.		X	
AE		X	
SAE		X	X
Return ED visits			X
Hospitalizations			X
Day Hospital Visits			X

* Assessments are to be performed Q 30 min (+/− 15 min). Assessments missed due to participant clinical care requirements will not be considered deviations.

For exploratory purposes, the power calculation for the secondary outcomes is also provided for the target sample size of 230 at 0.05 level (two-sided). Due to its exploratory nature, adjustment for multiple testing such as the Bonferroni method will not be used to preserve the overall type I error level. We will be conservative in the interpretation of secondary analyses, taking into account the degree of significance, and looking for consistency across outcomes to avoid over-interpretation. We do not expect any missing data in the secondary outcomes, as seen in the pilot study [11]. For ED length of stay, we have 83% power to detect a 30-minute difference in ED length of stay between the two analgesic protocols, assuming SD of 78. We have 94% power to detect a 15% difference in rates of hospital/day hospital admission/visit within 7 days with two-sided 0.05 type I error assuming rates of 20% and 5%, respectively, in the patient-specific and weight-based analgesic protocols. These assumptions are based on the observations in the pilot study [11].

2.10. Statistical analysis

Descriptive statistics will be used to summarize patient sociodemographic and clinical characteristics for all randomized participants and by randomized groups. We will compare the characteristics between groups with and without recorded ED visit (i.e., enrolled or not enrolled in study population) to determine if those enrolled with an ED visit differ from those who are not enrolled when the enrollment period ends. Furthermore, participants enrolled in the study with an ED visit will be described by the randomized groups. Means, standard deviations, medians, 25th and 75th percentiles, minimum and maximum will be presented for continuous variables; the number and frequency of patients in each category will be presented for nominal variables.

Statistical comparison of the two randomized arms with respect to the primary outcome will be accomplished by comparing the means of the pain score reductions between the two arms. Primary analysis will be based on linear regression with pain score reduction as the dependent variable to assess the treatment effect while adjusting for the prespecified covariates of initial pain score at ED time of placement in a treatment area, biological variables of SCD genotype, age, and gender. Depending on the direction of treatment effect, rejection of the null hypothesis of equal treatment effect hopefully would support our previously stated hypothesis that states the patient-specific protocol is superior to the weight-based protocol. In addition to the statistical hypothesis testing, 95% confidence intervals will be computed to

descriptively summarize the difference in outcome between the two arms, as well as outcome in each arm.

The secondary outcome to compare ED length of stay between the two arms, measured from ED arrival to discharge, will be assessed using a linear regression analysis similar to the primary outcome. For the hospital admission rate, chi-square test will be used to compare the admission rates between the two groups. For count data (e.g., ED re-visits or hospitalizations for VOE within 7 days after the recorded ED visit), these data will first be evaluated by collapsing the data into a binary outcome with a cut off at zero. A chi-square test or Fisher exact test (if frequency is below 5 or less) will be to compare the re-admission rates or rate of a returned ED visit between the two groups. If there is sufficient spread in the count data, a Poisson regression approach will be used to test for protocol differences in the count outcome.

Subgroup analyses will be carried out with sub-groups pre-specified based on the following variables: gender, age (< 30, ≥ 30 years old), genotypes (Hgb SS, SC, SB+, SB-), route (IV or SC), use (yes/no) of NSAIDS, agent used, number of repeated doses, and total administrated milligrams of drug. These analyses will be conducted by including interaction terms in the above primary and secondary analyses. For all analyses, a two-sided p-value ≤ 0.05 will be considered statistically significant.

The frequency with which various side effects, adverse event (AE) or serious adverse events (SAE) occur will be carefully tabulated and descriptively summarized. We will conduct exploratory statistical comparisons of the randomized arms with respect to these events using chi-square, Fisher exact, or other appropriate two-sample methods. This analysis will depend on the nature of the event, interpreting such comparisons in the context of differences between the two randomized arms in the primary and major secondary outcomes, and bringing to bear clinical judgment as to the relative seriousness of these side effects and various adverse events.

3. Discussion

Under, and untreated pain from VOE remains a significant problem with significant morbidity and mortality. Despite the publication of NHLBI recommendations in 2014, there has been little widespread change in the treatment of VOE. The most probable reason is likely the low level of evidence (consensus panel), of the recommendations. To date, only one RCT has been conducting comparing the suggested NHLBI VOE protocols. This trial included only two EDs and 52 patients [11]. All other studies investigating treatment of VOE have been either pre-post designs, small samples, and conducted mostly in the pediatric vs. adult population. Our current trial is important because it will be fully powered to determine if either protocol is more effective at managing VOE. Results of our trial can be used to provide much stronger and thus widespread support of the recommendations.

This trial is also important because the guidelines included a recommendation for an "*individualized prescribing and monitoring protocol written by the SCD provider, OR an SCD specific protocol whenever possible*". There was no further direction included in the NHLBI recommendations as to "how" to develop an individualized protocol, or "what" a SCD specific protocol would include, if it was impossible to write individualized protocols. The development of individualized analgesic protocols are somewhat cumbersome to write and impossible in hospitals where there are no SCD specialists available to write the protocols. In many centers, SCD patients are treated by general hematologists who may not be SCD specialists. In our protocol we have carefully developed a systematic method to determine individual doses based on the patient's use of opioids, both for acute and chronic pain. This "protocol" for development of individualized protocols will be beneficial to all providers treating SCD. In our protocol we are using standard weight based opioid dosing for the comparison standard protocol. It is possible that both protocols will be equally efficacious in reducing pain and neither will be superior. This finding is still very important and will help validate the use of weight-based opioids when it is not possible to write an individualized opioid protocol in a particular hospital.

There are several reasons this trial design is unique and complex. Unlike traditional randomized studies where randomization is carried out in study population, we will randomize a larger population than the study population ($n = 460$ vs. 230) to avoid randomization during emergency situations. In our previous pilot study 50% of randomized patients had a study ED VOE visit within the next 12 months [11]. There are several reasons for the need to over-enroll: 1) it is not ethically possible to randomize and consent a patient in the ED during a VOE due to severe pain; 2) individualized or weight based protocols must be written by the patient's hematologist, which requires time; and 3) these protocols must be uploaded into the electronic health record to be used for a future ED VOE study visit, should one occur. Thus, this trial has required close collaboration by site emergency medicine and hematology providers, as well as with each hospital's informatics specialists to allow for protocols to be uploaded and visible to the ED providers.

This study is also unique because of the close attention to the challenge to maintain and maximize blinding of the study protocol. The patient, ED research staff, and ED provider remain blinded to the study protocol. Only the drug name and doses are uploaded into the electronic health record protocol; there is no mention of whether this protocol is patient-specific or weight-based. If the patient has an ED visit and asks what they are receiving, they are told the drug name and dose. Only the hematologists know the treatment arm.

Finally, this study is unique because we will prospectively collect side effect and safety data every 30 minutes directly from the patient. Both protocols may use higher opioid doses than what providers may typically be comfortable with. Previous studies of VOE only measured safety based on retrospective medical record abstraction (REF PT 2015) [15]. Often this data may be incomplete. Our protocol will provide large-scale data on safety and side effects for high dose opioid protocols to treat VOE. If determined safe, as anticipated, this data will also provide more confidence to ED providers ordering higher opioid doses to treat VOE.

Conducting research in an emergency department setting is always challenging. In this RCT, we are using innovative methods (pre-enrollment), information technology in the electronic health record, and close collaboration between multiple specialties than can be used in other disease specific conditions if ED data collection is required.

The study has limitations. Specifically, some ED visits may be missed, however if an ED visit is missed and the patient has a future visit it may be possible to capture data at that subsequent visit. We are carefully monitoring missed visits at all sites and discuss on bi-weekly research calls. All study sites are academic medical centers with strong SCD outpatient programs and teams. However, the use of a systematic way to develop opioid analgesic protocols could be used by any provider, and data from the weight based protocol will also be an alternative.

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Declaration of Competing Interest

Stephanie Ibemere has received postdoctoral fellowship salary support from the NHLBI.

Sarah Dubbs declares no conflict of interest.

Huiman Barnhart declares no conflict of interest.

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Author contributions

All authors have contributed to the conception and design of the COMPARE-VOE study, critical review of the important intellectual content of the article and provided final approval of the version submitted.

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