Statistical Analysis Plan

A Comparison of Individualized vs. Weight-Based Protocols to Treat

Vaso-Occlusive Episodes in Sickle Cell Disease

SHORT TITLE: COMPARE VOE

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PROTOCOL SYNOPSIS

Title:	A Comparison of Individualized vs. Weight Based Protocols To Treat Vaso-Occlusive Episodes (VOE) in Sickle Cell Disease (SCD)
Short Title	COMPARE-VOE
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 Regimen	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.
Blinding	The provider is unblinded in the ED. The patient and research assistants are blinded to study arm.
Objectives:	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.
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, if not admitted to hospital on ED visits • Re-hospitalizations, if admitted to hospital on ED visit and was discharged – we ignore those still hospitalized within 7 days of the index ED visits • Day hospital visits, regardless admitted to hospital on ED visits or not • A composite of return ED revisits or hospital re-admissions or day hospital visits (binary outcome with a cutoff at zero)

Location:	6 clinical sites (Emergency Departments (ED)) in the United States
Duration of Treatment	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.
Duration of Study Overall	The study duration is from the time of placement in a treatment area to Day 7 Post ED Visit. The study enrollment is expected to be 24 months.

ABBREVIATIONS

ACS	Acute Chest Syndrome
ACEP	American College of Emergency Physicians
AE	Adverse Event
CCC	Clinical Coordinating Center
CRF	Case Report Form
DCC	Data Coordinating Center
ED	Emergency Department
EDC	Electronic Data Capture
EMR	Electronic Medical Record
ITT	Intent To Treat
KG	Kilogram
NHLBI	National Heart, Lung and Blood Institute
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCD	Sickle Cell Disease
SD	Standard Deviation
SpO2	Peripheral Saturation of Oxygen
VOE	Vaso-Occlusive Episode

Part I

Introduction

1. INTRODUCTION

This document is the statistical analysis plan (SAP) describing data summaries and analyses for the final report of this study, a comparison of individualized vs. weight-based protocols to treat vaso-occlusive episodes in sickle cell disease. Production of data summaries and analyses described in this SAP will be the responsibility of the Data Coordinating Center (DCC).

The reader of this Statistical Analysis Plan is encouraged to refer to the study protocol for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a patient in this study. This Statistical Analysis Plan is intended to provide guidance to the generation and presentation of the final statistical report.

2. OVERVIEW OF TRIAL DESIGN

This section summarizes the basic trial design, treatment arms, blinding, planned sample size, and randomization scheme.

2.1. Basic Study Design

A multi-site Phase III, single blinded, randomized clinicial trial 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 (from Section 4 of the protocol). The modified intent to treat (ITT) population is adult SCD patients with an ED visit due to VOE.

2.2. Treatment Arms

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. (section 6 of the protocol)

2.3. Blinding

The patient hematologist will be un-blinded to the analgesic protocol and will write the treatment plan based on the randomized assigned analgesic protocol to be uploaded in uploaded to the electronic medical record (EMR). However, the emergency physician will be 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. (section 6)

2.4. Planned Sample Size

A sample size of 230 subjects with ED visits provides 90% power to detect a 14-mm clinically significant reduction in pain scores for the patient-specific analgesic protocol versus the weight-based analgesic protocol with a 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. (section 13)

2.5. Randomization

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. (section 8)

3. OVERVIEW OF ELIGIBILITY AND PROCEDURES

This section summarizes eligibility criteria, study procedures, dosing regimen and visit schedule. (section 5)

3.1. Eligibility Criteria

The population eligible for randomization consists of adult SCD patients meeting 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.

3.1.1. Inclusion Criteria

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

3.1.2. 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

The enrolled population will consist of eligible patients meeting the following criteria.

3.1.3. Enrollment Inclusion Criteria:

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

3.1.4. Enrollment Exclusion Criteria

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

3.2. Study Procedures / Blinding

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 and 7-day post ED data are extracted from medical records. 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. (section 9 of the protocol)

3.3. Schedule of Assessment (section 18)

	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**

4. ENDPOINTS

4.1. Primary Endpoint and Hypothesis

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.

The Primary Hypothesis of the study population is that the patient-specific analgesic protocol is superior to the weight-based analgesic protocol. (section 11 of the protocol). The sample size of 230 subjects with ED visits provides 90% power to detect 14-mm clinically significant assumptions of the same standard deviations (SD) of 31 mm in pain score reductions in the two groups while accounting for 10% missing data rate.

Method of the Final Analysis will be linear regression used to test the primary hypothesis with pain score reduction (0-100mm) as the dependent variable and treatment indicator with pain score at arrival, biological variables of SCD genotype, age and gender as covariates (independent variables). The primary analysis for hypothesis-testing will be done on the observed data without imputation and without regard to the proportion of missing cases. Summaries of the p-value, 95% confidence intervals and the difference in outcome between the two arms, as well as outcome in each arm will also be computed and presented in tabular and graphic format.

Details will be presented later (section 7 of the SAP).

Missing Data and Sensitivity Analyses of the Primary Endpoint: If more than 5% of randomized patients have the pain score reduction missing, we will use multiple imputations in a **sensitivity analysis**, which would be considered supportive if it gave results consistent in direction and magnitude with the primary analysis. Highly inconsistent results would require further review of how and why the data were missing and suggest concerns with study conduct. 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. In **another potential sensitivity analysis**, we will also 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. (section 13.8. of the protocol)

If fewer than 5% of patients have a missing arrival or discharge pain score evaluation, we will perform the primary analysis on the patients without missing data. Two sensitivity analyses will be done:

1.) Worst case, assuming missing discharge pain scores are 0 in the weight-based arm and 100 in the patient-specific arm. Missing arrival scores will be assigned the mean of the study population arrival scores.
2.) LOCF – imputing missing discharge scores as the last score recorded on the Q 30-minute assessment prior to discharge. Missing arrival scores will be assumed to take the value of the first score recorded on the Q 30-minute assessment. {Although LOCF is in general not a recommended technique, it could be informative in this situation.} The missingness would be due to lack of assessment resulting from one of the four reasons below, each of which could be informed by the most recent pain score.
    i. The patient is discharged home
    ii. The patient is admitted to the hospital
    iii. The patient is assigned to observation status for continued pain management
    iv. The patient has received 6 hours of treatment

The best approach to missing data is to obtain complete data collection. Age, gender, and SCD type should be available for all patients. SCD type should be one of: Hgb SS, SC, or SB+, SB0 thalassemia. .

The trial will be closely monitored for missing time of bed placement or missing discharge, or 6 hours, pain scores. The first occurrence of missingness within a center will require explanation from the center and a plan to avoid missing data in subsequent patients.

For patients with dosing deviations, we plan to include them in the primary intent-to-treat analysis and collect all study measurements as planned.

Subgroup Analysis of the Primary Endpoint

We will examine whether the finding for the primary endpoint is similar for all patients, or whether it varies according to the following pre-specified subgroups. These will be assessed via interaction terms between treatment and subgroup categories tested at nominal 0.10 level.

1) Clinical site
2) Gender
3) Age (< 30, ≥ 30 years old)
4) Genotypes (Hgb SS + SB0 and SC + SB+)
5) Route (IV or SC) - this will not be carried out if 90% or more subjects receive the IV route.
6) Use (yes/no) of NSAIDS
7) Drug administered
8) Number of repeated doses

9) Total administered milligrams of drug

These analyses will utilize the regression models with main effects and interactions between the randomized groups and pre-specified subgroup variables.

Details of presentation of results are illustrated in section 7.

4.2. Secondary Endpoints

The secondary endpoints are as follows:

- ED length of stay
- Hospitalization for pain control
- Return ED visits
- Hospitalizations, if not admitted to hospital on ED visits
- Re-hospitalizations, if admitted to hospital on ED visit and was discharged – we ignore those still hospitalized within 7 days of the index ED visits
- Day hospital visits, regardless admitted to hospital on ED visits or not
- A composite of return ED revisits or hospital re-admissions or day hospital visits (binary outcome with a cutoff at zero)

Methods of the final analyses: For the ED length of stay (from ED admission 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 or re-hospitalizations, or day hospital visits 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. (section 13.9.)

4.3. Exploratory Analysis of 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.

5. OVERVIEW OF REPORT

This final report will be prepared by the Data Coordinating Center (DCC) and be used for the publication of study results.

The final report will summarize data and provide results of endpoints by treatment arm. All the calculations for the interim analyses will also be incorporated into the final analysis. These results will be intended for use by the Sponsor and other parties involved in the conduct of the study at the discretion of the Sponsor.

5.1. Purpose of Report

The primary purpose of the final report is to summarize selected baseline characteristics, adverse events, laboratory assessments, other safety measures, and results of study endpoints based on the final data. The final report will be based on modified intent-to-treat population only, and will include screening and baseline information on such subjects.

5.2. Report Production

SAS version 9.4 or later will be used to perform the analyses and create the graphics and tables for the report.

5.3. Abbreviated Report Outline

This report contains the following sections and chapters:

• Introduction
• Main Material
– Patient Accountability
– Baseline Characteristics
– Assessments at the ED Visit
– Adverse and Serious Adverse Events
– Study Endpoints
• Supporting Material
This section will provide the same content as in the Main Materials, but in a tabular format with more numeric details.

5.4. Source of Data Included in Report

Study data will be collected through a customized web-based electronic data capture (EDC) system. The system that will be used is the Merge Healthcare's eClinical OS (eCOS), which has features that enable 21 CFR Part 11 compliance. eCOS is a flexible system for capturing, managing and reporting clinical research data in Phase I–IV studies. Randomization activities will also be conducted within the eCOS system at the DCRI.

6. REPORT STRUCTURE

6.1. Treatment Labels

Tables and figures will be grouped by treatment arms and total.

6.2. P-values

Except for the primary, secondary endpoints and safety outcomes for which we pre-specified methods to use in section 4, *P*-values, where applicable, for continuous or ordered categorical data are computed using the nonparametric Kruskal-Wallis test. This test is appropriate for data with non-normal distributions and has power near that of the Student's *t*-test when the data are normal. Pearson's chi-square or Fisher exact is used for dichotomous (e.g., gender) and unordered (e.g., race) categorical data. The log-rank test is used to obtain *p*-values for time-to-event endpoints. Cox modeling will be used for time-to-event outcomes if there are covariates, such as the initial pain score at ED arrival, biological variables of SCD genotype, age and gender.

6.3. Graphical Conventions

6.3.1. Bar Charts

Bar charts indicate for categorical data the number or percent of subjects by category. They are used to display a single categorical variable with mutually exclusive categories. Bar charts of related dichotomous variables are sometimes grouped together to form a multiple bar chart. A more detailed bar chart is used to display categorical data which has additional ordered subdivisions, as in the display of lab tests.

6.3.2. Box Plots

Boxplots indicate the distribution of continuous data based on percentiles (for example, the display for age and change from baseline). The top and bottom edges of the box represent the 25th and 75th percentiles of the data. The 5th and 95th percentiles are represented by the "whiskers" extending from the top and bottom of the box. The plotting symbol inside the box represents the median of the data.

Change from baseline. For variables which are measured at several fixed time points, change from baseline is usually provided for the observed data. For continuous variables, change can be given either in the original units or as percent change. For dichotomous variables, change from baseline can be indicated by displaying follow-up data separately for each baseline group.

6.3.3. Scatter Plots

For correlations of two continuous variables, scatter plots are used.

6.3.4. Annotations

Figures indicate the number of subjects used for the analysis, under the corresponding portion of the plot. *P*-values corresponding to the comparisons of the treatment groups are included, where applicable. Figures are also annotated with the data source.

7. NOTES ON ANALYSES

This section of the report *Introduction* contains additional details about analysis conventions and the contents of specific chapters.

7.1. General Conventions

The study population: The ITT population will consist of all patients randomized. The modified ITT population will consist of randomized adult SCD patients with an ED visit due to VOE. Summary of baseline characteristics and analysis of the primary endpoint will be done using the modified ITT population. The safety population will consist of all patients in the modified ITT population for whom the AE CRF is completed. Summaries of AE and SAE will be done using the safety population.
Treatment A and B will be replaced with actual treatment names after the database lock and study's unblinding**. Baseline records** are defined as those before the time of placement in treatment area of ED. **Denominators** will be the number of non-missing values of the variable in the analysis.

7.2. Patient Accountability

This section will describe patient accountability, overall and by treatment. Bar charts will be used for the presentation.

7.3. Baseline Characteristics

This report displays treatment group comparisons for baseline variables including medical history and socio-demographic information. Bar charts for categorical variables and boxplots for continuous variables will be used for the presentation of baseline characteristics.

7.4. Assessments at the ED Visit

This section will include a scatterplot of pain assessment results at the ED Visit from ED bed placement to reach time point of every 30 minute over time, overall and by treatment. It will also include bar charts per question over time, regarding pain relief, change in pain, and pain medicine. Bar charts in the same format will be displayed for nausea, vomiting, and pruritus, including results at ED bed placement. Box plots of blood pressure, heart rate, SpO2, sedation score, and respiration rate will also be presented, including results at ED bed placement.

7.5. Dosing

We will present the percentage of agreement between the initial dose assigned and administered dose in a table format.

We will describe overall analgesic dosing by calculating descriptive statistics for the cumulative morphine equivalent dose delivered (total mg, total mg/hr, total mg/kg, and mg/kg/hr), where hr is the number of hours from ED arrival to discharge.

Adjustments of analgesic dose and regimen subsequent to the initial dose are determined by the SCD provider's current observation of the patient. As the CRF does not capture all of the information available to the SCD provider, post hoc analysis of adherence to the dose adjustment plan from study data is challenging.

7.6. Safety Outcomes

This section contains bar chart displays of protocol-specific expected adverse event (AE) data, such as nausea, vomiting, puritis, SPO2 < 95% requiring supplemental oxygen via nasal cannula due to opiod therapy, moderate to severe sedation, drowsiness, respiratory depression not requiring intubation, and low blood pressure.

This section also contains bar chart displays of the incidence of protocol-specific serious adverse events (SAE), including respiratory depression requiring naloxone administration given within the 2 hours of last administration of pain protocol drug, any event resulting in death, any event that is considered a life-threatening complication, any event requiring admission to the intensive care unit (ICU), any event requiring intubation, and hospitalizations with the primary reasons.

7.7. Study Endpoints

7.7.1. Primary Endpoint

As defined in the protocol, the primary endpoint is "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." Comparison of mean changes in pain scores and the difference between treatment arms will be done using linear regression, adjusting for the initial pain score at ED arrival, biological variables of SCD genotype, age and gender. Comparison of unadjusted means will also be done using a t-test. P-value, 95% confidence intervals and the mean difference will be displayed in tabular format. The predicted values will be displayed in a scatter plot by treatment.

Descriptive statistics such as n, mean, standard deviation (SD), median, 25^{th} and 75^{th} percentiles will be also presented for the primary endpoint.

For subgroup analysis of the primary endpoint, in addition to the formal assessment of randomized group by covariate interactions as described in section 4, effects of the treatments will be calculated and displayed (with 95% CI and p-values) for the pre-specified subgroups of patients in both tabular and graphic format. These descriptive summaries will be carefully interpreted in conjunction with the formal interaction tests.

Please refer to section 4 for methods of analysis.

7.7.2. Secondary Endpoints

P-value and descriptive statistics such as n, mean, standard deviation (SD), median, 25th and 75th percentiles and boxplots of summary statistics will be presented for ED length of stay.

P-values, frequencies and percentages by treatment arm will be displayed for hospitalizations for pain control and counts of the return ED visits, hospitalizations, re-hospitalizations, or day hospital visits within seven days of the index ED visit (recorded ED visit). Return ED visits, hospitalizations, re-hospitalizations, or day hospital visits will also be evaluated by collapsing the data into a binary outcome with a cut off at zero after the index ED visit. Bar charts will be used to compare the hospital admission or ED re-admission rates between the two groups. For each patient, the hospitalization rate in the 7-day period following discharge from the ED will be categorized as 0, 1, or 2+. Hospitalization for patients who proceed directly from ED discharge to the hospital will be counted as the first admission/ readmission.

7.8. Supporting Materials

Part III, *Supporting Material*, contains back-up tables of univariate statistics and detailed frequency counts for the graphical displays of the previous chapters. These tables are cross-referenced to and from the corresponding graphical pages.

Part II

Main Material

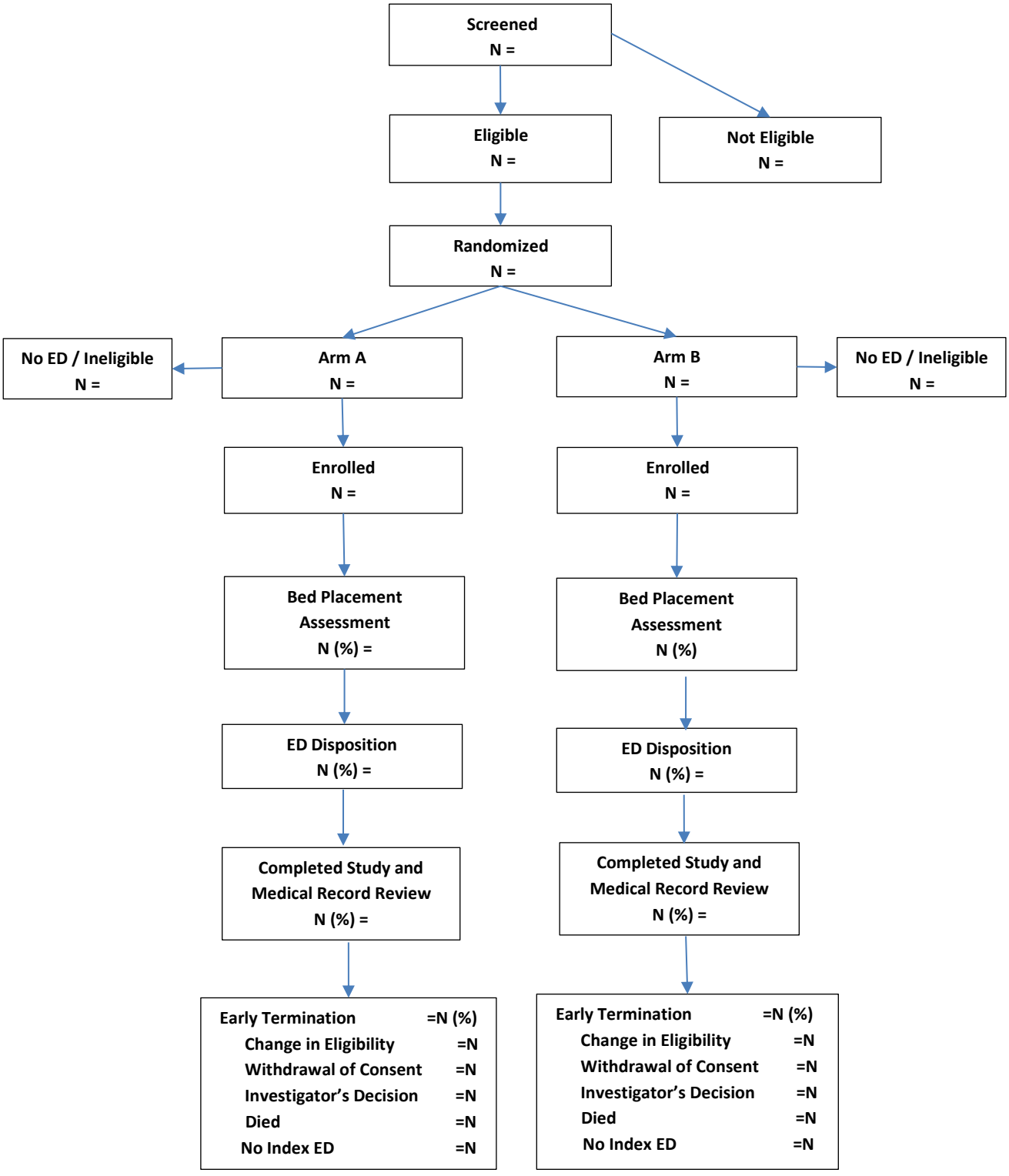
(supporting tables with numeric details are presented in Appendix A.2)

Chapter 1

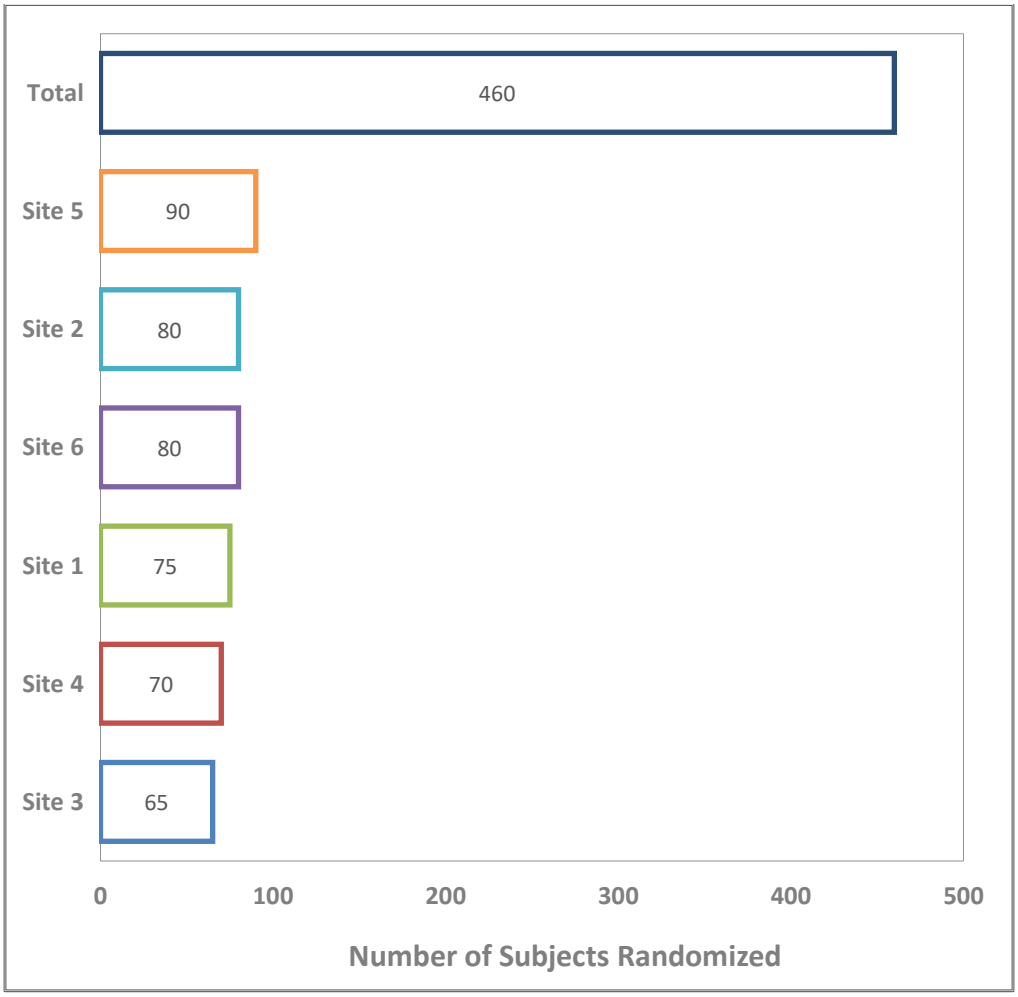
Patient Accountability

8. PATIENT ACCOUNTABILITY

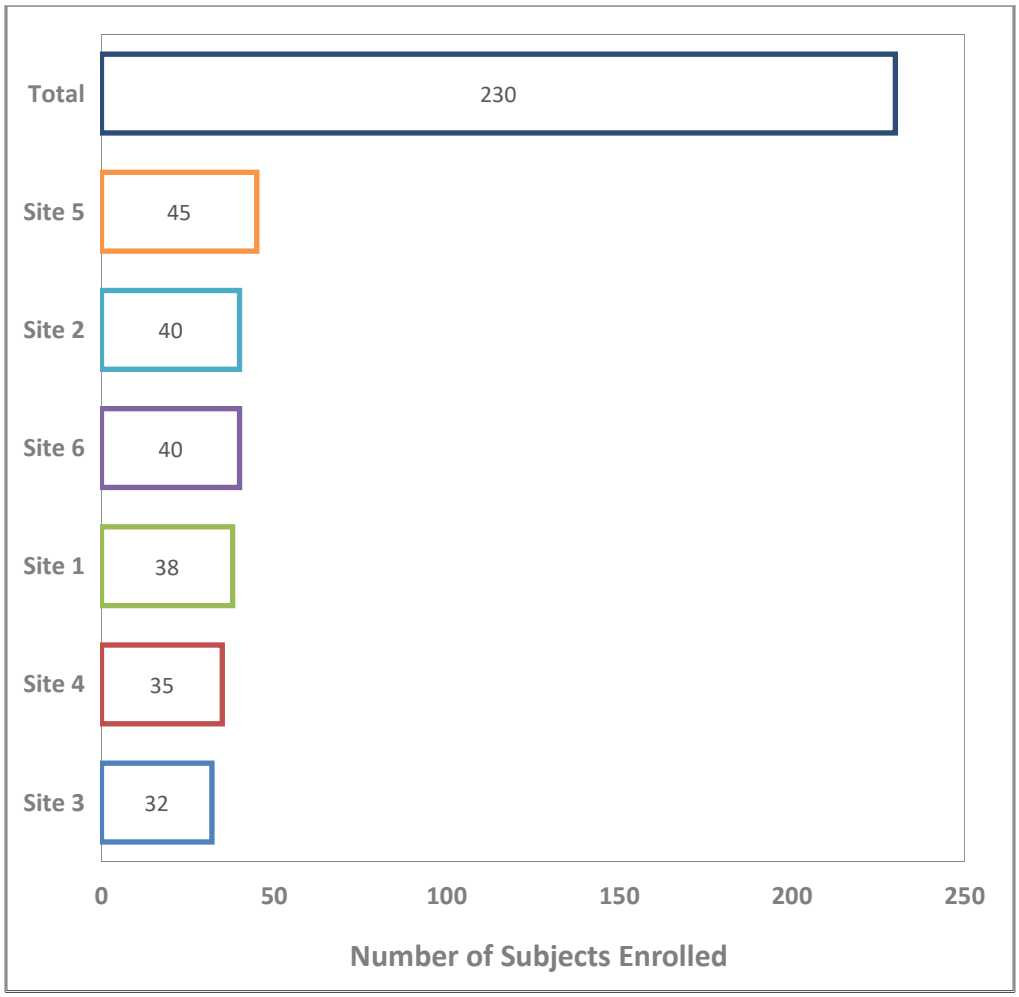
8.1. Patient Accountability



8.2. Number of Subjects Randomized by Site



8.3. Number of Subjects Enrolled by Site

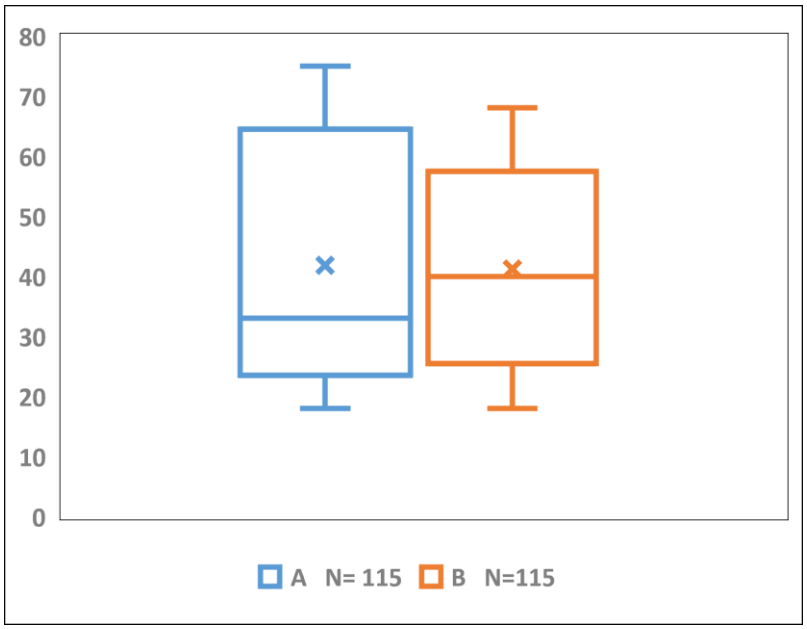


Chapter 2

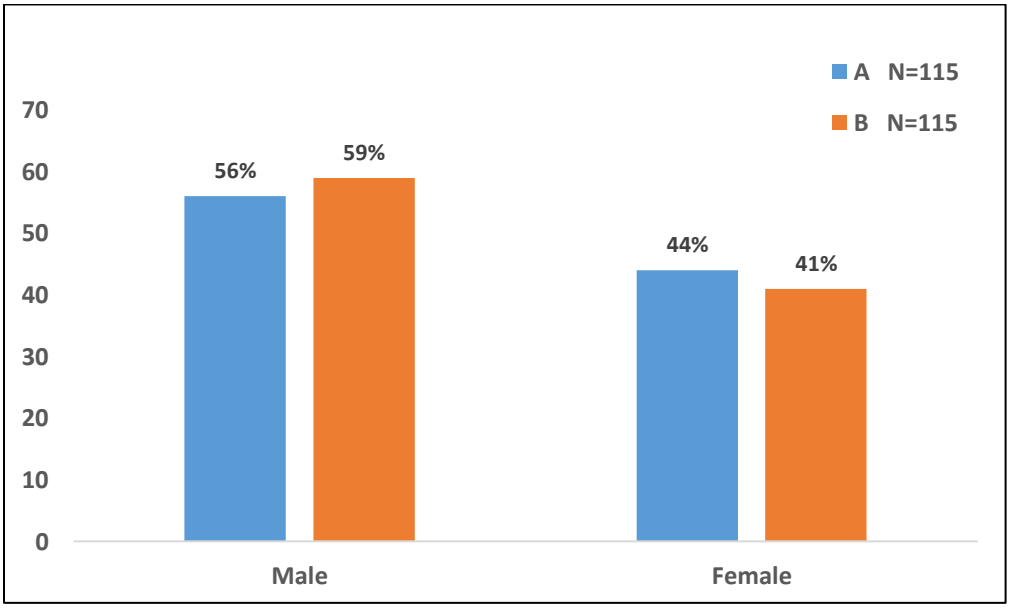
Baseline Characteristics

9. BASELINE CHARACTERISTICS

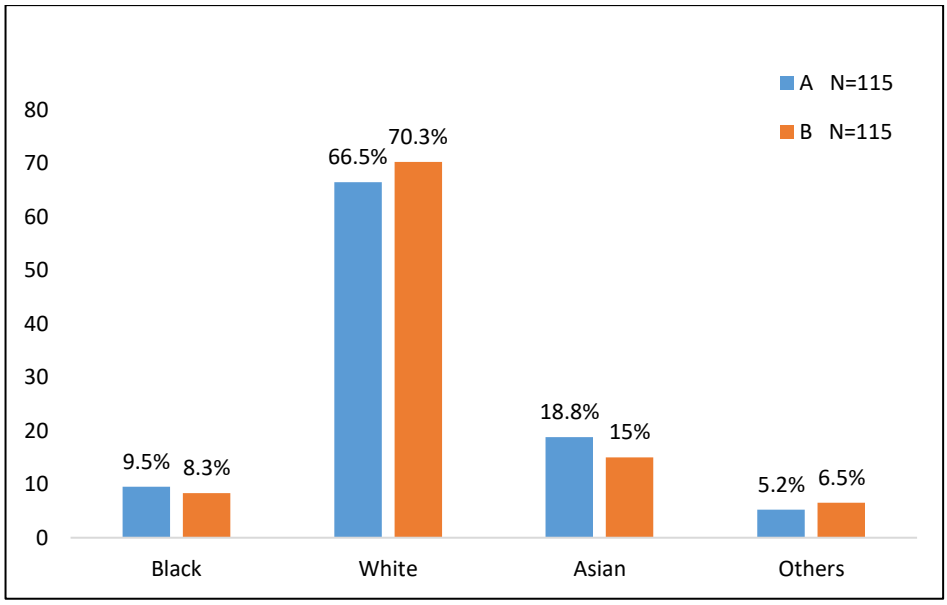
9.1. Age by Treatment



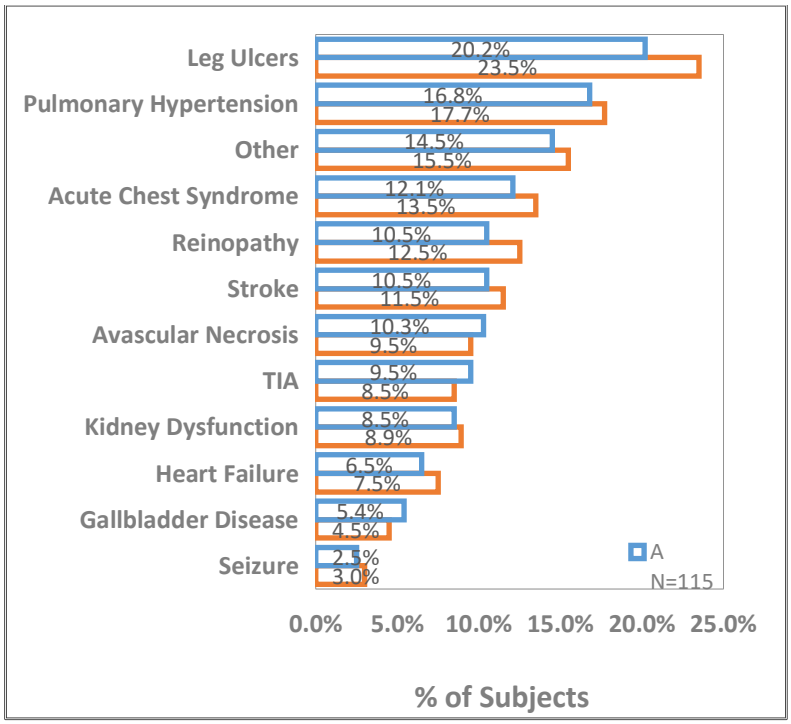
9.2. Gender by Treatment



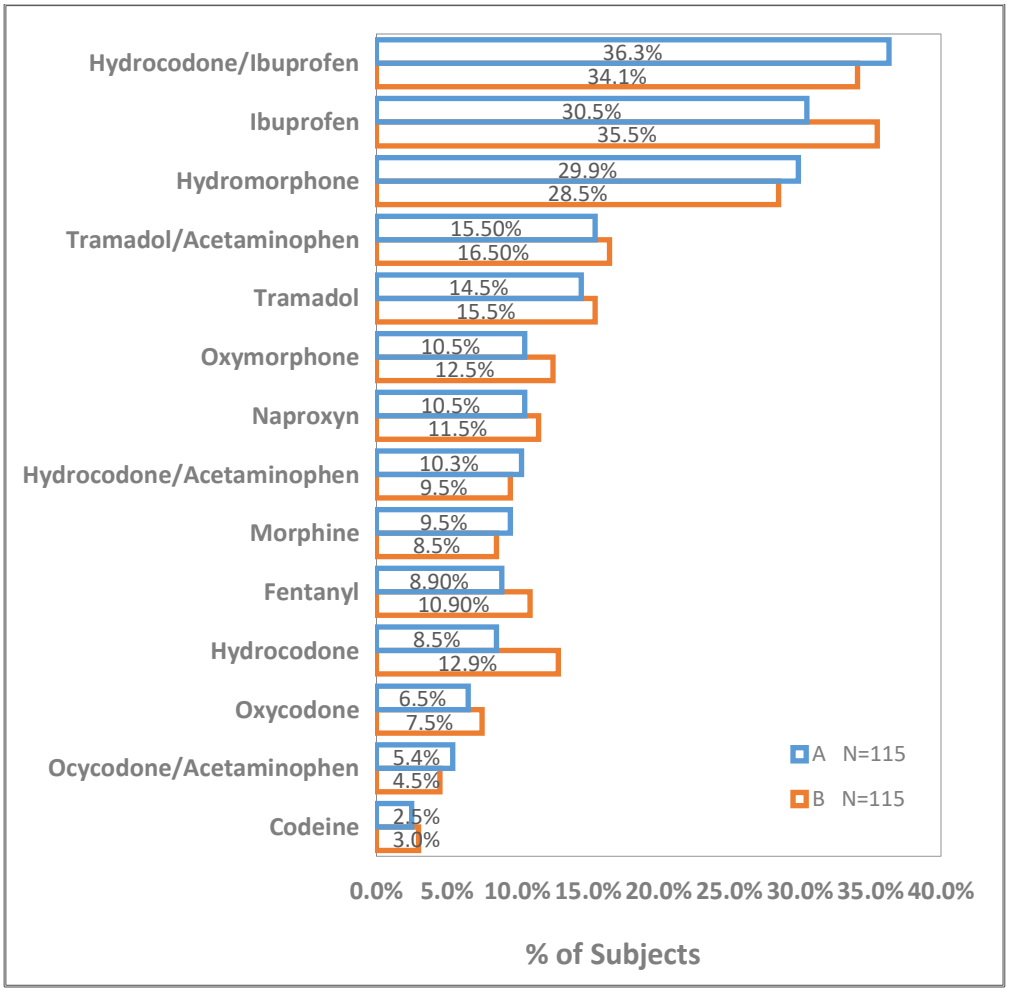
9.3. Race by Treatment



9.4. Medical History by Treatment



9.5. Prior History of Pain Medications by Treatment



Chapter 3

Assessments at the ED Visit

10. ASSESSMENTS

10.1. Pain Score Over Time - Every 30 minute
(Figure to be created as example below)

10.2. Blood Pressure Over Time - Every 30 minute
(Figure to be created as example below)

10.3. Heart Rate Over Time - Every 30 Minute
(Figure to be created as example below)

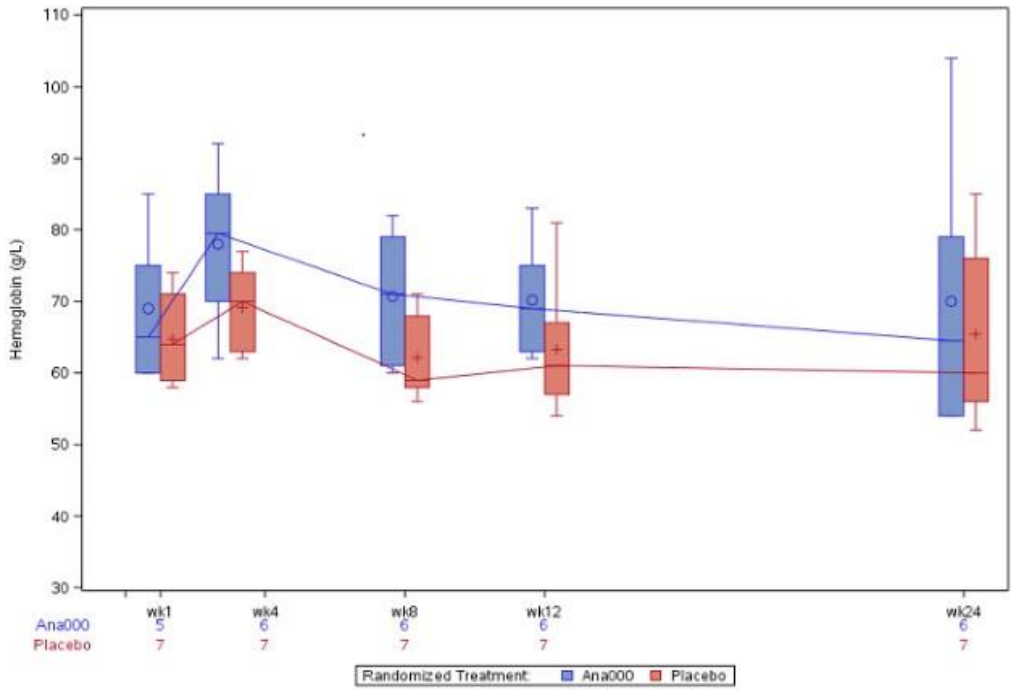
10.4. SpO2 Over Time - Every 30 Minute
(Figure to be created as example below)

10.5. Sedation Score Over Time - Every 30 Minute
(Figure to be created as example below)

10.6. Respiration Rate Over Time - Every 30 Minute
(Figure to be created as example below)

Example

(Note: this is only an example/template for our study. It does not indicate the time range or numbers from our study)

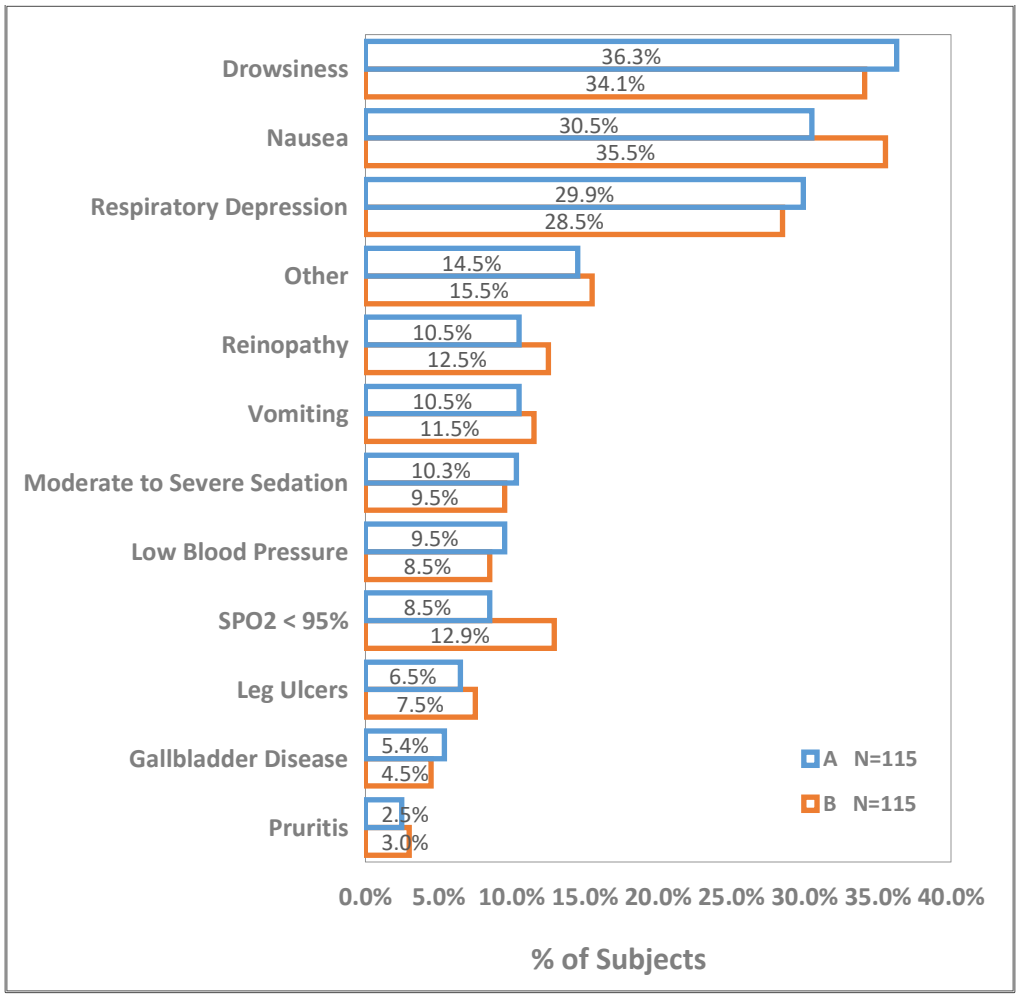


Chapter 4

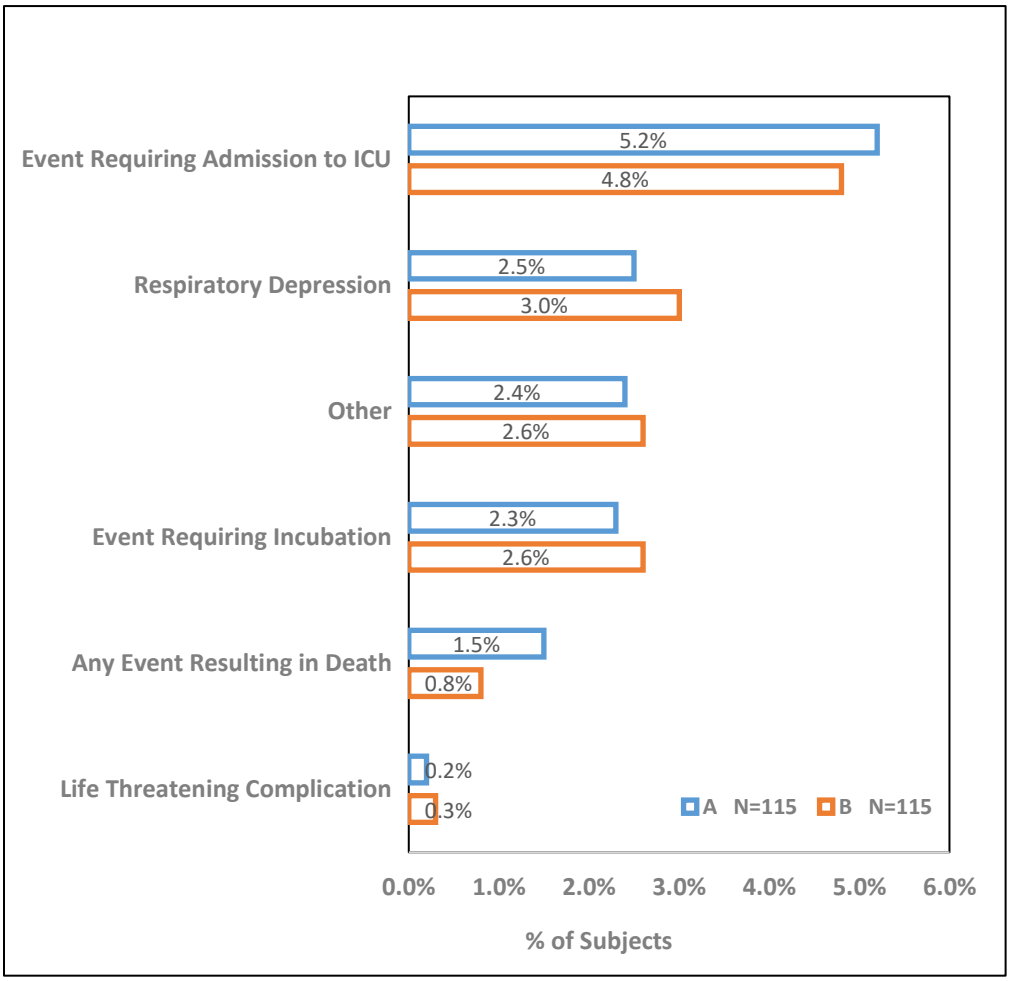
Adverse and Serious Adverse Events

11. Adverse and Serious Adverse Events

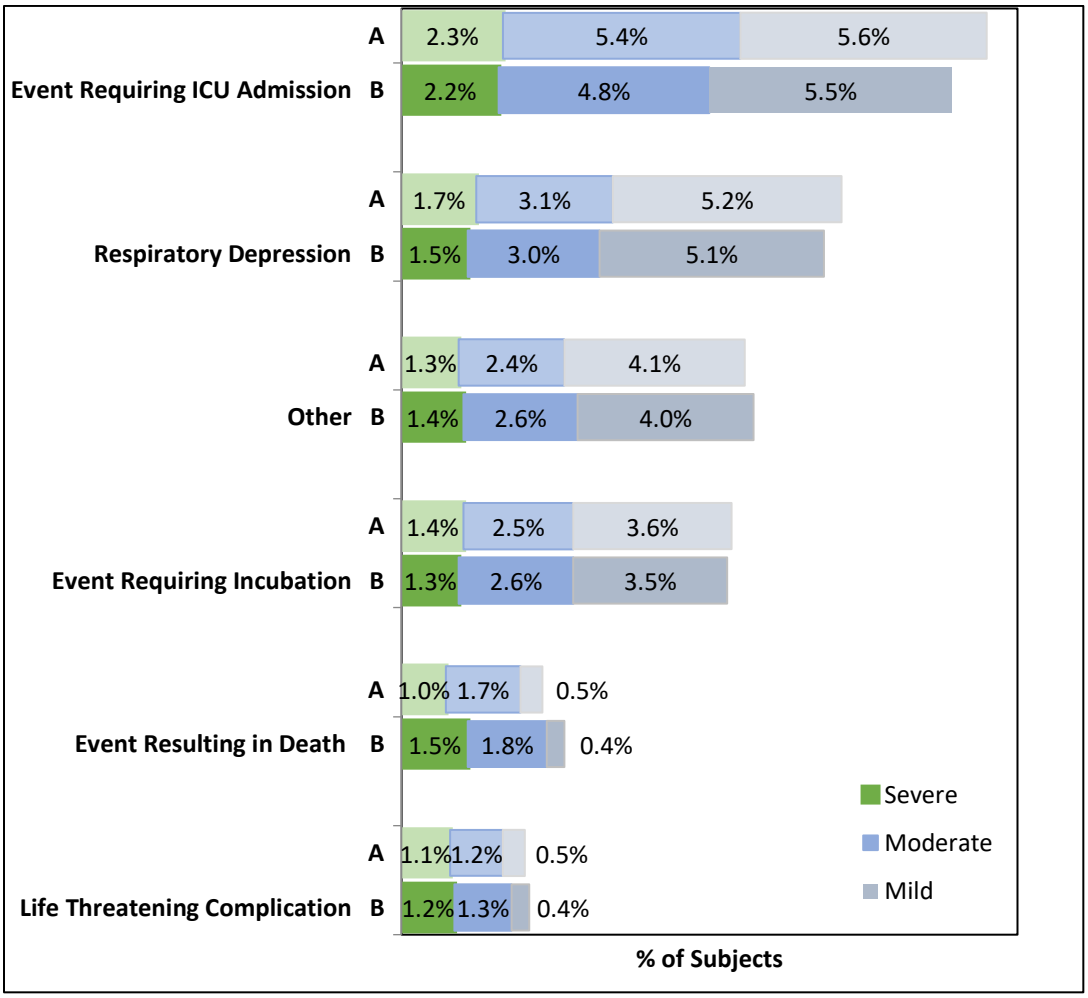
11.1. Protocol-Specific Expected Adverse Events



11.2. Protocol-Specific Expected Serious Adverse Events



11.3. Severity of Expected Serious Adverse Events



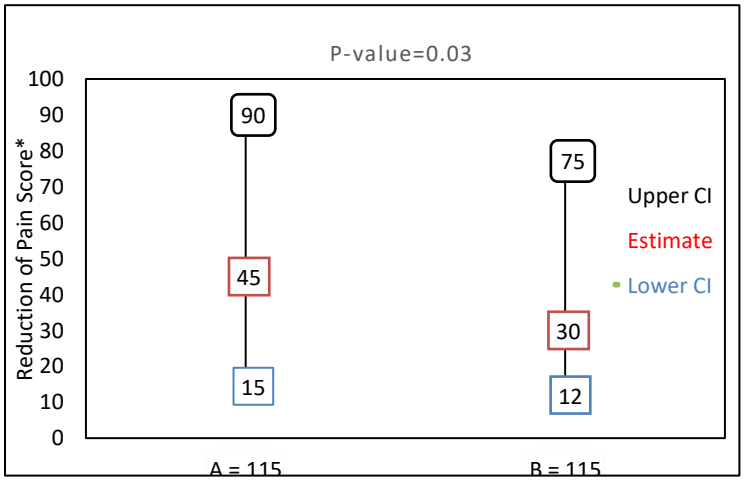
Chapter 5

Study Endpoints

12. ENDPOINTS

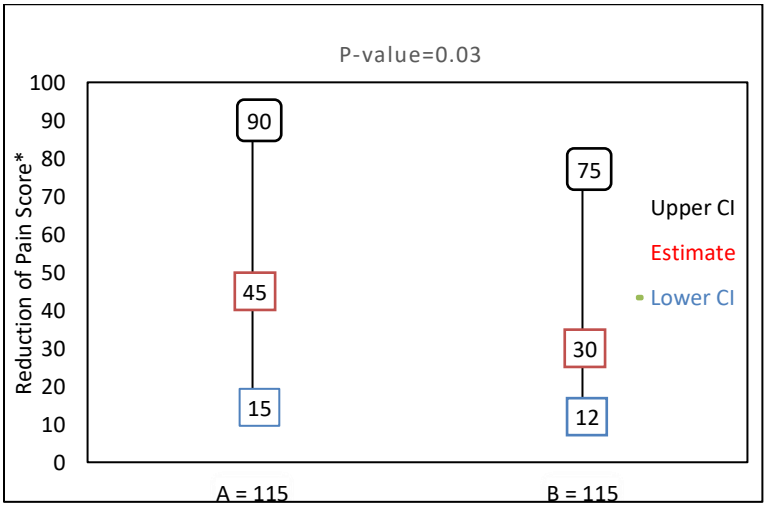
(Note: Additional numbers and details will be presented in Part III in tabular format)

12.1. Primary Endpoint - Reduction of Pain Score by Treatment – Adjusted



Note: In this figure, reduction of pain score is calculated as pain score at time of placement in treatment area minus pain score at time of disposition

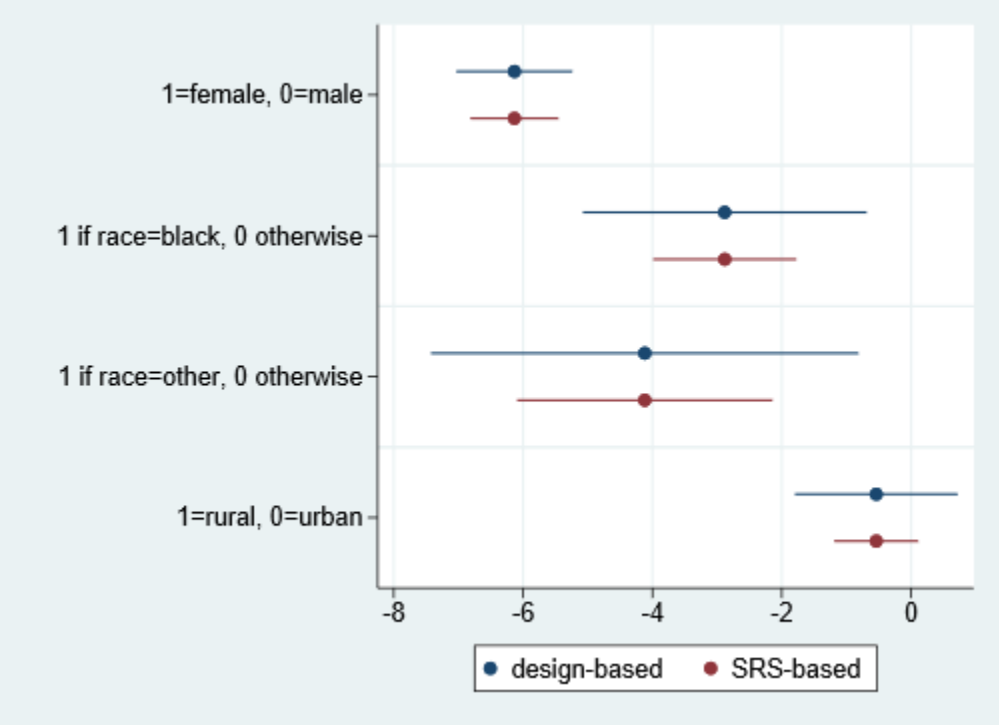
12.2. Primary Endpoint - Reduction of Pain Score by Treatment – Unadjusted



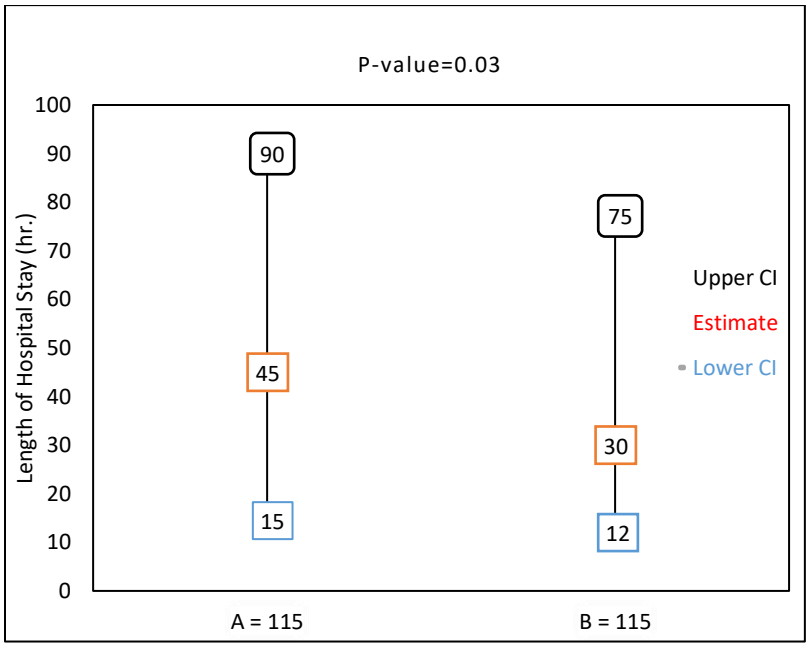
Note: In this figure, reduction of pain score is calculated as pain score at time of placement in treatment area minus pain score at time of disposition

12.3. Subgroup Analyses of the Primary Endpoint

(Note: this is only an example/template for our study. It does not indicate the time range or numbers from our study)

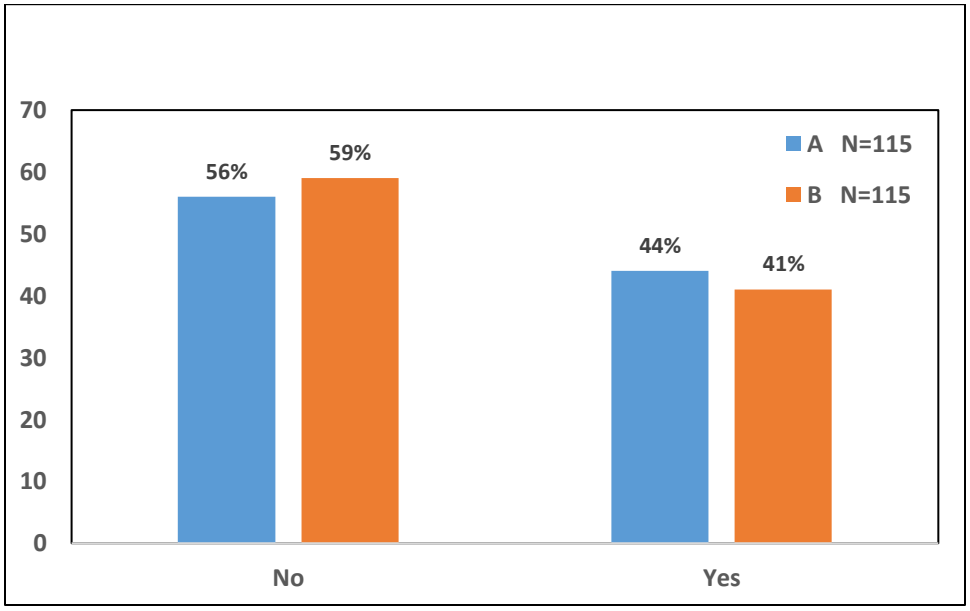


12.4. Secondary Endpoint – Length of Index ED Stay (hr.) – Descriptive

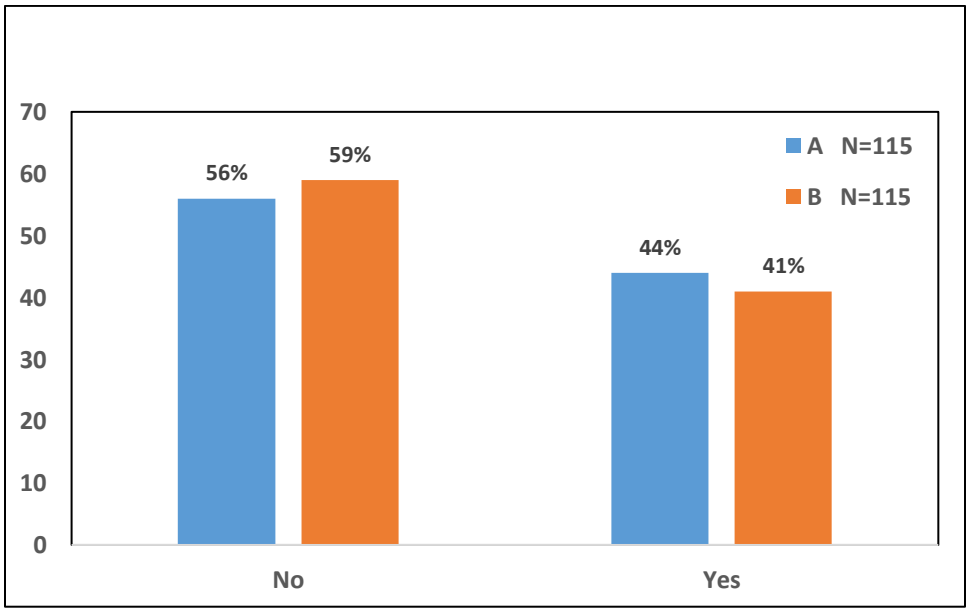


Note: length of ED stay refers to the period from ED admission to the end of ED visit.

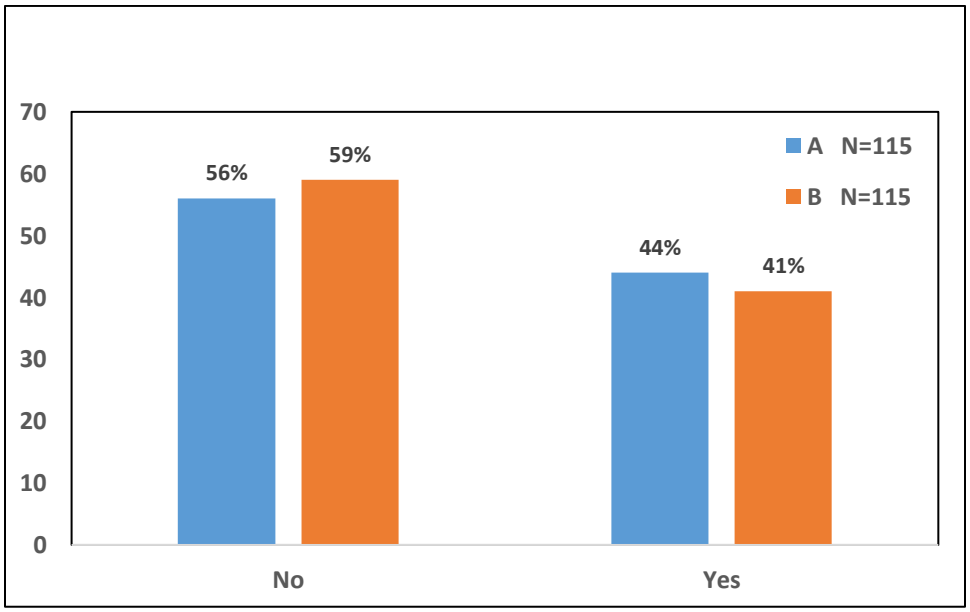
12.5. Hospitalization for Pain Control – Descriptive



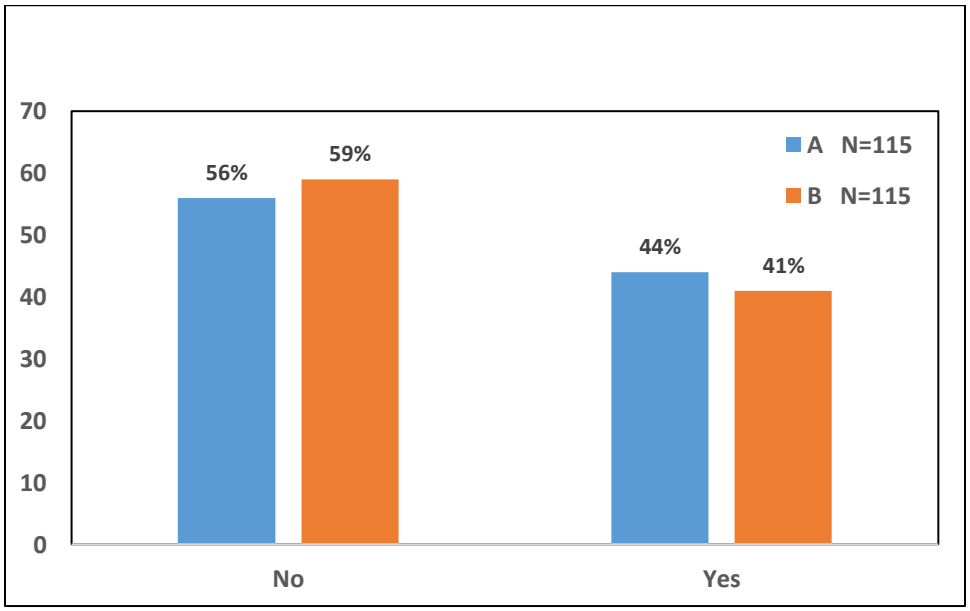
12.6. Return ED Revisits



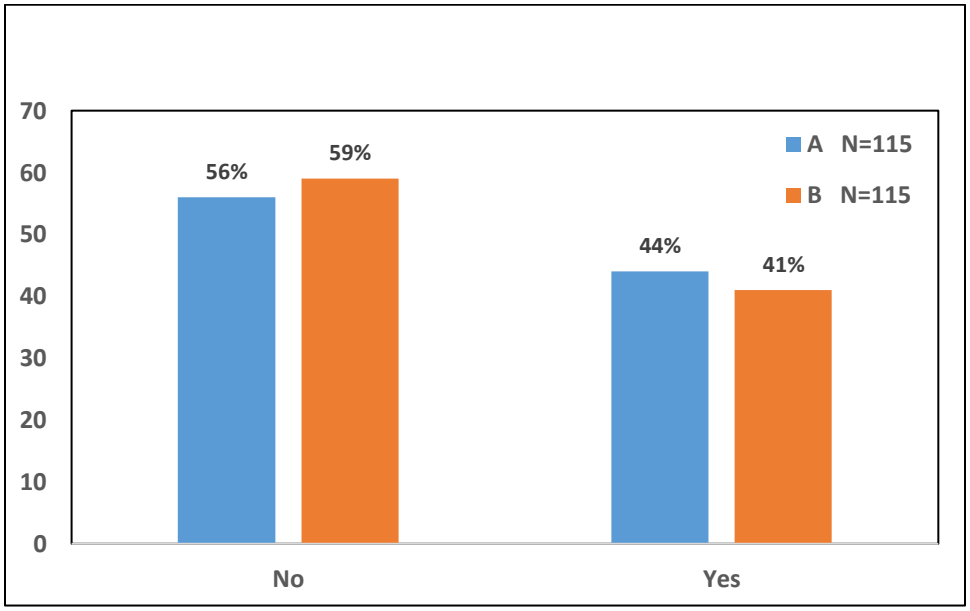
12.7. Hospitalizations (if not admitted to hospital on Index ED visit)



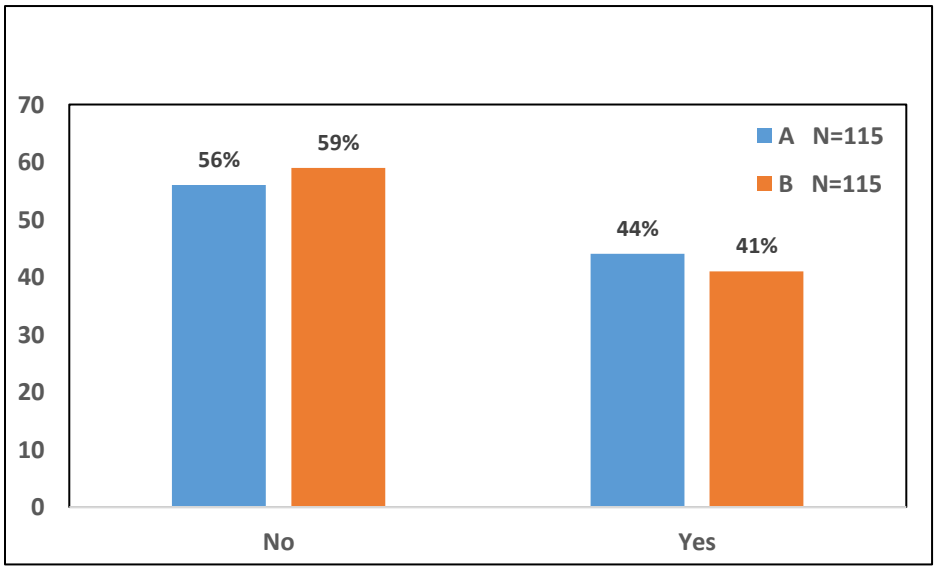
12.8. Re-hospitalizations (if admitted to hospital on Index ED visit, but discharged)



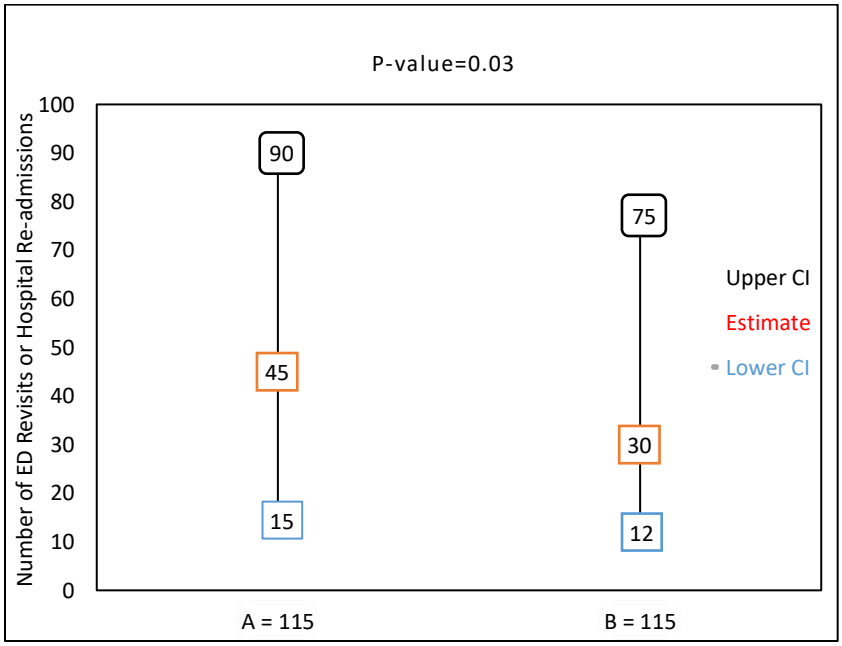
12.9. Day Hospital Visits



12.10. ED Revisits or Hospital Re-admissions or Day Hospital Visits Within 7 Days After Index ED visit (Binary Outcome with A Cutoff at Zero)



12.11. Number of ED Revisits or Hospital Re-admissions or Day Hospital Visits Within 7 Days After Index ED visit



Appendix A. 2

Supporting Materials

13. BASELINE CHARACTERISTICS (TABLES)

13.1. Baseline Characteristics and Medical History

	Treatment A N=	Treatment B N=	Total N=
Age			
Genotypes **SS + SB-** **SC + SB+**			
Gender **Male** **Female** **Refused** **Don't Know**			
Ethnicity **Hispanic** **Not-Hispanic or Latino** **Refused** **Don't know**			
Race			
African American/Black			
American Indian/Alaskan Native			
Asian			
Caucasian/White			
Native Hawaiian/Pacific Islander			
More than One			
Other			
Refused			
Don't Know			
Weight (kg)			
Acute chest syndrome			

Stroke			
Seizure			
TIA (transient ischemic attack)			
Avascular necrosis of the hips or shoulders			
Pulmonary hypertension			
Heart Failure			
Kidney dysfunction			
Liver dysfunction			
Retinopathy			
Leg ulcers			
Gallbladder disease			
Other			
NSAID **Each Day:** **Ibuprofen** **Naproxyn** **Day with Severe Pain:** **Ibuprofen** **Naproxyn**			

13.2. Prior History of Pain Medications by Treatment

	Treatment A N=	Treatment B N=	Total N=
Codeine			
Hydrocodone			
Hydrocodone/ acetaminophen**			
Hydrocodone / ibuprofen**			
Hydromorphone			
Morphine			
Oxymorphone			
Oxycodone			
Oxycodone/ acetaminophen**			
Tramadol			
Tramadol / acetaminophen**			
Fentanyl* (mcg)			
Other (specify)			

14. ADVERSE AND SERIOUS ADVERSE EVENTS (TABLES)

14.1. Adverse Events

	Treatment A N=	Treatment B N=	Total N=	P-value
Nausea				
Vomiting				
Pruritis				
SPO2 < 95% requiring supplemental oxygen *via nasal cannula* due to opioi therapy				
Moderate to Severe Sedation (*Sedation Score of* ≥ 3)				
Drowsiness				
Respiratory Depression not requiring intubation				
Low Blood Pressure (SBP< 90mmHg and/or DBP < 50 mmHg)				

14.2. Serious Adverse Events

	Treatment A N=	Treatment B N=	Total N=	P-value
Respiratory depression requiring naloxone administration given within the 2 hours of last administration of pain protocol drug **Mild** **Moderate** **Severe** **Total**				
Any event resulting in death **Mild** **Moderate** **Severe** **Total**				
Any event that is considered a life-threatening complication **Mild** **Moderate** **Severe** **Total**				
Any event requiring admission to the Intensive Care Unit (ICU) **Mild** **Moderate** **Severe** **Total**				
Any event requiring intubation **Mild** **Moderate** **Severe** **Total**				

15. HOSPITALIZATION (TABLE)

15.1. Hospitalization

	Treatment A N=	Treatment B N=	Total N=	P-value
Hospitalization				
Acute Chest Syndrome				
Unresolved Pain				
Other				
Admitted for ACS				

16. ASSESSMENTS AT ED VISIT (TABLE)

16.1. Assessments

	Treatment A N=	Treatment B N=	Total N=
Pain Score **30 min** **60 min** **90 min** **120 min** **150 min** **180 min** **210 min** **240 min** **270 min** **300 min** **330 min** **360 min**			
Blood Pressure (SBP) **30 min** **60 min** **90 min** **120 min** **150 min** **180 min** **210 min** **240 min** **270 min** **300 min** **330 min** **360 min**			
Blood Pressure (DBP) **30 min** **60 min** **90 min** **120 min** **150 min** **180 min** **210 min** **240 min** **270 min**			

300 min **330 min** **360 min**			
Heart Rate (RR) **30 min** **60 min** **90 min** **120 min** **150 min** **180 min** **210 min** **240 min** **270 min** **300 min** **330 min** **360 min**			
SpO2 **30 min** **60 min** **90 min** **120 min** **150 min** **180 min** **210 min** **240 min** **270 min** **300 min** **330 min** **360 min**			
Sedation Score (0-4) **30 min** **60 min** **90 min** **120 min** **150 min** **180 min** **210 min** **240 min** **270 min** **300 min** **330 min** **360 min**			

Respiration Rate (RR) **30 min** **60 min** **90 min** **120 min** **150 min** **180 min** **210 min** **240 min** **270 min** **300 min** **330 min** **360 min**			

17. STUDY ENDPOINTS (TABLE)

17.1. Endpoints

	Treatment A N=	Treatment B N=	Estimate (95% CIs), SD	P-value
Change in Pain Score (Primary Endpoint)				
Length of Index ED Stay				
Hospitalization for Pain Control				
Return ED Visits				
Hospitalizations (if not admitted to hospital on Index ED visit)				
Re-hospitalizations (if admitted to hospital on Index ED visit, but discharged)				
Day Hospital Visits				
ED Revisits or Hospital Re-admissions or Day Hospital Visits Within 7 Days After the Index ED Visit (Binary Outcome with a Cutoff at Zero)				
Number of ED Revisits or Hospital Re-admissions or Day Hospital Visits After the Index ED visit				

17.2. Endpoints (Sensitivity Analyses)

	Treatment A N=	Treatment B N=	Estimate (95% CIs), SD	P-value
Change in Pain Score (Primary Endpoint)				
Length of Index ED Stay				
Hospitalization for Pain Control				
Return ED Visits				
Hospitalizations (if not admitted to hospital on Index ED visit)				
Re-hospitalizations (if admitted to hospital on Index ED visit, but discharged)				
Day Hospital Visits				
ED Revisits or Hospital Re-admissions or Day Hospital Visits				

Within 7 Days After the Index ED Visit (Binary Outcome with a Cutoff at Zero)				
Number of ED Revisits or Hospital Re-admissions or Day Hospital Visits within 7 days after the Index ED visit				

17.3. Subgroup Analysis of the Primary Endpoint

	Treatment A **N=**	**Treatment B** **N=**	**Estimate (95% CIs), SD**	**P-value**
Gender **Male** **Female**				
Age **< 30** **≥30**				
Genotypes **SS + SB-** **SC + SB+**				
Route **IV** **SC**				
NSAID **Yes** **No**				
Drug Administered **Yes** **No**				
Number of Repeated Doses				
Total Administered Milligrams of Drug				