Study Protocol

A Comparison of Individualized vs. Weight Based Protocols to Treat Vaso-Occlusive Episodes in Sickle Cell Disease

SHORT TITLE: COMPARE VOE

ClinicalTrials.gov Identifier:

NATIONAL, HEART, LUNG AND BLOOD INSTITUTE

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PROTOCOL VERSION AND AMENDMENT TRACKING

Version Number/Amendment	Approval Date
1.0	01/08/2019
2.0	4/30/2019

TABLE OF ABBREVIATIONS

ACS	Acute Chest Syndrome
ACEP	American College of Emergency Physicians
AE	Adverse Event
CCC	Clinical Coordinating Center
CI	Confidence Interval
Co-I	Co-Investigator
CRF	Case Report Form
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EC	Executive Committee
ED	Emergency Department
EDC	Electronic Data Capture
EMR	Electronic Medical Record
GCP	Good Clinical Practices
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Counsel for Harmonisation of Technical Requirements for Pharmaçeuticals for Human Use
ITT	Intent To Treat
IV	Intravenous
IVMSE	Intravenous Morphine Sulfate Equivalents
KG	Kilogram
MG	Milligram
MoP	Manual of Operations
MM	Millimeter
NHLBI	National Heart, Lung and Blood Institute
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
PHQ	Patient Health Questionnaire
PI	Principal Investigator
RA	Research Associate
RCT	Research Clinical Trial
RR	Respiratory Rate

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCD	Sickle Cell Disease
SD	Standard Deviation
SpO2	Peripheral Saturation of Oxygen
TBD	To Be Determined
VOC	Vaso-Occlusive Crisis
VOE	Vaso-Occlusive Episode

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Protocol Changes from Version 1.0 (January 8, 2019) to 2.0 (March 20, 2019)

Section 8.2.2
Changes made on page 17 to **Table 1. Weight-Based Doses for Morphine Sulfate and Hydromorphone to capture a dose for Morphine for participants weighing less than 50Kg and to revise dose of Hydromorphone for participants into 3 categories rather than the original 4**

Sections 13.7 and 13.8

Corrections made on pages 23, 24 and 26 are to clarify that the primary outcome of change in pain scores is not from ED arrival to discharge, but from the time of placement in a treatment area to the time of disposition (hospital admission, discharged home, assigned to observation status) or a maximum treatment duration of 6 hours, whichever comes first.

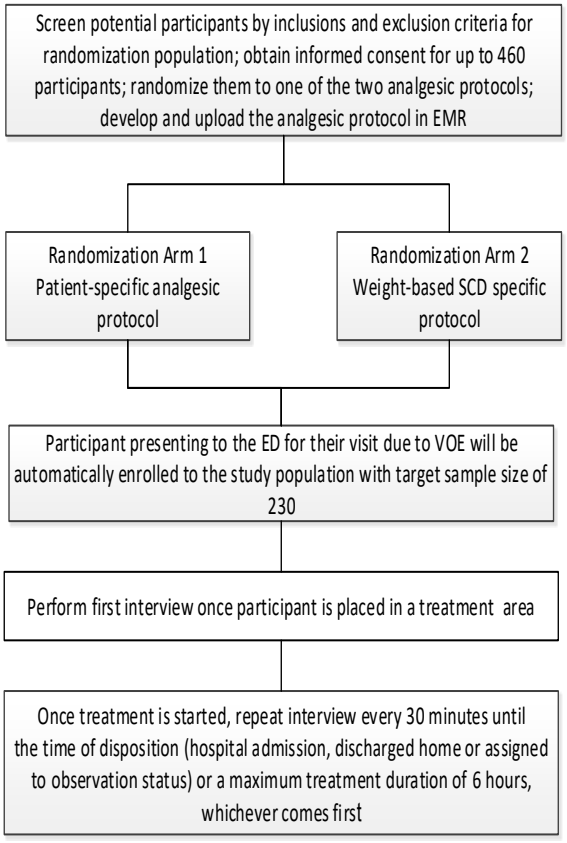
Section 13.9

Correction made on page 26 is to clarify that the secondary outcome of ED length of stay is from ED arrival to discharge.

1. EXECUTIVE SUMMARY

Title:	A Comparison of Individualized vs. Weight Based Protocols To Treat Vaso-Occlusive Episodes in Sickle Cell Disease (COMPARE VOE)
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.
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 with site as the stratification variable. Subjects 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 hours, 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

Study Flow Chart



2. HYPOTHESES AND OBJECTIVES

2.1 Primary Objectives and Hypothesis

The primary objective of the COMPARE-VOE study is to compare change in pain scores in response to two different treatment regimens for treating acute painful VOE in SCD. All patients will be followed for a maximum of 6 hours in the ED, or until time of placement in observation status, discharge or inpatient admission.

Our ***primary hypothesis*** is that that the patient-specific analgesic protocol is superior to the weight-based analgesic protocol. A sample size of 230 subjects with ED visits provides 90% power to detect a 14-mm clinically significant reduction in pain scores between the two groups with 0.05 type I error using a horizontal Visual Analogue Scale 100 mm in length. This assumes the same standard deviation (SD) of 31 mm in pain score reductions in the two groups while accounting for 10% missing data rate.

2.2 Secondary Objectives

The secondary objectives of this study protocol will be the following endpoints:

- ED length of stay
- Hospitalization for pain control
- Return ED visits, hospitalizations or day hospital visits within seven days of the index ED visit

3. BACKGROUND AND RATIONALE

Burden of SCD: Sickle cell disease (SCD) is a genetic disorder and the most common hemoglobin disorder in the United States (U.S.). It affects an estimated 90,000-100,000 Americans and was ranked as the fifth most common principal diagnosis for Medicaid's super-utilizer hospital stays (super-utilizers have 4 or more hospital stays in 1 year) in 2012.[9] SCD affects vulnerable populations, occurring in 1 in 365 African American births and 1 in 16,305 Hispanic American births in the U.S.[10] Although data reported in 2013 cite an improvement in childhood mortality,[11] the median age of death in 2005 was 38 and 42 years for males and females, respectively.[12] These mortality figures are essentially unchanged from data published in the mid-1990s, and result from increased mortality in early adulthood, as youth transition from the pediatric to the adult-oriented health system.[13, 14] Causes of death include stroke, sepsis, acute chest syndrome, and multi-system organ failure.[14] However, painful vaso-occlusive episodes (VOE) are the most common manifestation of SCD experienced by patients and the most common reason for ED visits.[7] Severe VOE has been defined as a new onset of pain (7/10 or greater) for at least four hours for which there is no other explanation than vaso-occlusion, requiring treatment with parenteral opioids or with ketorolac.[1] The cause of VOE relates to abnormal red blood cells. Under conditions of stress and de-oxygenation, red cells change shape and are unable to deliver sufficient oxygen to the tissues. This results in tissue ischemia and debilitating pain. Pain from VOE occurs suddenly, is excruciating and unpredictable.[15] VOE often requires treatment in an ED and patients with an increased frequency of VOE have higher morbidity and mortality rates.[16] It is critical that patients with VOE receive evidence-based, timely pain relief. (Of note, VOE was historically referred to as vaso-occlusive crisis (VOC)).

Current Evidence Base for ED Management of VOE: As demonstrated by the recent national survey of emergency physicians (ACEP survey), treatment of VOE is variable and only 12% of ED physicians reported using the National Heart, Lung and Blood Institute (NHLBI) recommendations to treat VOE.[6] This lack of guideline use may be due in part to the lack of evidence on how to best treat VOE. In one pediatric ED, improvement in pain scores and hospital admission rates were seen over a period of six years after the implementation of pediatric patient-specific analgesic protocols [4]. In a second pediatric ED, the use of a weight-based VOE analgesic protocol and use of intra-nasal fentanyl resulted in improved time to initial and repeat analgesic administration, as well increased number of children being discharged home.[5] While these findings are encouraging, both projects were conducted in pediatric EDs. Our R34 is the only study directly comparing weight-based and patient-specific analgesic protocols for VOE in adult EDs.[21] Patient-specific analgesic protocol development and maintenance is labor intensive; high-level evidence will be required to support widespread dissemination.

Patients Perception of ED Treatment of VOE: Given the lack of both a standard of care, or evidenced-based analgesic protocols to treat VOE, it is not surprising that in the ED, SCD patients often report dissatisfaction with care. 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 experience influenced this decision.[3] However, patients often require treatment in the ED to not only manage pain but also because other serious complications may exist that require immediate evaluation and treatment.[20] ED management of VOE must be evidence-based.

NHBLI Recommendations for ED Management of VOE: NHLBI recognized the need to provide evidence-based recommendations for SCD, including VOE. In September 2014, NHLBI formed an expert panel that published 17 recommendations for treatment of VOE Dr. Tanabe was an invited member of the panel. None of the recommendations supports the current variability in practice. Only one recommendation (use of opioids) was supported by high-level evidence with a strong recommendation.[8] The remaining recommendations do not have supporting high-level evidence. A key recommendation was the use of patient-specific analgesic protocols for pain management. When unavailable, a standard VOE analgesic protocol specific for SCD was recommended. However, NHLBI did not define "standard analgesic protocol". In a 2015 review of the NHLBI recommendations, specific gaps, as well as the need for additional research were identified. The need to conduct research to compare and assess the value of patient-specific and weight-based analgesic protocols for VOE was indicated as a priority research area,[2] which this Phase III RCT aims to address.

***Significance of this Study*:** Sickle cell disease (SCD) is a chronic disease associated with many medical problems, especially the severe pain referred to as vaso-occlusive episodes (VOE) that leads to an emergency department (ED) visit. We do not know the best way to treat painful VOE in the ED. This phase III randomized clinical trial will identify the best analgesic approach for treating adult SCD patients with VOE during an ED visit. It will determine whether the patient-specific analgesic approach is superior to the weight-based analgesic approach in decreasing the severe pain due to VOE. The trial's results will shape the health care paradigm for the thousands of SCD patients suffering from severe pain.

4. BASIC STUDY DESIGN

A multi-site Phase III, single blinded, RCT will be conducted to address the study aims. The trial will be conducted at six U.S. sites, with an enrollment period of 24 months. Approximately 460 patients will be consented and randomized in order to obtain the study population of 230 patients with at least one ED visit.

The modified intent to treat (ITT) population is adult SCD patients with an ED visit due to VOE. The primary outcome will be change in pain scores from the time of placement in a 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. Due to the logistical difficulty in consenting and randomizing patients during an ED visit due to VOE (see Section 7.2), we plan to screen, consent, and randomize patients in a larger population than the target population of adult SCD subjects with ED visits. There is no reason to think the patients randomized are any different from those who eventually do have an ED visit for VOE. The occurrence of VOE is very unpredictable and not related to overall disease severity. Consented adult SCD patients will be randomized to receive analgesic management for VOE via a weight-based SCD analgesic protocol, or via a patient-specific analgesic protocol developed by their hematologist/sickle cell team, which will be used in the patient's future ED visit due to VOE.

Patients will be told what drug and dose they are receiving during their study ED visit, however, they will remain blinded to which analgesic protocol they are randomized. The primary difference between the two analgesic protocols is the starting opioid dose. Other elements of both analgesic protocols reflect the recommendations in the NHLBI expert panel recommendations document, including recommended route and re-dosing intervals. All analgesic protocols, patient-specific and weight-based, will be written by the SCD provider and uploaded to the electronic medical record (EMR) prior to an ED study visit.

5. STUDY POPULATION AND ELIGIBILITY CRITERIA

5.1 Population for Randomization

The population for randomization is adult SCD patients with the following Inclusion and Exclusion criteria.

The selection criteria below were designed to be inclusive and representative of the SCD population, including appropriate representation of women.

5.1.1. Inclusion Criteria

1) ≥ 18 years of age
2) SCD patients with the following genotypes:
    a. Hgb SS, SC and SB+, SB- thalassemia

5.1.2. Exclusion Criteria

1) Patients with sickle cell trait
2) Patients with a treatment protocol that does not allow administration of opioids
3) Patients with an existing ED protocol that includes oral opioids only
4) Patients prescribed buprenorphine-containing medication in the outpatient setting
5) Patients prescribed methadone

5.2 Population for Enrollment

The population for enrollment is randomized patients with the following inclusion and exclusion criteria.

5.2.1. Enrollment Inclusion Criteria:

1) Patient is randomized
2) ED visit for VOE requiring parenteral opioid analgesia

5.2.2. Enrollment Exclusion Criteria

1) 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

6. TREATMENT INTERVENTIONS

6.1. Overview of Treatment Interventions

This will be a single-blinded two-arm randomized clinical trial comparing:

- Patient-specific analgesic protocol to treat VOE in adults with SCD
- Weight-based analgesic protocol to treat VOE in adults with SCD

There is currently no standard approach to managing VOE pain in the ED, resulting in wide variability in ED-based pain management. Patients will be randomized to either a patient-specific analgesic protocol or a weight-based analgesic protocol to treat VOE during an ED visit.

6.2. Blinding

The provider will be un-blinded to the analgesic protocol at the time of the patient visit to the ED.
Patients will be told what drug and dose they are receiving during their study ED visit. However, they will remain blinded to the analgesic protocol to which they are randomized. The research assistant performing the study assessments will also remain blinded to the randomized analgesic treatment protocol until all assessments have been completed.

6.3. Patient Safety and Concomitant Therapies

This study will evaluate and compare analgesic treatment protocols to treat VOE in adult patients with SCD during an ED visit.

7. RECRUITMENT AND SCREENING PROCEDURES

7.1. Common Recruitment/Screening Procedures

Patients meeting eligibility criteria for randomization population will be approached regarding participation in this study. The Site Investigators will train all research staff in screening and approaching patients for participation, consent, and data collection. Patients will be recruited during an outpatient visit at hematology/SCD clinic, during an inpatient hospitalization, or at the end of an ED visit. Patients will consent for participation in the study during a subsequent ED visit for VOE, should one occur during the study

enrollment period. This procedure is very effective because patients can provide a more informed consent when not in severe pain. It would also not be feasible to enroll patients during an actual ED visit because the delay in analgesia associated with consulting the hematologist for the immediate development of the analgesic protocol and placement in the EMR. Community recruitment is also not feasible because we need a local hematologist to write the analgesic protocol and implement it in the hospital's EMR.

Inpatient Hospital Recruitment – The study staff at each site will round daily on the inpatient units to recruit subjects. Patients admitted to the hospital will be approached for possible participation only after obtaining permission to speak with the patient from a member of the clinical care team. If the patient is in too much pain, the study staff will return at a later date/time to discuss possible enrollment.

Hematology/SCD Clinic Recruitment – Study staff at each site will work closely with the clinic providers to determine the least intrusive manner to approach patients for participation and consent during routine clinic visits. All patients meeting study inclusion criteria will be approached for possible participation.

ED Recruitment – Study staff at each site will recruit those ED patients being discharged home who have not previously declined participation or already not been consented for this study. If the patient agrees to participate, they will sign the consent to participate in the study during a subsequent ED visit for VOE.

7.2 Estimated Enrollment Period

This study will randomize approximately 460 patients at approximately six U.S. study sites in order to enroll 230 subjects with an ED visit for VOE in the study population. The projected timeline for enrollment is approximately 24 months.

8. INITIAL STUDY EVALUATIONS AND RANDOMIZATION

A complete schedule of assessments throughout the study is provided in Appendix A.

8.1. Screening for Informed Consent and Patient Randomization

Potential trial patients believed to meet study selection criteria for the randomization population will be approached and willing patients will be consented for trial participation. After providing informed consent and signing the informed consent form (ICF), trial eligibility criteria will be formally confirmed. Patients will be randomized. Patients' characteristics will be collected at the time of randomization. After we have reached the target ED visit sample size in the study population, we will notify the patients remaining in the randomization population by phone, a subsequent clinic visit or by mail that the study enrollment has been completed and their randomized analgesic protocol will be removed from the EMR.

8.2. Randomization and Patient Analgesic Protocols

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. 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 DCC senior statistician with block size randomly chosen 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 DCC data management team. Treatment plans can be updated as needed by the hematologist.

8.2.1 Patient-Specific Analgesic Protocol

If the patient is randomized to the patient-specific analgesic protocol, the outpatient SCD provider will develop a patient-specific analgesic protocol based upon chronic opioid therapy, if relevant, and past successful ED treatment. The procedure for developing patient-specific analgesic protocols is as follows: A member of the outpatient SCD provider team will review the patient's medical record to determine: 1) the patient's maximum home opioid dose, and 2) previous ED analgesic medication(s) and doses that have been effective and safe in the past.

Starting Dose determination:

Step 1: Calculate maximum home opioid dose and determine initial intravenous (IV) / subcutaneous (SC) ED VOE dose. IV and SC doses will be identical.
Maximum home opioid dose is defined as the maximum dose of prescribed opioids typically taken by the patient at home in any 24-hour period. The maximum will be calculated by combining all long acting and short acting opioids taken within a 24-hour period and converting that medication to IV morphine sulfate equivalents (IVMSE). The SCD team member will use the maximum home opioid dose to generate a suggested starting dose of IV opioid for severe VOE pain in the ED as follows: preliminary calculation of IV dose for next ED visit (based on home opioid consumption) = 20% of patient's maximum 24-hour home opioid dose converted to IV morphine and IV hydromorphone.

Step 2: Reconcile with past ED doses.
The first choice of opioid (Morphine or hydromorphone) will be based on review of the patient's medical record for pertinent medical history and which drug has been used in the past with greater success. The preliminary calculations above will then be compared to doses of opioids that have been administered to the patient in the ED in the past. If the ED doses and the calculated preliminary doses are within 10% of each other, the preliminary dose will be finalized for that patient's suggested patient-specific analgesic protocol for use at the next ED visit for VOE. If the discrepancy is greater than 10%, the SCD team member will adjudicate this case with the Pain Management Protocols, Clinical Oversight and Implementation Committee to choose a safe dose in the following manner. Whichever of the two doses (preliminary calculations based on home consumption or prior ED doses) is lower will be chosen as the final suggested dose for use at the next ED visit. The lower dose was chosen because it is perceived to be safer. In addition, dose escalation is

permitted at the SCD provider's discretion. For example, if the highest prior ED dose is less than half of the preliminary calculated dose, the highest prior ED dose would be selected and could be increased by 25% for use in the patient-specific analgesic protocol. However, if the previously used ED dose is less than a weight-based dose, a weight-based dose will be used to avoid use of an unreasonably low dose. Per the NHLBI recommendations for the treatment of VOE, the dose frequency for IV pain medication administration will be set at 20-30 minutes unless the SCD provider feels this is not safe.

8.2.2 Weight-Based Analgesic Protocol

The NHLBI recommendations will be used to develop the weight-based analgesic protocol; there are some similarities to the patient-specific analgesic protocol, namely dosing intervals and routes. The NHLBI recommendations include a starting dose be based on prior analgesic use. This can be difficult for a patient to accurately report at times. ED providers are typically not proficient in calculating and converting oral, or patch, opioid dosing to intravenous doses and are unlikely to do this on a widespread, national basis. Instead, we opted to make one adaptation to the expert panel recommendations for a "standard" VOE protocol; the initial dose will be weight-based. We chose weight-based because there is no current "standard" VOE protocol and weight-based opioid dosing is an acceptable alternative in other pain conditions, including cancer. As recommended by the NHLBI guidelines, the weight-based analgesic protocol will include re-assessment and re-dosing every 20-30 minutes, with one possible dose escalation of 25%. Table 1 provides an example of typical weight-based doses. A 5:1 conversion of morphine sulfate to hydromorphone (7.5 mg:1.5 mg morphine sulfate to hydromorphone) was used to calculate doses for both the weight and patient-specific doses.[30]

Table 1. 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

8.3 Odd Volume Doses for both analgesic **protocols***:* One barrier to analgesic protocol implementation was the odd doses that resulted in the need to administer a volume of drug less than the amount in which it was supplied. This required "wasting" by the ED nurses and verification by a second nurse. We have consulted with a multidisciplinary team consisting of a pain expert, adult hematologist, and an emergency department physician to determine a strategy to select a final dose that will minimize the need for odd doses and wasting procedures (e.g. morphine 4.3 mg, or hydromorphone 1.3 mg). All doses of morphine can be ordered in increments of 2 mg and doses of hydromorphone can be ordered in increments of 0.5 mg. These doses remain consistent with the patient-specific and weight-based doses with rounding to a safe dose, and will significantly reduce the need to waste drug in most cases. We used this information when creating Table 1. Table 2 describes differences between analgesic protocols in agent, dose, route, monitoring, repeat doses and hydration. The primary difference between analgesic protocols is dose and the provision to increase weight-based doses if insufficient pain relief.

Table 2: Comparison of NHLBI Recommendations: Patient specific vs. Weight-based analgesic **Protocol**

	Patient-specific analgesic **protocol**	**Weight-based SCD** 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, if applicable, 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 Q 30 minutes per research protocol / research assistant (sedation level, SpO2, BP, HR, RR).	Per routine standard of care Q 30 minutes per research protocol / research assistant (sedation level, SpO2, BP, HR, RR).
Repeat doses	TBD by SCD provider – Q 20-30 minutes as required to treat unrelieved pain. No maximum dose set.	Q 20-30 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.

Once the patient's analgesic protocol has been developed (patient-specific or weight-based) by the hematologist/sickle cell team, the research team will be notified. The research team will ensure the analgesic protocol is uploaded to the electronic medical record (EMR) within one week of receipt. The analgesic protocol will be available in the EMR for future ED visits.

9. STUDY ENROLLMENT AND COMPLETION AT ED VISIT

When the randomized patient has an ED visit for VOE, this patient is enrolled in the study population. The provider (un-blinded) in the ED will access the patient's randomized analgesic protocol from the EMR for treatment. The patient will only be told what drugs and doses they will receive, but will not be told which analgesic protocol (weight-based or patient-specific) to which they have been randomized, thus the patient is blinded to the randomized arm. Research assistants (RAs), who are also blinded to study arm, will

interview the patient during an ED visit to obtain pain score data for the primary outcome. Only one ED visit per patient is recorded for the primary and secondary outcomes. The study is complete as soon as one post-randomization ED visit is recorded. The patient's randomized analgesic protocol will be removed from the EMR after the study ED visit is recorded. In the event where the ED visit is missed due to no availability of a RA (e.g., in the middle of the night), the next ED visit will be recorded. The RA will periodically review the EMR to obtain information on the missed ED visits for tracking purposes. During the ED visit, the maximum amount of time for study participation is six hours, which begins at placement in an ED treatment area. A brief interview will be conducted every 30 minutes until 1) discharge home, 2) admission 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. Each patient will be allowed to contribute only one ED visit to the study data.

10. FOLLOW-UP DATA COLLECTION.

After the completion of the patient's recorded ED visit, the RA will periodically review the EMR to obtain the number of ED visits and number of hospitalizations within 7 days of the recorded ED visit for collection of secondary outcomes.

11. OUTCOME DETERMINATIONS

1.1 Primary Endpoint

The primary endpoint of the study population is the change in pain scores from the time of placement in a treatment area to the time of disposition (hospital admission, discharged home, assigned to observation status) or a maximum treatment duration of 6 hours, whichever comes first.

1.2 Secondary Endpoints

The secondary outcomes of the study population include the following:

- ED length of stay
- Hospitalization for pain control
- Return ED visits, hospitalizations, or day hospital visits within seven days of the index ED visit

12. PARTICIPANT SAFETY AND ADVERSE EVENTS

12.1 Institutional Review Boards

All sites will submit the study protocol, informed consent form, and other relevant study documents to the Central Institutional Review Board (IRB) for approval.

12.2 Informed Consent

A signed ICF is a requirement for patient inclusion in the study. All patients will have the

purpose of the study, the study interventions and evaluations, and the potential risks and benefits of participation explained to them and their questions answered. If patients consent to participation in this study, they will review and sign the ICF. Study staff at the enrolling site will administer the ICF during hospitalization, a clinic or at the end of an ED visit (for enrollment in future ED visits). At the time of ICF discussion, patients will receive study informational materials and the contact information for the site study staff at the enrolling site.

12.3 Voluntary Withdrawal from the Study

Patients may withdraw at any time during the study without giving reasons and will not suffer disadvantage as a result. In cases of study withdrawal, patient care will continue per the discretion of healthcare providers. Investigators may withdraw patients from the study at any time if upon review the patient meets exclusion criteria.

12.4 Summary of the Risks and Benefits

We do not anticipate that participation in this study will be associated with increased risk beyond that of standard care. Potential side effects for the medications used in the study, such as morphine and hydromorphone, include drowsiness and sedation, nausea, vomiting, light-headedness, and itching. Less common side effects include respiratory depression and lower blood pressure. Both morphine and hydromorphone are currently used in routine clinical practice. The benefit of participation in the study is the generation of an evidence-based treatment analgesic protocol for SCD patients with an ED visit for VOE.

12.5 Collection and Reporting of Adverse Events

An Adverse Event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug related. Only protocol- specific expected AEs occurring during the enrollment ED visit will be collected and reported on the AE eCRF.

12.5.1 Protocol-Specific AEs

The following events are considered expected AEs for this protocol and are reported on the AE eCRF.

- Nausea
- Vomiting
- Pruritis
- 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

AEs are summarized and reported to DSMB in bi-annual meetings.

12.6 Collection and Reporting of Serious Adverse Events

An adverse event is considered a serious adverse event (SAE) if, in the view of the investigator or sponsor, results in any of the following: death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization,* is a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly/birth defect, or an important medical event. Only protocol-specific SAEs will be collected and reported on the SAE eCRF. Specific timing on collection and reporting of SAEs is specified below.

*For this protocol, if the study ED visit resulted in a hospitalization for pain control, this hospitalization will be considered the *index* hospitalization and will not be considered an SAE. Hospitalizations for VOE treatment within 7 days post the ED visits will also not be considered SAEs.

12.6.1 Protocol-Specific SAEs

SAEs are collected from the time of first administration of pain protocol drug during the study ED visit through 7 days post ED visit and reported on the SAE eCRF. The following SAEs are to be considered.

- Respiratory depression requiring naloxone administration given within 2 hours 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.

SAEs occurring during the protocol administration or within 7 days post enrollment ED visit, along with the investigator's assessment of relatedness, will be recorded by the site on the SAE eCRF in the EDC within 24 hours of knowledge of the event. The Data Coordinating Center (DCC) will receive an EDC email notification of SAE data once entry by the site. The DCC will notify the NHLBI within two business days of receipt of the email notification. Once notified, the NHLBI will notify the DSMB.

If patients experience any SAEs during the ED visit, the treatment protocol will be discontinued. Subsequent VOE treatment will be determined by the ED provider.

Assessment of Serious Adverse Event Causal Relationship

The investigator must assess the relationship of any SAE to the use of the drug, based on available information, using the following guidelines:

Not Related: There is not a reasonable causal relationship to the product and the adverse event.

Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

Assessment of Serious Adverse Event Intensity
The determination of serious adverse event intensity rests on medical judgment of a medically qualified investigator. The severity of SAEs will be graded using the following definitions:

- **Mild:** awareness of sign, symptom, or event, but easily tolerated;
- **Moderate:** discomfort enough to cause interference with usual activity and may warrant intervention;
- **Severe:** incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.

12.7 Expedited Reporting
Adverse events that are assessed as serious, drug-related, and are evaluated by the site PI as unexpected, per the current product label, qualify for expedited reporting to the FDA. For the events identified as serious, drug-related, and unexpected, site investigators are required to complete and submit the MedWatch Online Voluntary Reporting Form (3500) at https://www.accessdata.fda.gov/scripts/medwatch/.

12.8 Acute Chest Syndrome
1) Reported Acute Chest Syndrome (ACS) events will be reviewed to verify the diagnosis of ACS by an adjudication committee consisting of study site investigators specializing in hematology and emergency medicine within 15 days of event entry into the Hospitalization eCRF. 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 will be recorded. Committee members will not review events from their site. The adjudication results will be entered into the ACS eCRF by the Clinical Coordinating Center within 5 business days of the completed adjudication.

13. STATISTICAL CONSIDERATIONS
13.6. Overview
Detailed description of the plan for statistical analysis of each endpoint will be detailed in a Statistical Analysis Plan (SAP) that will be prepared after the final study protocol is approved. The SAP will be prepared by the DCC senior statistician under Dr. Barnhart's supervision.

Descriptive statistics will be used to summarize patient socio-demographic and clinical characteristics. The analyses of primary and secondary outcomes as well as the summary description of pain-related side effects and safety will be carried out by the DCC statistical service. Means, standard deviations, medians, 25^{th} and 75^{th} 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. For all analyses, a two-sided p-value ≤ 0.05 will be considered statistically significant. Analyses will be performed using SAS version 9.4 or higher software (SAS Institute, Inc., Cary, NC).

Multiple Comparisons: With the pre-specified primary and secondary analyses, we

recognize that there is a multiplicity of analyses to be performed, which leads to an increased probability that at least one of the comparisons could be "significant" by chance. There are adjustments (e.g., based on the Bonferroni inequality) that can be used to preserve the overall type I error level. To attempt to adjust for the effects of the repeated significance testing that will occur as part of potential interim monitoring (discussed below), plus to adjust for the multiplicity of secondary outcomes, would require that very small significance levels be used for every comparison. Rather than taking this approach we will be conservative in the interpretation of secondary analyses, taking into account the degree of significance, and looking for consistency across outcomes. The actual p-value for each comparison will be reported to aid in the overall interpretation. In addition to the pre-specified primary outcome, we will use pre-specified secondary outcomes and pre-specified subgroups to help avoid over-interpretation and to help guard against and reduce the problems inherent with multiple testing.

13.7. Clinically Significant Difference, Sample Size and Power Justification

Clinically Significant Difference: The primary outcome for this superiority study is the change in pain scores from the time of placement in a treatment area to the time of disposition (hospital admission, discharged home, assigned to observation status) or a maximum treatment duration of 6 hours, whichever comes first between, two possibly effective treatments. The primary outcome will be measured using a 0-100 mm visual analog scale. Since both analgesic protocols may significantly decrease pain, we chose 14 mm as the minimal clinically significant difference between the two analgesic protocols based on 1) the literature supporting an additional 14 mm pain reduction as clinically important relative to the weight-based analgesic protocol in patients with an initial high pain score[17] and 2) data from our R34 trial. Todd et al.[18] first explored the concept of "minimally clinically significant" change in pain using a 0-100 mm visual analog scale (VAS) in the setting of an urban county hospital emergency department with a Level I trauma center. In that investigation, the numeric change on the VAS was compared to the patients' subjective change in pain. The investigators found that a mean change of 13 mm on a VAS was estimated with a patient assessment of a "little less" pain, thus an estimation of clinical significance in pain reduction. In a 2nd ED study[19] of 74 subjects with vaso-occlusive sickle cell crisis, a change of 13.5 mm was estimated as the minimum clinically significant change based on patients describing their pain as "a little better," validating Todd's findings. Both of these studies are based on one treatment group and this clinical minimal change can only be used as clinically significant difference between two groups if the reference group is assumed to have zero change. Because the weight-based analgesic protocol has non-zero pain reduction based on the R34 study, 13 mm is not used for the clinically significant difference between the two analgesic protocols. The IMPROVE trial[20] was designed to compare two patient-controlled analgesia (PCA) dosing strategies in adults and children with SCD and it used 25 mm as the clinically significant difference between the two strategies in their design. Most relevant to our proposed study, Bird and Dickson[17] argued that the clinically significant change for patients with high initial levels of pain, especially with a VAS between 67-100 mm, required a larger improvement in pain scores. Specifically, they reported that patients with "a lot less" pain had a mean (95% CI) VAS pain reduction to be 48 mm (43, 53) if initial VAS core is within 67-100 mm. We expect that the SCD patients with ED visit due to VOE will have a high initial pain score and this was the case in the R34 study where nearly all of the patients in our R34

reported an arrival pain score between 67-100 mm. Thus, it is important that patients must experience a reduction of at least 43 mm from arrival to discharge in order to feel "a lot less" pain. In the R34 study where we restrict data to the 1st ED visit, patients in both analgesic protocols achieved a clinically meaningful change of 13 mm in pain scores from arrival to discharge (Table 3).

Table 3. Primary and Secondary Outcomes Observed from the R34 Study

Outcomes	**Total (N=52)**	**Patient-specific Analgesic Protocol (N=26)**	**Weight-based Analgesic Protocol(N=26)**
Primary outcome: Change in pain scores from arrival to discharge or inpatient admission (maximum elapsed time of 6 hours); n, mean ±SD	n=48, 36±30	n=25, 43 ± 31	n=23, 29 ± 27
Secondary Outcomes:			
Length of the 1st ED visit in minutes, mean ±SD	278±78	302±70	254±79
Hospital admission in the 1st ED visit, %	38.5%	34.6%	42.3%
Returned ED visit within 7 days of the 1st ED visit, %	15.7%	19.2%	12.0%
Hospital admission within 7 days of the 1st ED visit, %	9.8%	11.5%	8.0%

However, to justify the additional workload of patient-specific analgesic protocols it is important to justify how much better improvement in pain scores is achievable and meaningful, especially in the population with high arrival pain score when compared to a weight-based analgesic protocol. The mean VAS pain reduction was 29 mm in the weight-based analgesic protocol in the R34 study. Thus, an additional 14 mm in pain reduction will bring the pain reduction to 43 mm (achieved in the patient-specific group in the R34 study), which is the pain reduction needed (based on the lower bound of 95% CI7) to have "a lot less" pain for patient with an initial high pain score. Therefore, 14-mm difference in pain reduction between the two analgesic protocols is chosen as the meaningful and clinically significant difference for patients experiencing SCD VOE with an initial high pain score.

Sample Size and Power: The primary null hypothesis is the equality of the pain score reduction (from the time of placement in a treatment area to the time of disposition (hospital admission, discharged home, assigned to observation status) or a maximum treatment duration of 6 hours, whichever comes first) between the dosing protocols. A two-sample t-test will be used to test the primary hypothesis. A sample size of 230 subjects with ED visits provides 90% power to detect 14-mm clinically significant difference of pain score reductions between the two groups with 0.05 type I error, with the assumptions of the same standard deviation (SD) of 31 mm in pain score reductions in the two groups while accounting for 10% missing data rate. Assuming that 50% of randomized subjects will have an ED visit during the 24-month enrollment period, we expect to consent and randomize a total of 460 adult SCD patients. We will continue to consent and randomize subjects until we have the targeted 230 subjects with ED visits, even if we need to consent and randomize beyond 460 patients. Table 4 provides sample size and power calculations for various scenarios to support our target sample size of 230 for this

trial.

Table 4. Sample size, power and total enrollment needed

Sample size in study population (modified ITT population)	Missing data rate	SD in pain score reduction	Power	% enrolled with ED visit	Total sample size in pre-randomization population
230	10%	31	90%	50%	460
230	15%	31	88%	50%	460
230	5%	31	91%	50%	460
230	10%	30	92%	50%	460
245	10%	31	92%	75%	460
230	10%	32	88%	50%	460
230	10%	33	85%	50%	460

The previous R34 study indicated that 49% of the subjects had at the ED visit over the 13 months of enrollment. The observed missing data rate in pain score reduction is 8%, due to either missing pain score at arrival or at discharge. No enrolled patient died in the previous R34 study. The overall SD of the pain score reduction from arrival to discharge was 30, with 27 and 31 in the weight-based and patient-specific analgesic protocol groups, respectively. Therefore, our assumptions of 10% missing data rate and a SD=31 in pain score reduction are conservative. With a 24-month enrollment period in this study, nearly double the enrollment time in the R34 study, it is conservative to assume that 50% of the randomized subjects will have a qualifying ED visit within the 24-month enrollment period. Thus, a total target sample size of 230, with 460 randomized subjects, is a reasonable and conservative estimate. As detailed in Table 4, we varied the missing data rate from 5%-10%, the SD of pain score reduction from 30-33, and percent of randomized subjects with an ED visit from 50% to 75%. All scenarios give 85% or higher power to detect a 14-mm clinically significant difference with the target sample size of 230 in the ITT population at 0.05 level. While the R34 study didn't have sufficient power to detect a 14-mm difference, the proposed study will have 90% power to detect this difference if outcome data is similar to the R34 study. Our sample size calculation assumes the pain score reduction follows a normal distribution based on data from the R34 study that indicated that the normality assumption was not violated.

Power calculation for the secondary outcomes are performed for the target sample size of 230 at 0.05 level. We do not expect any missing data in the secondary outcomes, as seen in the R34 study. For the length of ED stay from arrival to discharge, we have 83% power to detect a 30-minute difference in length of ED stay between the two analgesic protocols, assuming SD of 78. In the R34 study restricting to the first ED visit, the mean (SD) length time from arrival to discharge was 278 minutes (SD=78). For the secondary outcome of (yes/no) hospital admission in the 1st ED visit, returned ED visit or hospital admission within 7 days of the 1st ED visit, we use 15% as clinical significant difference. We have 64%, 78% and 94% power to detect a 15% difference in hospitalization rates in the 1st ED visit, in rates of returned ED visits within 7 days, and in rates of hospital admission within 7

days, respectively, with 0.05 type I error. We have assumed that hospitalization rates are 35% and 50%, the 7-day returned ED rates are 30% and 15%, and 7-day hospitalization rates are 20% and 5%, in the patient-specific and weight-based analgesic protocols, respectively. The assumptions on the hospitalization rates and the return ED visit rates are based on the observations in the R34 study.

13.8. Analysis of Primary Endpoint

The statistical comparison of the two randomized arms with respect to the primary outcome is comparing the means of the pain score reductions between the two arms. A comparison between two groups will be performed, adjusting for the initial pain score at ED time of placement in a treatment area, biological variables of SCD genotype, age and gender. This analysis will utilize linear regression with pain score reduction as the dependent variable and treatment indicator with pain score at time of placement in a treatment area as covariates (independent variables). Rejection of the null hypothesis stating that coefficient for the treatment indicator is zero will provide evidence for presence of the treatment effect. This comparison will utilize subjects with available measure of the primary outcome. In addition to the statistical hypothesis testing, 95% confidence intervals descriptively summarizing the difference in outcome between the two arms, as well as outcome in each arm will be computed.

Missing Data: Because the outcome data are collected during an ED visit over a time period up to 6 hours, we don't expect missing data due to any subject deaths during this time or withdrawal from the study. However, the pain score reduction may be missing if the pain score at thebeginning or the end is not recorded (e.g., if patient left without doing the interview prior to discharge or hospital admission). We will make every effort to prevent missing data on pain score at the beginning and document reasons for missing pain score at final disposition (discharge or admission). If more than 5% of randomized patients have the pain score reduction missing, we will use multiple imputations in the primary analysis to mitigate potential bias of the complete case analysis. This analysis is valid under the missing at random (MAR) assumption. First, an imputation model via linear regression will be developed (based on available data) relating the pain score reduction with a collection of covariates including initial pain score, treatment indicator, baseline characteristics, and possible interactions of covariates with treatment. A total of 1000 data sets with imputations of pain score reduction utilizing the imputation model will be generated. Each of such data sets will be analyzed with linear regression (as described above), and the combined results comparing two groups will be reported by taking into account of variability due to multiple imputations.

Sensitivity analysis: Unfortunately, the MAR assumption cannot be verified with the observed data alone and we will consider sensitivity analysis to examine impact of departure from the MAR assumptions on the treatment effect. We will consider the best and worst scenarios where the worst scenario is to impute the pain score reduction to be zero for patient-specific analgesic protocol and observed maximum pain reduction for the weight-based analgesic protocol and the reverse is used for the best scenario.

13.9. Analysis of Secondary Outcomes

Analysis of secondary outcomes will be carried out as follows. For the ED length of stay from ED arrival to discharge, a linear regression analysis similar to the primary outcome will be used to compare the length of stay between the two arms. For the hospital admission rate, chi-square test will be used to compare the admission rates between the two groups. For the count data (e.g., ED re-visits or hospitalizations for VOE within 7 days after the recorded ED visit), it will be first evaluated by collapsing the data into a binary outcome with a cut off at zero and a chi-square test or Fisher exact test (if frequency is below 5 or less) 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.

13.10. Analysis of Exploratory Safety Outcomes:

The frequency with which various side effects, adverse event (AE) or serious adverse events (SAE) occur will be carefully tabulated and descriptively summarized. Statistical comparisons of the randomized arms with respect to these events will use chi-square, Fisher exact or other appropriate two-sample methods depending 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.

13.11. Analysis of Subgroups

If the data provide evidence of an overall difference in outcome between the randomized arms, we will examine whether the effect is similar for all patients, or whether it varies according to the pre-specified subgroups. We will also explore if treatment effect differs by enrolling clinical sites. These analyses will utilize the regression models with main effects and interactions between the randomized groups and pre-specified subgroup variables. We recognize that in our study the power of interaction tests is low, especially for the site by treatment interaction. Hence, in addition to the formal assessment of randomized group by covariate interactions, effects of the treatments will be calculated and displayed (with 95% CI) for the pre-specified subgroups of patients. These descriptive summaries will be carefully interpreted in conjunction with the formal interaction tests. The following variable are used to pre-specify subgroups in the subgroup analyses: gender, age (< 30, ≥ 30 years old), genotypes (Hgb SS, SC, SB+, SB-), route (IV or SC), use (yes/no) of NSAIDS, drug administered, number of repeated doses, and total administrated milligrams of drug. In the R34 study, the IV route was administrated in over 95% of subjects. The subgroup analysis by route will not be carried out if 90% or more subjects receive the IV route.

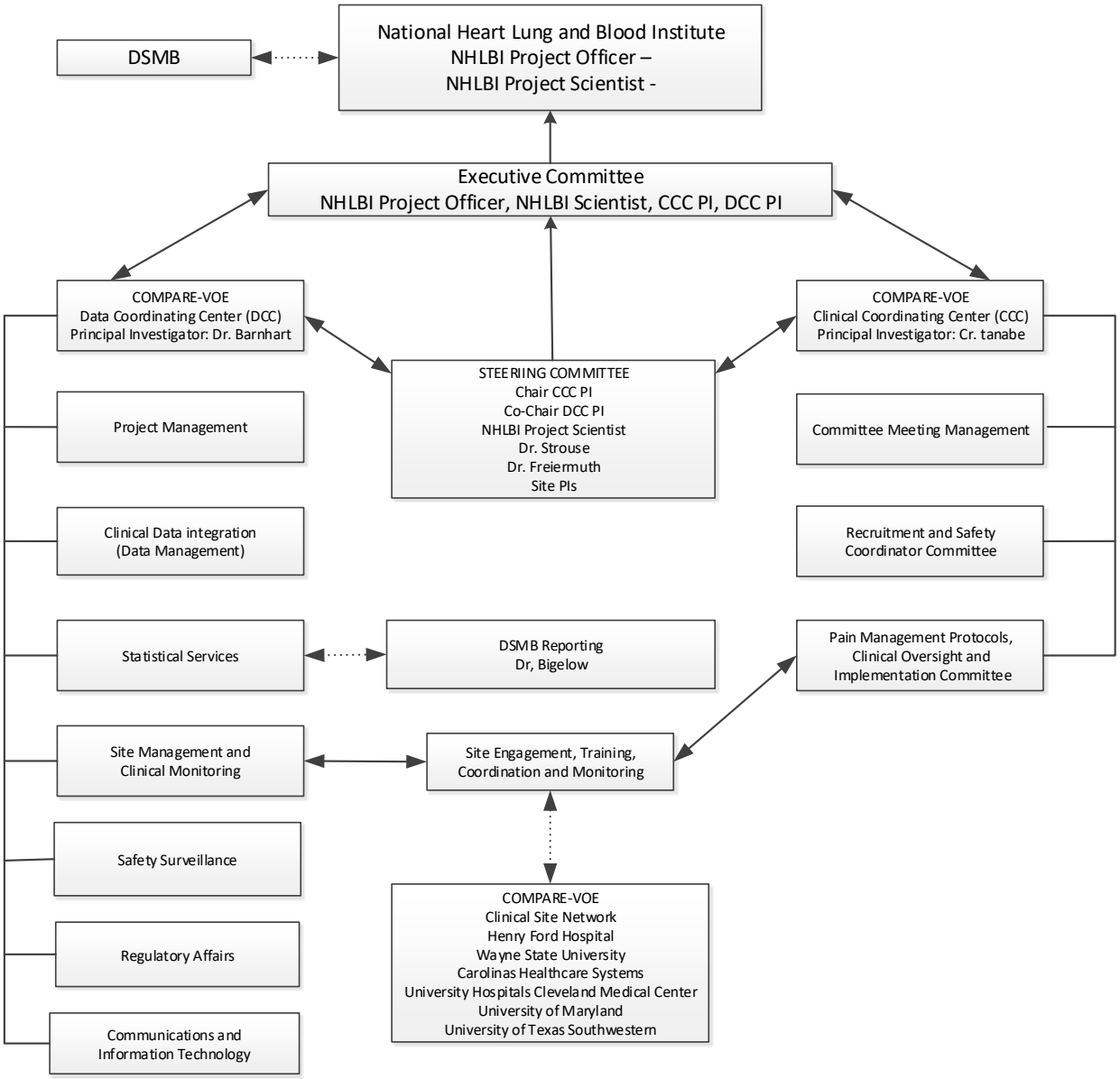
13.12. Analysis of Planned Interim Monitoring

For ethical reasons, an interim examination of key safety data will be performed at regular intervals during the course of the trial. In addition, the interim monitoring will also involve a review of the SD of the primary outcome for a blinded sample size re-estimation; as well as patient recruitment, compliance with the study protocol, status of data collection, and other factors which reflect the overall progress and integrity of the study. The interim results will be carefully and confidentially reviewed by the DSMB. No

efficacy analysis is planned in this trial unless it is requested by the DSMB and after careful discussion with the Executive Committee. Two interim analyses for futility using conditional power approach will be conducted when approximately one-third (N~77 patients with ED visits) and two-thirds (N~154 patients with ED visits) of the total 230 patients in the modified ITT population have completed the ED visits with measurements on the primary outcome. This timeline can be altered based on the input from the DSMB. The goal of the interim analysis is to determine whether to stop the trial early because it is unlikely to show superiority. If the conditional power falls below 10% then the DSMB may consider recommending to stop the trial due to futility. To reduce the likelihood of an underpowered study due to incorrect sample size assumptions, a blinded sample size re-estimation will be conducted at the time of the two planned futility analyses. The sample size re-estimation plan is for the sole purpose of avoiding an underpowered trial due to a higher SD of pain score reduction or higher missing data rate than assumed. It is not for interim testing of a treatment effect. The two interim analyses for futility and the blinded sample size re-estimations will be carried out by the senior statistician under the supervision of Dr. Bigelow. Dr. Bigelow will be blinded to the observed trend of treatment effect and will present the conditional powers under different scenarios of treatment trend for the remaining subjects to the DSMB. Even if the formal futility interim analyses are presented to the DSMB, the DSMB will consider all the relevant issues related to a potential decision to stop the trial and most likely will not base such a decision entirely on the statistical arguments.

14. STUDY ADMINISTRATION

An overview of the organizational structure is presented below in Figure 1.



14.6. Role of NHLBI

The NHLBI project officer will appoint a Project Scientist who will participate actively in study leadership in conjunction with the CCC and DCC PI, and Site Investigators. The project officer will participate in final protocol and site approvals, monitoring study progress, attend and participate in meetings of the Executive Committee, Steering Committee, and DSMB.

14.7. Executive Committee

The executive committee is the decision and policy making body of the study with oversight in the day to day activities and overall direction of COMPARE-VOE. The EC will review and have final sign-off on the study protocol, manual of operations (MoP), risk-based monitoring plan, approval of final study sites, all site materials, data management plan and statistical analysis plan (SAS). On issues regarding a vote, one vote per member will be allowed. The committee will meet at least once per year in person at the annual NHLBI Sickle Cell Disease research meetings in August or as designated by NHLBI. The committee will be composed of the chair of the COMPARE-VOE Steering Committee, the NHLBI Project Scientist/ Program Official/Scientific Advisor and the principal investigator of the DCC. This group will convene bi-weekly by teleconference alternating with the Steering Committee calls.

14.8. Steering Committee

The Steering Committee will include the CCC and DCC PIs, a SCD hematologist, an ED physician, the six study site Co-I's, as well as the NHLBI Project Scientist/Program Official/Scientific Advisor. Dr. Tanabe (CCC PI) will serve as the Chair, and Dr. Barnhart as Co-Chair. The Steering Committee will assume overall responsibility for all aspects of COMPARE-VOE, including the design and conduct of the studies, quality control, data analysis, and publications. Other supporting committee's from the CCC will report to the SC. The SC will meet monthly and will occur by webinar. The COMPARE-VOE SC will meet face-to-face at a scheduled time during the yearly investigator meetings held annually at Duke; this meeting will not conflict with other agenda items. The steering committee will provide clinical oversight and review side effect data on a monthly basis. The SC will develop a publication plan including specific papers, journals, and authorship criteria. Each member has one vote on the COMPARE-VOE Steering Committee and decisions will be determined by a majority vote.

14.9. Recruitment and Study Coordination Committee

The role of this committee is to monitor recruitment and study site data collection. Specifically, this group will report and discuss recruitment progress and challenges, as well as progress and challenges with data collection during ED visits. This committee consists of all study site project coordinators, study monitors and project coordinator at the CCC. The site coordinators have enormous responsibility for the smooth operation of the project. Each site investigator will be asked to lead this committee for 6-9 months throughout the length of the project. The committee will bring any operational issues to the Steering Committee and implement decisions by the Steering Committee. They will begin meeting in year 1 approximately 3 months before enrollment begins and will meet at least monthly. Either Dr. Tanabe or Barnhart will also attend these meetings.

14.10. Pain Management Protocols, Clinical Oversight and Implementation Committee

The purpose of this committee is to 1) finalize the pain management protocol, 2) develop the pain management protocol training for site hematologists and ED physicians and nurses and 3) provide clinical oversight during implementation. The committee will meet bi-monthly until the study protocol is finalized and monthly thereafter. A designated ED nurse (see LOS) at each site will participate in these meetings and lead the training of the

nursing staff at each site. The committee will bring any operational issues to the Steering Committee and implement decisions by the Steering Committee.

14.11. DSMB

A DSMB will be appointed by the NHLBI in collaboration with Drs. Tanabe and Barnhart for the COMPARE-VOE trial. The DSMB will be to monitor patient safety and review the performance of the study. The DSMB will be responsible for providing recommendations regarding trial's conduct and guidance to ensure the safety and well-being of participating patients. The composition of the DSMB will be specified in the overall DSMB Charter for the study.

14.12. Committee Meeting Management

The Project Coordinator for the CCC will be responsible to schedule, coordinate, record, and distribute agendas and minutes from all meetings including the Executive Committee, Steering Committee, Recruitment and Study Coordination, and Pain Management Protocols and Oversight Committees. Responsibility will include identification of optimal meeting times and a web-based meeting platform including a conference call number and ability to view and share a computer screen. For in-person meetings the Project Coordinator will find the venue, reserve meeting rooms and audio-visual equipment, develop and circulate agendas, and distribute and archive meeting minutes

15. ETHICS AND GOOD CLINICAL PRACTICE

This study must be carried out in compliance with the study protocol. These procedures are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

ICH Harmonized Tripartite Guidelines for Good Clinical Practice (ICH E6) 1996.
US 21 Code of Federal Regulations Title 45 Part 46 Protection of Human Subjects dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

Participating investigators agree to adhere to the instructions and procedures described in the study protocol. This study protocol was designed to conform to principles of Good Clinical Practice and investigators agree to adhere to these principles.

18. APPENDICES

18.1 Appendix A. 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 minutes (+/- 15 minutes). Assessments missed due to participant clinical care requirements will not be considered deviations.

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