Regional Health Command-Central (RHC-C)
Institutional Review Board
Brooke Army Medical Center

HUMAN SUBJECTS RESEARCH
PROTOCOL APPLICATION – Part B

1. PROTOCOL TITLE: Nasally Inhaled Isopropyl Alcohol Versus Oral Ondansetron for the Treatment of Nausea in the Emergency Department: A Double-Blind Randomized Controlled Trial

2. ABSTRACT. Nasally inhaled Isopropyl alcohol (ISO) has outperformed placebo in treating nausea among Emergency Department (ED) patients.[1] Inhalation of ISO pads is without known adverse effects,[2-4] relatively inexpensive and readily available compared with antiemetic drugs, making ISO a potentially safer, cost effective and faster antiemetic intervention. This agent has yet to be compared to conventional, commonly-used anti-emetics in randomized controlled trials. This study will study the efficacy of ISO and conventional anti-emetics with three study arms: (1) inhaled isopropyl alcohol plus oral ondansetron; (2) inhaled isopropyl alcohol plus oral placebo; (3) inhaled placebo plus oral ondansetron.

3. OBJECTIVES/SPECIFIC AIMS/RESEARCH QUESTIONS. The purpose of the study is to determine whether nasally inhaled isopropyl alcohol provides better nausea relief compared to ondansetron oral solution in patients presenting to the ED with nausea.

4. MILITARY RELEVANCE. Nausea is a common complaint seen not only in the ED but also in multiple deployed medical settings. Establishing the use of inhaled ISO for nausea and/or vomiting as an evidence-based intervention outperforming antiemetic drugs may relieve the nausea and/or vomiting symptoms to a significant degree and in a shorter amount of time. ISO preps are readily available in every military/deployed medical setting. If nausea in ED patients can be controlled with inhaled ISO, then its use can possibly be extended in other settings, specifically pre-hospital or combat use. Inhaled ISO is less expensive and has been proven safer than antiemetic drugs.[4]

5. BACKGROUND AND SIGNIFICANCE. A recent Cochrane review of aromatherapy for the treatment of nausea investigated 1386 articles; 44 articles were deemed relevant.[4]Nine of these specifically studied ISO inhalation in post-operative patients. Summation of this literature is challenging given heterogeneous outcome measures. Several non-blinded studies examined time to 50% reduction in nausea as measured on a verbal numerical rating scale (VNRS), 0-11, finding isopropyl alcohol achieved this more rapidly than conventional anti-emetics such as promethazine and ondansetron (times ranging 6.5-15.0 minutes).[5-7] A fourth study was single-blinded and reported absolute VNRS (0-11) for isopropyl alcohol versus usual anti-emetics (not otherwise specified). This study found scores decreased from a mean of 5.7 pre-inhalation to 2.7 post-inhalation though this was not significantly better than the usual care arm.[8] A fifth study compared inhaled isopropyl alcohol plus ondansetron versus ondansetron alone concluding no significant differences in nausea as measured on a 0-11 VNRS.[9] An additional three studies compared inhaled isopropyl alcohol to inhaled placebo, all of which concluding that isopropyl alcohol resulted in superior nausea relief.[10-12] Finally, a randomized trial with three arms including inhaled peppermint, inhaled isopropyl alcohol, and inhaled placebo found no difference in nausea scores as measured by a visual analogue scale (VAS).[13] In total, the Cochrane review article broadly concluded efficacy for isopropyl alcohol in treating post-operative nausea and vomiting. These studies were limited in that none were performed in an outpatient or pre-hospital setting. More recently, a randomized controlled trial at San Antonio Military Medical Center (SAMMC) demonstrated efficacy at 10 minutes among ED patients with nausea or vomiting.[1] Of note, although traditional anti-emetics (e.g., ondansetron, promethazine, metoclopramide) have demonstrated efficacy in specific patient populations such as cancer patients receiving chemotherapy,[14] multiple studies have found these agents are no better than placebo in treating nausea among undifferentiated ED patients.[15-17] Despite the absence of efficacy data, these agents are frequently used in the treatment of nausea among ED patients. Our objective is to compare the efficacy of inhaled isopropyl alcohol to ondansetron in treating nausea among undifferentiated patients.

6. **RESEARCH DESIGN** This study is a prospective randomized controlled trial. We will test the hypothesis that nasally-inhaled ISO plus oral placebo has greater anti-emetic efficacy compared to nasally-inhaled saline plus oral ondansetron oral solution. By design, the study will be double-blinded insofar as neither investigators nor subjects will be notified of the identity of the substances they are inhaling or swallowing. We anticipate blinding to scent may be challenging and the

study will include a post-study survey to ascertain the extent to which this blinding was achieved. Potential subjects are those presenting to the SAMMC ED with symptoms of nausea and/or vomiting. For the purposes of this study, nausea is defined as the subjective sensation associated with the urge to vomit, and vomiting is defined as the forceful expulsion of gastric contents. Investigators will approach subjects at the time of initial triage and/or while in the waiting room. This will mitigate interruptions in the subject's treatment, possible withdrawals from the control group, and lack of subject interest in the study. Part of the screening process will entail solicitation of nausea on a VNRS scored from 0-10 with those patients reporting scores of 3 or greater eligible for study. Informed consent will be obtained from each subject. Upon enrollment, a study team member will record the patient's date of visit, FMP + sponsor social security number, and date of birth (month, day, year) on the study key which will be maintained in a locked cabinet in the principal investigator's office.

Regarding blinding, subjects will be informed they will be nasally inhaling one of two common medical preparation pads saturated with different ingredients and taking orally one of two common oral solution substances. Subjects will be allocated to one of three arms: (1) inhaled isopropyl alcohol plus oral ondansetron; (2) inhaled isopropyl alcohol plus oral placebo; (3) inhaled placebo plus oral ondansetron. No subject will receive both inhaled and oral placebo; all subjects will be allocated to at least one therapeutic intervention for nausea Both investigators and study subjects will be blinded to subject allocation. Randomization will be performed prior to study start with a computer-generated assignment (simple randomization sequence) by an individual not otherwise involved in the study. A copy of the randomization key will be in a sealed envelope and placed in the study file box along with study packets as to be readily available in the ED in case un-blinding must occur. Another copy of the randomization key will be submitted to pharmacy personnel (Ms. Irene Lo). Based on the randomization sequence, the pharmacy will store doses of either ondansetron or placebo oral solution oral solution in the ED pharmacy. The oral solution and the placebo packets will appear identical in order to blind the medication – only pharmacy personnel with the randomization key will know which packet contains which oral solution. Also based on the randomization sequence, one pre-assembled study packet will be maintained in the Department of Emergency Medicine (DEM) administration area for each study ID number. Each packet will contain consent forms, data collection forms, order for the study drugs and ten identical (either ISO or saline) de-identified preparation pads for nasal inhalation. The preparation pads are commercially prepared single-use pads of ISO for the ISO + oral placebo and ISO + oral ondansetron study groups and commercially prepared single-use saline pads for the inhaled saline + ondansetron oral solution group that are identical with the exception of the labeling. Both pads will remain in their original packaging. The individual pads have been de-identified, with exception of expiration dates, utilizing brown tape over original packaging that tears open with packing so as to not reveal manufacturer's labeling.

Regarding the interventions, upon recruitment and packet receipt, a study team member will enter an order in CHCS for the study medication (listed under C.2016.091 and listed as an investigational drug to prevent accidental ordering for non-study patients). The study investigator will then go to the ED pharmacy and retrieve the study oral solution (either ondansetron or placebo) from pharmacy personnel by submitting the subject's study identification number and receiving the study oral solution according to subject study assigned number. Study team members enrolling patients and treating providers will all remain blinded to the oral solution contents. The study team member will then administer the medication to the patient. A study team member will then instruct the subject to inhale one of the blinded prep pads, to hold the pad approximately 1 centimeter from their nares, and to take deep nasal inhalations as needed for nausea relief. Subjects will be encouraged to take inhalations as frequently and deeply as they feel is necessary to achieve nausea relief. If a subject is unable to or prefers assistance with nasal inhalation or oral solution consumption, the patient's nurse will provide any assistance needed. The investigator will remain at arm's length from the patient at all times to avoid detecting prep pad scent. Additionally, investigators will also instruct subjects to avoid any behavior or actions during the study that would indicate which preparation pad is being used. Examples of behavior to avoid would be verbally describing the scent of the preparation pad or taste of the oral solution.

The investigators will record their findings on data collection forms. The primary outcome will be nausea as measured on a 10 cm visual analogue scale (VAS) at 30 minutes. This time horizon was selected as ondansetron's labeled use is administration 30 minutes prior to receipt of chemotherapy to treat chemotherapy-related nausea. Nausea measurements will also be collected at 10, 20, 40, 50, and 60 minutes, and then every hour up to 5 hours, then at disposition at which time the patient will provide one final nausea VAS score. The study team member will not be present in the patient's room during the intervals between these evaluations. At the time of each nausea measurement, patients will be offered another preparation pad (up to ten pads). We will notify the patient's treating provider to prompt consideration for treatment with a rescue anti-emetic (such as metoclopramide or promethazine) if the patient vomits or if the patient requests an anti-emetic at any time. At the time of each nausea measurement, a pain score will also be measured on a 10 cm VAS. At the time of final disposition, the patient will provide a satisfaction score on a 10-cm VAS and be asked to indicate his/her belief as to whether the pad was a treatment or placebo and whether the oral solution was a treatment or placebo. Similarly, at

study conclusion the patient's provider will be asked to indicate his/her belief as to whether the pad was a treatment or placebo and whether the oral solution was a treatment or placebo. Other data collected will include times and doses for all medications (including preparation pads) and fluids administered, episodes of vomiting (defined as forceful expulsion of gastric contents separated by at least 2 minutes), disposition (admission versus discharge), final clinical impression at the time of disposition, and time to disposition. Subjects will be followed and data collected for the entirety of their ED stay. A lockbox identified as "Nausea study" will be maintained in the ED for data collection form storage to which only the investigators and ED staff will have the key. ISO prep pads, saline prep pads, Ondansetron oral solution, and its matching placebo do not require storage in a hazardous material cabinet. This study will be registered on ClinicalTrials.gov.

Subjects will comprise a convenience sample. Study investigators will log hours of recruitment on a password-protected excel spreadsheet which will not contain any PHI. To confirm the sample is representative of all patients presenting to the ED with nausea, we will examine CHCS ad hoc data already generated by the ED on a routine basis for performance improvement purposes for all patients whose registration chief complaint contains either the words "nausea" or "vomiting" Including patients not enrolled in our study. Comparison of the characteristics of enrolled patients with patients not enrolled will enable us to establish whether there was selection bias in our study. These patients' FMP prefix and sponsor last 4 will be cross-referenced against our enrolled subjects. With our enrolled subjects removed, we will extract only the following data: age, sex, ESI category, diagnoses, receipt of any anti-emetics to include drugs and doses, and whether or not admitted. Any patient on the Ad Hoc list who is 89 or older will be recorded as ≥89. We will also need to access cross-reference the SSN or MRN of all these patients along with the dates of treatment data to establish whether a given CHCS data point represents a visit from a patients recruited into the study or a non-recruited patient. No PHI will be extracted from the ad hoc data. These extracted data will be maintained on a password-protected, CAC-enabled government laptop.

The prospective chart review (CHCS ad hoc data query) portion of the study will be conducted under a waiver of informed consent. This portion of the research involved no more than minimal risk to subjects as medical records are reviewed for limited information that is not of a sensitive nature. Adequate precautions are in place to protect the confidentiality of the information. Waiving consent will not adversely affect the rights and welfare of the subjects as the study reviews medical records for care already provided and cannot impact or change the care received. The research could not be practically carried out without the waiver as contacting hundreds of subjects is not feasible for review of medical records for information that would not change the care that the subjects have already received. A HIPAA Waiver of Authorization is also submitted to access patients' medical records for the prospective chart review portion of the study.

This study will pose no more than minimal risk to participants. Our use of isopropyl alcohol and ondansetron will not significantly increase the risks associated with the use of these medications in our study. These medications should quality for IND exemption (see section 7.2.1). All data for research purposes will be collected by non-invasive means.

7. RESEARCH PLAN

7.1 Selection of Subjects

7.1.1. Subject Population.

Patients ages 18 and older presenting to the Emergency department with a complaint of nausea and/or vomiting. All presumed causes of nausea will be included. Inclusion/exclusion criterion is based on safety considerations that were discussed with SAMMC clinical pharmacist. Other considerations are circumstances that altered smell or perception, exogenous emetics, concomitant antiemetic therapy and alcohol exposure. No specimens will be obtained.

7.1.2. Source of Research Material.

Source of Research Material	Conducted for Clinical Purposes(Y/N)	Conducted for Research Purposes
VAS Nausea Score	N	Y
Case Report Form	N	Y

VAS Patient Satisfaction Survey	N	Y
CHCS ad hoc data for all ED patients with nausea or vomiting including those not enrolled in the study for purpose of ruling out selection bias in study population	N	Y

7.1.3. Inclusion and Exclusion Criteria.
Inclusion Criteria:
(a) ages 18 and older
(b) complaint of nausea and/or vomiting reported at 3 or above on VRNS at the time of ED triage

Exclusion Criteria:
(a) allergy to isopropyl alcohol or ondansetron
(b) inability to breathe through nose (e.g., recent upper respiratory infection)
(c) intake of cefoperazone, disulfiram, or metronidazole within the last 24 hours
(d) mental status precluding informed consent including intoxication
(e) known QT-prolongation
(f) clinical suspicion for serotonin syndrome
(g) intravenous catheter in place prior to study start
(h) medications administered since patient arrival to ED (e.g., in triage)
(i) suspected or known pregnancy

7.1.4. Description of the Recruitment and Prescreening Process. ED providers and RN triage nursing staff (none of whom will be study team members) will be apprised of the study inclusion criteria to notify study team members of potential subjects. Potential subjects will be asked to quantify their nausea on a VNRS (0-10) for the purposes of discerning study eligibility by triage nurses, the RNs assigned to the patient, or the patient's provider. Efforts will be made to perform this prescreening process early in the patient's ED course (ideally at the time of triage or initial arrival to treatment room). No other history, physical exam or other evaluations beyond those normally conducted as the standard of care shall be performed for the purposes of screening. Triage nurses, the RNs assigned to the patient, the provider assigned will, through their standard of care assessments and VNRS ascertainment, be able to identify potential subjects (those who meet inclusion criteria). Triage nurses will notify research staff of potential patients for study enrollment.

7.1.5. Consent Process. Either the PI or one of the AIs will conduct the informed consent process, which will be accomplished in the ED while the patient is not receiving active-intervention. The process will take place with the curtain drawn or door closed to provide the subject appropriate privacy. The subject will have ample opportunity to ask questions of the investigators and to look over the consent form and HIPAA authorization. The subject will be offered the option of having a family member present and to be allowed the option of deferring a decision until later into their ED stay. Subjects unable to provide informed consent for themselves due to diminished decision-making capacity are excluded per paragraph 7.1.3. The informed consent will notify patients that they will be receiving one of two oral solutions and one of two preparation pads being studied for the treatment of nausea. They will not be informed of the identity of the substances or that one of the substances is inert (placebo) given that it is impossible to blind to smell hence we believe that effective blinding to the preparation pad contents would be impossible without withholding this information. Given the safety profile of these medications, we believe this research will pose no greater than minimal risk to the participants.

7.1.6. Subject Screening Procedures. Subjects will be recruited exclusively by the study investigators. Investigators will approach eligible subjects as identified by either the triage nurse, treating nurses, or treating providers. The recruiting investigator will inquire as to whether the patient is amenable to possible participation in a study of nausea treatments. If the patient agrees, the investigator will then verify the potential subject meets inclusion criteria without exclusion through subject self-report. Agreeable patients will undergo a complete, informed consent process. Data regarding potential subject's age, sex, and nausea VNRS will be recorded for all patients declining to participate in the study. No personal health information will be collected on these patients.

7.1.7. Compensation for participation. No compensation will be provided to the subjects.

7.2 Drugs, Dietary Supplements, Biologics, or Devices.

7.2.1 Drugs

Professional Disposable International (PDI) Alcohol prep pads. NDC 10819-3914-2, C69900

Professional Disposable International (PDI) Sterile Saline prep pads. C22370

Ondansetron Oral Solution 4mg/5ml . NDC 0054-0064-47. 5 ml (4 mg) per subject study dose.

Placebo oral solution – 0.25ml of Oral Sweet Sugar Free NDC 0574-0302-16 with 4.75ml of Sterile Water for Irrigation NDC 0264-2101-00

We will be requesting an investigational drug exemption for the isopropyl alcohol pads IAW 32 CFR 312.2 for the following reasons. We have no intentions of utilizing the results of this study to seek a new indication for the use of isopropyl alcohol or to otherwise support any significant changes in the labeling of this product. Similarly, we have no intentions of using the results of this study to support a significant change in the advertising of this product. Our route of administration of this product will not significantly increase the risks associated with its use.

We will also be requesting an investigational drug exemption for the Ondansetron IAW 32 CFR 312.2 for the following reasons. We have no intentions of using the results of this study to seek a new indication for use of ondansetron or to otherwise support any significant changes in its labeling. Similarly, we have no intentions of using the results of this study to support a significant change in the advertising of this medication. Our routes of administration of this medication will not significantly increase the risks associated with its use.
Both the saline and isopropyl alcohol pads are lawfully marketed over the counter products and meet the conditions of being generally safe and effective by the U.S. FDA due to their active ingredients and labeling. We consider the use of the ISO (administered via the pad) as a drug in this research which meets the IND exemption criteria as outlined above.

Specifically regarding ondansetron, we will be using the conventional dose (4 mg) and route of administration for ondansetron. While the patient population in this study (all patients with undifferentiated nausea and vomiting) differs from that for which this medication is approved (chemotherapy patients), this agent has been extensively studied at this dose in ED patient population without safety concerns.[15-17] Moreover, this medication is routinely used at this dose in our Emergency Department for the purpose of treating nausea and is incorporated into our triage protocols. Finally, this investigation will be conducted in compliance with the requirements for IRB review and obtaining informed consent.

7.2.2 Devices. Not applicable.

7.3. Study Procedures/Research Interventions. Upon presenting to ED, meeting inclusion criteria and obtaining consent, the subject's nausea and pain levels will be recorded initially. For the oral solution, they will be instructed to swallow the oral solution. Receipt of oral solution (ondansetron or placebo) should occur prior to pad inhalation to be followed within 5 minutes by initiation of inhalations from the allocated study pad (normal saline or ISO). For the preparation pads, patients will be instructed to hold the pad approximately 1 inch from their nares and take deep nasal inhalations as needed for nausea relief. Initiation of inhalations will mark time 0 for the study. If a subject is unable to or prefers assistance with either nasal inhalation or oral solution consumption, the patient's nurse will provide any assistance needed. The investigator will remain at arm's length from the patient at all times to avoid detecting prep pad scent. Additionally, investigators will also instruct subjects to avoid any behavior or actions during the study that would indicate which intervention is being used. Examples of behavior to avoid would be verbally describing the scent of the preparation pad or taste of the oral solution. Investigators will not inform subjects which substances are being tested. The preparation pads are commercially prepared single-use pads of ISO for the ISO + oral placebo and the ISO + oral ondansetron study groups and commercially prepared single-use saline pads for the inhaled saline + ondansetron oral solution group that are identical with the exception of the labeling. Both pads will remain in their original packaging. Pain and nausea measurements will be gathered at 0, 10, 20, 30, and 60 minutes and then again hourly up to 5 hours, and then finally at the time the patient's attending physician makes a disposition decision. The patient may withdraw from the study at any time. At any time during the study, a rescue antiemetic drug can be considered by subject request or provider preference. The individual pads will be de-identified, utilizing brown tape over original packaging that tears open

with packing as not to reveal manufacturer's labeling. The oral solution packaging will similarly be de-identified. The only scenarios in which a study team member will prompt a provider to consider a rescue anti-emetic is if the patient vomits or if the patient actively requests an alternative medication. A study data form will be completed for each subject by the study investigators and secured daily in a locked cabinet, along with locked study file box, in the EM APD-R office.

Assessment		**Visit / Follow Up (F/U) Interval Times**				
Study period/interval	Initial Presentation	0 min (patient drinks oral solution and starts inhalations)	q10 min until 30 min	1 hour	Hourly until 5 hours	Disposition decision made by patient's attending physician
Screening	x					
Informed Consent, discuss Plan, etc.	x					
Allocation according to pre-generated simple randomization sequence	x					
Demographics, History of Present Illness	x					
Medication use	x					
Preparation pad provided		x				
Additional preparation pad offered if needed (up to 10)			x	x	x	
Oral solution provided		x				
Provider contacted for consideration of rescue anti-emetic if vomiting or if subject requests			x	x	x	
Nausea Vomiting VAS		x	x	x	x	x
Episodes of Vomiting		x	x	x	x	x
Pain VAS		x	x	x	x	x
Use of Antiemetic Medication		x	x	x	x	x
Type/Doses of fluids/medications		x	x	x	x	x
Clinical impression						x
Overall Satisfaction VAS						x
Pt perception of pad contents						x
Pt perception of oral solution contents						x
Provider perception of pad contents						x
Provider perception of oral solution contents						x
Investigator perception of pad contents						x
Investigator perception of oral solution contents						x
Summary of adverse events						x

This study concludes at the time of disposition and patient satisfaction will be solicited regardless of outcome.

7.3.1 Collection of Human Biological Specimens. Not applicable.

7.3.1.1 Laboratory evaluations and special precautions. Not applicable.

7.3.1.2 Specimen storage. Not applicable.

7.3.2 Data Collection.
-Times of subject arrival to ED, bed arrival, study medication receipt (gathered prospectively from order sheet or Essentris)
-Patient initial nausea as measured by screening VNRS (0-10): self-reported by the subject.
-Demographics: Age in years, sex, FMP/SSN, DOB will be recorded on the study key. Age in years and sex will also be reported on the case report form (CRF). This information will be obtained from the patient's ED medical record labels.
-The patient's estimated height, weight, race, smoking history, alcohol use will be recorded on the CRF as self-reported by the patient.
-History of Present Illness- Nausea and/or vomiting symptoms of timing, duration, severity, provocation and palliation along with any other symptoms (i.e. pain) will be recorded on the CRF. This information will be self-reported by the subject.
-Pertinent Personal Medical/Surgical History will be recorded on the CRF. This information will be self-reported by the subject.
-Current medications, supplements being taken and any allergies will be recorded on the CRF.
-Level of nausea, episodes of vomiting, pain level, adverse events, use of antiemetic medication at the 0, 10, 20, 30, and 60 minutes, then hourly up to 5 hours and finally at the time of patient disposition will be recorded on the CRF. Satisfaction level will be recorded at study conclusion (time of patient disposition) on a VAS. This information will be self-reported by the subject.
-Numbers of episodes of vomiting (discrete episodes separated by 120 seconds) will be recorded on the CRF as reported by the patient or the patient's treating nurse.
-Time and doses for all drugs and fluids administered in the ED will be recorded on the CRF.
-Clinical impression at the time of patient disposition decision will be recorded on the CRF.
-Time of patient disposition decision made by attending physician will be recorded on the CRF.
-Any adverse events will be recorded on the CRF.
-Patient, provider, and study investigator perceptions of pad and oral solution contents will be recorded on the CRF.

7.3.3. Human Biological Specimens/Tissue/Data Banking. Not applicable.

7.4 Statistical Consideration

7.4.1 Sample Size Estimation.
We expect the standard deviation of the change in baseline to 30 minute VAS scores to be approximately 28.7.[17] We define a clinically significant difference as 20 mm on the VAS.[18] Given alpha = 0.025 (reflecting a Bonferonni correction for testing of two hypotheses) and beta = 0.2 with two-tailed testing, we estimate we will require 40 patients per arm.

Estimate Required Sample Size	**120**
Estimate Participant Drop Out / Withdrawal	**60**
Total Enrollment Requirement	180

Enrollment at Each Site	
SAMMC	**180**

7.4.2 Primary (i.e., primary outcome variables) and secondary endpoints. Primary outcome is nausea VAS measurement at 30 minutes. Secondary outcomes include nausea VAS measurement at study disposition (the time at which the patient leaves the ED), receipt of rescue anti-emetics, time to disposition, and patient satisfaction.

7.4.3 Data analysis. In this study, the primary outcome will be evaluated using a two-tailed independent sample student t test. The primary outcome will further be evaluated using a multiple regression model. For secondary outcomes, scale data will be compared using a two-tailed independent sample student t test while categorical data will be compared using a chi-squared test.

7.7 Confidentiality.

Protection of Data. Subjects will be assigned a study number upon enrollment in order to facilitate subsequent removal of identifiers upon completion of data analysis. The study number will be recorded on the data collection form and on a study key, which links the study number with the subject's name, FMP, SSN, and DOB. Otherwise patients will be de-identified by eliminating names and collecting only demographic (with ages greater than 89 categorized as "greater than 89"), general description of chief complaint, personal medical, surgical, and medication history; and any other information specific to inclusion and exclusion criteria. The case report forms, signed consent forms, and signed HIPAA authorizations will be stored in a locked cabinet only accessible to the study investigators within the secure EM APD-R office.

7.7.1 Certificate of Confidentiality. N/A.

8.0 RISKS/BENEFITS ASSESSMENT

8.1 Risks. There is a risk to the subjects related to loss of confidentiality. However, this risk is minimized by using a unique study code while collecting study data and limiting access to subject records to the study team. Since all patients will be receiving treatment for nausea (either inhaled isopropyl alcohol, oral ondansetron, or both), we believe the risks of delay in treatment or symptom relief are minimal. Nevertheless, if the treatment to which subjects are allocated is not effective in treating their symptoms, they may experience a delay in rescue therapy and so a delay in symptom relief. We seek to minimize this risk by permitting, subjects to request an antiemetic at any time and to withdraw from the study at any time.

Additionally, there may be an extremely rare incident of a subject that may have a sensitivity to inhaling ISO. The exclusion criteria were defined to minimize the risks of such reactions by excluding patients recently exposed to medications such as cefoperazone, disulfiram, or metronidazole.

Some patients may also have an adverse reaction from swallowing ondansetron oral solution. These may include the following:

Central nervous system: Headache (oral: 9% to 27%; IV: 17%), fatigue (oral: ≤9% to 13%), malaise (oral: ≤9% to 13%)

Gastrointestinal: Constipation (6% to 11%)

1% to 10%:

Central nervous system: dizziness (7%), agitation (oral: ≤6%), anxiety (oral: ≤6%)

Dermatologic: Pruritus (2% to 5%), skin rash (1%)

Gastrointestinal: Diarrhea (oral: 6% to 7%)

Genitourinary: Gynecologic disease (oral: 7%), urinary retention (oral: 5%)

Hepatic: Increased serum ALT (>2 times ULN: 1% to 5%; transient), increased serum AST (>2 times ULN: 1% to 5%; transient)

Local: Injection site reaction (IV: 4%; includes burning sensation at injection site, erythema at injection site, injection site pain)

Respiratory: Hypoxia (oral: 9%)

Miscellaneous: Fever (2% to 8%)

8.2 Potential Benefits. Shortened time to relief of nausea and/or vomiting may be a benefit to the two groups allocated to inhaled isopropyl alcohol. The group not receiving inhaled isopropyl alcohol will receive oral ondansetron which has been shown to improve nausea in previous studies (though nausea relief is commensurate to that of intravenous fluids alone). Therefore, we anticipate that all study groups will receive some benefit from the study.

9.0 ADVERSE EVENTS, UNANTICIPATED PROBLEMS, AND DEVIATIONS

9.1 Hines et al found no adverse effects of inhaled ISO in their November 2012 Cochrane review.[4] An allergy to isopropyl alcohol which is extremely rare but could be serious. Previous toxicological rat studies of inhaled isopropyl that would reproduce adverse effects in humans are not applicable considering this study's minuscule inhalation.[19] Only 1 case of death associated to ISO inhalation was found in the literature review, however the deceased was a child that was also bathed with ISO.[10] The study excludes children and there will be no direct contact of ISO to the subject or investigator.

<1% (Limited to important or life-threatening): Abdominal pain, accommodation disturbance, atrial fibrillation, cardiorespiratory arrest (IV), depression of ST segment on ECG, dyspnea, extrapyramidal reaction (IV), flushing, hepatic failure (when used with other hepatotoxic medications), hiccups, hypersensitivity reaction, hypokalemia, hypotension, laryngospasm (IV), liver enzyme disorder, mucosal tissue reaction, myocardial infarction, neuroleptic malignant syndrome, positive lymphocyte transformation test, prolonged Q-T interval on ECG (dose dependent), second-degree atrioventricular block, serotonin syndrome, shock (IV), Stevens-Johnson syndrome, supraventricular tachycardia, syncope, tachycardia, tonic-clonic seizures, torsades de pointes, transient blindness (lasted ≤48 hours), transient blurred vision (following infusion), vascular occlusive events, ventricular premature contractions, ventricular tachycardia, weakness

Adverse events will be recorded on the data collection form, and required Brooke Army Medical Center Institutional Review Board Tracking Log for Adverse Events, Serious Adverse Events & UPIRSOs / UADE Internal Report Log (P52I) and the subject will be clinically managed in the ED.

9.2 Reporting Unanticipated Problems Involving Risks to Subjects or Others, Serious Adverse Events and Deaths to the RHC-C IRB Office.

All unanticipated problems involving risk to subjects or others, unexpected serious adverse events, and all subject deaths related or possibly related to the study will be reported promptly providing initial notification of the event as quickly as possible after the research team's knowledge of the event, but within five (5) business days of identification by phone (210-916-0606/2598), by e-mail (usarmy.jbsa.medcom-bamc.mbx.bamc-irb@mail.mil), by facsimile (210-916-1650) or via letter addressed to IRB Administrator, Regional Health Command-Central Office of the Institutional Review Board, Brooke Army Medical Center, Attn: MCHE-ZQ, Department of Quality and Safety, 3551 Roger Brooke Drive, Fort Sam Houston, TX 78234-6315. A complete written report will follow the initial notification within 10 working days.

9.3 Research Monitor. The research monitor will review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event to the RHC-C IRB. Other responsibilities may be assigned by the IRB. The research monitor will comment on the outcomes of the event or problem and in the case of a serious adverse event or death comment on the relationship to participation in the study. The research monitor will also indicate whether he/she concurs with the details of the report provided by the study investigator. Reports for events determined by either the investigator or research monitor to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the RHC-C IRB office.

10.0 WITHDRAWAL FROM STUDY PARTICIPATION. Patients may withdraw their consent at any time and discontinue further participation in this study without affecting their eligibility for care or any other benefits to which they are entitled. They may withdraw for any reason. Should they choose to withdraw, they must notify the principle investigator or any other member of the research team. They may do this during the study in person by verbally stating to the research team member that they wish to withdraw. After the study, they may withdraw by calling or writing the principle investigator (PI contact information provided to all study participants on the informed consent document). We will analyze any data collected on these patients prior to withdrawal unless requested by the subject to destroy their data form. There are no risks associated with withdrawing from the study.

11.0 USAMRMC Volunteer Registry Database. N/A

12.0 REFERENCES.

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13.0 TIME REQUIRED TO COMPLETE THE RESEARCH (including data analysis). 2 years.

14.0 STUDY CLOSURE PROCEDURES. Upon study completion, all data collection forms and the study key will be destroyed. The ICDs and HIPAA authorizations will be stored within the EM APD-R Residency office for three and six years after completion of the study, respectively. A protocol closure form will be submitted.