COVER PAGE FOR PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official Study Title: A Randomized Control Equivalence Study of Emergency Medical Services Use of Isopropyl Alcohol Aromatherapy Versus Ondansetron for Treatment of Pre-hospital Nausea

NCT number: NCT02618343

IRB Approval Date: 10/21/2015

Protocol Template Form

Item 1 UTHSCSA Tracking Number	HSC20150859H

Item 2 Abstract / Project Summary	Provide a succinct and accurate description of the proposed research. State the purpose/aims. Describe concisely the research design and methods for achieving the stated goals. This section should be understandable to all members of the IRB, scientific and non-scientific. **DO NOT EXCEED THE SPACE PROVIDED**.

Purpose/Objectives: Nausea is a common symptom encountered in the Emergency Medical Services (EMS) environment that is often treated with oral or intravenous anti-emetic medications. **Research Design/Plan:** This will be a randomized equivalence study comparing the reduction in a patient's reported level of nausea after treatment with either Ondansetron or Isopropyl Alcohol **Methods:** Patients who report nausea and/or vomiting in the normal evaluation and care of after calling 911 for Emergency Medical Care will be offered enrollment in the study. A short script will be attached to the outside of each study packet providing information about the study and its risks and benefits. Verbal or written (waiver of informed consent will be requested) permission will be obtained to start randomization. If the patient agrees to enroll then the study packet will be opened and utilized. All Advanced Life Support Ambulances in the San Antonio Fire Department will have sealed numbered opaque boxes or envelopes with either: 70% Isopropyl Alcohol swabs or ondansetron. Six Visual Nausea Severity Scoring cards will be provided with a marking pen to record timed nausea levels before and upon arrival to the Emergency Department and 15 minutes after treatment whichever comes first. **Clinical Relevance:** This treatment has not been studied in the unique environment encountered by Paramedics in the Pre-Hospital setting. If this treatment is found to be effective, it many offer a very simple, extremely inexpensive and non-invasive (basic life support) approach for the treatment of nausea.

Item 3 Background	
Describe past experimental and/or clinical findings leading to the formulation of your study. For research involving unapproved drugs, describe animal and human studies. For research that involves approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.	Nausea is a common symptom encountered in the Emergency Medical Services (EMS) environment that is often treated with oral or intravenous anti-emetic medications. Post-operative patients with modern anesthesia techniques and processes still have a 20-30% incidence of Nausea and/or vomiting. Nausea is a complicated symptom that is tough to arise from the vomiting center in the lateral reticular formation in the brainstem. Afferent inputs form the cerebellum, higher cortical centers, the vestibular apparatus, the glossopharyngeal nerve and the vagal nerve inputs contribute to the process of the perception of nausea. Chemoreptors in the Chemoreceptor Trigger Zone (CTZ) are located on the brain surface and are highly vascularized leading to increased exposure to neurotransmitters such as Serotonin (5-HT-3), histamine (H1) acetylcholine and dopamine. Blocking such neurotransmitter stimulation with targeted medications such as antihistamines or 5-HT-3 antagonists such as Ondansetron. Nausea is a common symptom encountered in the Emergency Medical Services (EMS) environment that is often treated with oral or intravenous anti-emetic medications. Many patients do not respond well to this therapy, and EMS services that have only basic life support (BLS) capabilities may not have any good treatment currently. Additionally, because of the configuration of modern day ambulances, the patient is transport in a rear facing position in the patient compartment with very limited view of the environment. This method of transport frequently causes motion sickness. Motion sickness is thought to be caused by inadequate adaption of the body to conflicts between vestibular, visual, other proprioceptive inputs and inhibition of the vestibular cerebellum. Common therapies may include antihistamines, benzodiazepines, tricyclic antidepressants and or scopolamine. 3 Sakata

	Behavioral strategies such a watching the true horizon, steering the vehicle, tilting head into turns and laying down with eyes closed have been shown to alleviate some symptoms of motion sickness. But these strategies are not available in the EMS environment. Scopolamine administered well before motion stimulus has been shown to prevent motion sickness and acute treatment is best when using sedating antihistamines. Non-sedating antihistamines, Ondansetron and ginger root have not been found to effectively prevent nor treat motion sickness. Multiple agents have been studied for the treatment of nausea in the emergency department with equivalency of effect and time on onset. Common agents include ondansetron, metoclopramide, promethazine and prochlorperazine. Such agents have also been used in the EMS environment to some degree, but require parenteral administration with exposure to the risks for side effects or sedation. There are also not options at the BLS level. Post-operative oxygen therapy has not been shown to decrease post nausea after c-section delivery which is disappointing as this is a ubiquitous therapy in the EMS environment of care, is inexpensive and easy to administer. Ondansetron has been shown to be safe and effective in the prehospital environment with a low incidence of side effects but cost and need for parenteral administration is often a barrier to care. Multiple studies have shown Isopropyl Alcohol (IPA) 70% aromatherapy to be as effective as Ondansetron with a more rapid onset of nausea relief. This therapy was performed by holding a folded saturated 70% IPA pad under the nares with the patient inhaling the vapors. The patient is simply instructed to take three deep breaths through their nose. In animal experiments, toxicity from inhalation of IPA is very low at doses allowable by inhalation as compared with dermal or oral ingestion. Dermal application of IPA is routinely used by EMS personnel to cleanse the area of skin immediately surrounding the insertion point of an intravascular catheter for medication administration, or blood draw.
Item 4 Purpose and rationale *Insert purpose, objectives and research questions/hypotheses here. If you cut and paste from another document, make sure the excerpted material answers the question*	Insert purpose: IPA Therapy may offer a very inexpensive, easy to administer, and effective alternative to medication therapy for nausea and vomiting in the prehospital

Item 5 Study Population(s) Being Recruited In your recruitment plan, how many different populations of prospective subjects do you plan to target? Provide number: 1	Identify the criteria for **inclusion**:	Identify the criteria for **exclusion**:

e.g., a population can be individuals with type 2 diabetes controlled with diet and/or a population of healthy controls. Or a population can be individuals attending an education program, etc. List each different population on a separate row and provide a short descriptive **label**: *(e.g., normal-healthy, diabetics, parents, children, etc.)* *To add rows use copy & paste*		
EMS patients complaining of nausea	Adults (non-pregnant) age 18 years or older with a symptom of nausea and/or vomiting requiring treatment by EMS	•Children not yet 18 years of Age •Prisoners or those under arrest •Patients known or suspected to be Pregnant •Clinical Intoxication •Patients unable to provide informed consent •Recent Upper respiratory Tract infection •Inability to follow instructions •Inability to inhale through Nares

Item 6
Research Plan / Description of the Research Methods *a.* *Provide a **comprehensive narrative** describing the **research methods**. Provide the **plan for data analysis** (include as applicable the **sample size calculation).***

Step-by-Step Methods:

RECRUITMENT AND RANDOMIZATION PROCESS
Patients who report nausea and/or vomiting in the normal evaluation and care of after calling 911 for Emergency Medical Care will be offered enrollment in the study.
A short script will be attached to the outside of each study packet providing information about the study. Verbal (waiver of documentation informed consent will be requested) permission will be obtained to start randomization. If the patient agrees to enroll then the study packet will be opened and utilized.

PROCEDURES AND LOGISTICS
All Advanced Life Support Ambulances in the San Antonio Fire Department will have sealed numbered opaque boxes or envelopes with either:

- Three large 2 ply 70% Isopropyl Alcohol swabs

OR

- Ondansetron (Zofran) 4mg for IV/IM use (standard of care)

These study packets will have similar weight, shape and contour despite the contents. If needed, props may be includes to make packages similar in weight, contour or sound when shaken so as to not reveal its true contents. The goal is to enroll at least 400 patients over a 1 year period.

For each arm, the package will contain a step by step instruction checklist. Six Visual Nausea Severity Scoring cards will be provided with a marking pen to record timed nausea levels before and upon arrival to the Emergency Department and 15 minutes after treatment whichever comes first. The treatment protocol for each arm will be:

70% Isopropyl Alcohol
1. Mark Time and Visual Nausea Severity Score 0-10
2. Remove alcohol prep with gloved hand
3. Place under nares of the patient

4. Instruct the patient to take three separate deep inhalations of the Isopropyl vapors through their nose
5. Record time of treatment on back of first Visual Nausea Severity Score card.
6. Mark time and Subsequent Visual Nausea Severity Scores upon arrival to the Emergency Department at indicated time intervals.
7. If patient still has significant nausea and or vomiting after ten minutes provide rescue Ondansetron therapy with 4mg of Ondansetron slow IV push or IM
8. Mark time and Visual Nausea Severity Score upon arrival to the Emergency Department on third card.
9. Document all interventions on electronic Patient Care record as per usual procedures.
10. Complete Paramedic evaluation tool.
11. Envelope or box, with Consent, score cards and Paramedic evaluation tool will be returned to Medic Officer on duty and a new study packet will be replaced.
12. Used Study Packets will be collected by the Investigators

Ondansetron 4mg IV/IM (standard of care)

1. Mark Time and Visual Nausea Severity Score 0-10 on first enclosed card.
2. Start IV if not already done so.
3. If unable to obtain IV access in two attempts use intramuscular route.
4. Inject 4mg of Ondansetron slow IV push or IM.
5. Record time of treatment on back of first Visual Nausea Severity Score card.
6. Mark time and Second Visual Nausea Severity Score upon arrival to the Emergency Department or 10 minutes after treatment whichever comes first.
7. If patient still has significant nausea and or vomiting after ten minutes provide rescue an additional dose of Ondansetron therapy with 4mg of Ondansetron slow IV push or IM
8. Mark time and Visual Nausea Severity Score upon arrival to the Emergency Department on third card.
9. Document all interventions on electronic Patient Care record as per usual procedures.
10. Complete Paramedic evaluation tool.
11. Envelope or box, with Consent, score cards and Paramedic evaluation tool will be returned to Medic Officer on duty and a new study packet will be replaced.
12. Used Study Packets will be collected by the Investigators.

Data Analysis Plan: A secure excel spreadsheet tool will be used to abstract data from the research data collection documents and the EMS electronic patient care record. The patient will only be identified by the randomization number, incident number, age (if greater than 89 age will be indicated by <89 years), sex and date of service in the database and on all study packet materials. All relevant time intervals and Visual Nausea Severity Scores will be recorded for enrolled patients. Time to treatment will be compared between the two arms of the study as well as changes in Visual Nausea Severity Scores. Treatment failures requiring additional Ondansetron will be characterized. Paramedic will be asked to evaluate the treatment provided for ease of use, time needed to complete the treatment and their impression of effectiveness of the assigned treatment. T-test and confidence intervals will be utilized to determine statistical significance.

Item 7 Risks Section:

Complete the following table to describe the risks of all **research procedures** listed in Step 2, Institutional Form (items 28-34). *Do not list risks of Routine care procedures here.*

☐ N/A, Risks are described in the informed consent document – do not complete this table.

Research procedures *example:* • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Risks** List the reasonably expected risks under the following categories as appropriate:
Isopropyl Alcohol	Serious and likely; ○ none Serious and less likely; ○ none Serious and rare; ○ none Not serious and likely; ○ dizziness, nausea, abdominal pain Not serious and less likely ○ hypotension
Ondansetron(standard of care)	Serious and likely; ○ none Serious and less likely; ○ none Serious and rare; ○ decrease in urine output, uncontrolled twisting movements of the neck, trunk, arms, or legs (Dystonia), death, Not serious and likely; ○ confusion, dizziness, blurred vision, fixed position of the eye, hiccups, redness of the skin, fast heartbeat, fever, headache, shortness of breath, weakness, Not serious and less likely ○ none