Official title: Etomidate versus ketamine for emergency endotracheal intubation: a prospective randomized clinical trial

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Etomidate versus ketamine for emergency endotracheal intubation: a prospective randomized clinical trial

Short Title: The EvK Trial

Departments of Anesthesiology, Emergency Medicine, Internal Medicine, Surgery and Pharmacy
at Parkland Memorial Hospital

Principal Investigator

Gerald Matchett, MD
UT-Southwestern Dept. of Anesthesiology
5323 Harry Hines Blvd, MC 9068
Dallas, TX 75390-9068

Co-Investigators

[redacted]

Technical Consulting

[redacted]

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Contents

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1. Plain Language Summary

Patients who are critically ill may require emergency placement of a breathing tube in their mouth and windpipe. The purpose of this breathing tube is to save the patient's life. Usually the treating medical team administers a drug to sedate the patient before the breathing tube is placed. For critically ill patients it is common to choose either etomidate or ketamine to sedate the patient. These drugs are often chosen because they have few effects on the patient's blood pressure and heart rate. Etomidate has some other serious side effects which include interference with the production of steroids by the adrenal glands. Previous studies have suggested that etomidate may cause greater long-term illness and even death because of this side effect. The purpose of the EvK Trial is to evaluate which drug (etomidate or ketamine) is better for patients who are critically ill. We believe that ketamine is associated with improved chance of survival after emergency endotracheal intubation because it does not interfere with steroid production. Because this study involves research of an emergency medical procedure, we have created a comprehensive Community Consultation Plan and Post-Enrollment Notification Plan that meets U.S. Food and Drug Administration regulations for emergency research.

2. Introduction and Purpose:

Patients who are critically ill may require emergency placement of an endotracheal tube. The purpose of the endotracheal tube is to save and sustain the patient's life. Prior to placement of an endotracheal tube, it is common for the supervising medical team to administer a drug intravenously to sedate the patient to make this placement of the tube tolerable. Several drugs are commonly used for this purpose, including etomidate, ketamine and propofol. Both etomidate and ketamine are useful in critically ill patients because they offer relative hemodynamic stability compared to propofol. Ketamine has few, if any, serious long-term side effects.

[redacted]

Etomidate is known to suppress adrenal steroidogenesis, and thereby may place patients at risk for adrenal insufficiency or death (Coursin et al., 2013). A recent Cochrane Collaboration Review concluded that etomidate is associated with increased risk of adrenal dysfunction and multi-organ dysfunction in critically ill patients (Bruder et al., 2015). There is ongoing controversy regarding the routine use of etomidate in critically ill patients.

The **purpose** of the EvK Trial is to compare and contrast the safety of etomidate with ketamine in the setting of emergency endotracheal intubation in critically ill patients. In this study we will randomize patients to receive either etomidate or ketamine. Our **hypothesis** is that ketamine is associated with increased chance of survival in critically ill patients. The proposed **mechanism** of this effect is that ketamine does not affect the adrenal axis. The **specific aim** of the study is to conduct an adequately powered trial suitable to compare etomidate and ketamine in terms of proportions survived at 7-days post-intubation. The **primary endpoint** is survival at 7 days after intubation. **Secondary endpoints** include long-term survival (28-day), Sequential Organ Failure Assessment (SOFA) scores, anesthetic complications, intubating conditions, duration of ventilator support, duration of catecholamine therapy, neurological scores, measures of ICU outcomes, measures of long-term functional status, changes in blood pressure, new diagnoses, and others. Appendix 1 lists primary and secondary endpoints for the study.

3. Detailed Background, Evaluation of Prior Research and Internal QA/QI Data:

Both etomidate and ketamine are standard-of-care for emergency endotracheal intubation, and both are frequently used locally, nationally and internationally. Etomidate is often used at our institution (Parkland Memorial Hospital), based on our last QA/QI survey of our practices (Figures 1 and 2). There is considerable controversy regarding the long-term safety of the use of

[redacted]

etomidate for emergency endotracheal intubation. The largest study to date that evaluated this question (the KETASED Trial, Jabre et al., 2009) randomized patients requiring emergency endotracheal intubation to either etomidate (n=234) or ketamine (n=235). The patients who received etomidate experienced a much-higher frequency of adrenal dysfunction, and a slight but not statistically significant increase in multi-organ dysfunction and mortality. Other published reports echo concerns about etomidate. A sub-group analysis within the CORTICUS Trial (Sprung et al., 2008) (n=99 receiving etomidate, n=403 receiving other agents) found that one dose of etomidate was associated with evidence of adrenal insufficiency and increased mortality (Cuthbertson et al., 2009). Another sub-group analysis from a different clinical trial (Arabi et al., 2010) of cirrhotic patients with septic shock (n=23 receiving etomidate, n=39 receiving other agents) reported increased ICU mortality associated with a single dose of etomidate (Cherfan et al., 2011). A recent meta-analysis incorporating these and other studies concluded that a single dose of etomidate is associated with adrenal insufficiency and increased mortality (Chan et al., 2012).

In late 2014 and early 2015 the Department of Anesthesiology at Parkland Memorial Hospital performed a Quality Assessment/Quality Improvement (QA/QI) project that evaluated techniques and outcomes from emergency endotracheal intubations done by the Anesthesia Code Team (ACT). [redacted]

[redacted]

The purpose of the EvK Trial is to be the largest trial to date that randomizes critically ill patients to etomidate (n=375 patients) versus ketamine (n=375). Additionally, the EvK Trial has been designed to address some of the shortcomings of the KETASED trial. First, the KETASED trial was not powered to detect a difference in mortality, although did find a trend in survival benefit in those patients randomized to receive ketamine. We have designed the EvK Trial to be powered to detect a 10% difference in survival in our patient population (See Section 14 for a discussion of our statistical approach). Second, the primary endpoint of the KETASED trial was the maximum SOFA score in the first 72 hours as the primary endpoint. From our QA/QI data, we believe that a more appropriate endpoint in our patient population is survival at Day 7. Third, the KETASED trial enrolled a large percentage of patients (approximately 70% in each group) who were intubated for "neurological" reasons, and relatively few patients (approximately 10% in each group) who were intubated for shock or sepsis. Prior work has suggested that patients with sepsis and shock are much more vulnerable to the side effects of etomidate. In our QA/QI data, approximately 50% of the patients intubated by the ACT are in shock, and at least 25% have sepsis. This suggests that our patient population is more likely to benefit from use of ketamine compared to the patient population in KETASED.

4. Concise Summary of Project:

[redacted]

The EvK Trial is a prospective randomized clinical trial that will be done at Parkland Memorial Hospital. Individual patients requiring emergency endotracheal intubation will be randomized to receive either etomidate (n=375 patients) or ketamine (n=375 patients). The trial will be conducted by members of our study team and colleagues in the Departments of Anesthesiology, Emergency Medicine, Internal Medicine, Critical Care Medicine, and Surgery, in close collaboration with the Department of Pharmacy. The study will be done exclusively at Parkland Hospital. A provisional list of collaborators and co-investigators is listed on Page 1 of this protocol, and provisional liaison assignments are listed in Appendix 2. The liaisons will help orient their colleagues to the study and study procedures.

Figure 5 shows a block diagram of the flow of patients through the study. Eligible patients will be identified by the participating medical teams (anesthesia team, emergency department, critical care medicine, surgery). Patients will be screened and enrolled by two teams: The Anesthesia Code Team (ACT) and/or the Emergency Department (ED). Pre-randomized envelopes will be included in the emergency airway medication boxes used by the Anesthesia Code Team and the Emergency Department. Alternatively, these pre-randomized envelopes will be immediately available to the aforementioned teams. These envelopes will have inclusion and exclusion criteria printed on the outside. Immediately before administering a sedative medication, the randomization envelope will be opened, and this will determine which drug a patient receives (either etomidate, n=375 patients, or ketamine, n=375 patients). Standard doses of these drugs will be recommended to the treating medical teams (etomidate 0.2-0.3 mg per kg intravenous, ketamine 1-2 mg per kg intravenous). Other therapies, including vasopressors, paralytic agents and other adjunctive agents will be at the discretion of the treating medical and surgical teams. Following randomization, study data will be gathered remotely through the EPIC

[redacted]

Electronic Medical Record. The only subsequent patient contact will involve post-randomization notification of study enrollment, which is discussed below in Appendix 5.

5. Study Procedures:

Figure 5 shows a simplified block diagram for how the study will be conducted. Individual patients who are in need of emergency endotracheal intubation will be identified by the treating medical or surgical teams, many of whom are co-investigators on this project. For patients in the Emergency Department (ED), the ED team will screen, randomize and enroll the patient. For patients elsewhere in Parkland Hospital, the Anesthesia Code Team (ACT) will screen, randomize and enroll the patient. The ACT and ED teams will have access to the study randomization envelopes and drug boxes. The drug boxes are already in use by the ACT and ED teams. Randomizing a patient in the study will involve opening a pre-printed envelope that will be included with the emergency medication boxes, or will be immediately available to the ACT or ED teams. The envelopes will have printed inclusion criteria (Section 7) and exclusion criteria (Section 8) on the outside to facilitate rapid and accurate screening of patients. The envelopes will contain a card that indicates which drug the patient should receive for sedation (etomidate or ketamine). Recommended doses of these medications will be printed as well (etomidate 0.2-0.3 mg / kg intravenous, ketamine 1-2 mg / kg intravenous). All other medical and surgical management will be at the discretion of the treating team.

Following randomization the ACT or ED team will notify the Principal Investigator by secured internal email or telephone / pager call regarding enrollment of the patient. The study team will conduct the remainder of the study retrospectively by extracting information from the EPIC Medical Record system to fulfill the primary and secondary endpoints of the study. The study will have no impact on the patient's medical or surgical management, or subsequent care,

[redacted]

beyond the initial choice of sedative agent. Formal notification of study enrollment, in accord with U.S. Food and Drug Administration regulations, will be performed by the PI and / or Co-Investigators. A final, written report(s) of the study results will be published in an open, public forum. No Protected Health Information (PHI) will be disclosed. The written report(s) will include results of the primary and secondary endpoints, in addition to study methodology. We will likely also publish an assessment of our Community Notification Plan (Appendix 5).

6. Sub-Study Procedures:

None.

7. Criteria for Inclusion of Subjects:

A) Adult patient requiring emergency endotracheal intubation at Parkland Memorial Hospital.

8. Criteria for Exclusion of Subjects:

A) Children (<18 years old).

B) Women who are known to be pregnant.

C) Any patient who has been previously randomized in the EvK Trial.

D) Patients who require endotracheal intubation without sedative medication. For example, patients in full cardiac arrest.

E) Patients with a known allergy to ketamine or etomidate.

F) Any individual wearing a MedAlert bracelet indicating that he/she has formally opted out of the EvK trial. These bracelets are discussed below.

9. Sources of Research Material:

The EvK Trial will be conducted at Parkland Memorial Hospital. The physical location of patient enrollment in this trial will include any location in Parkland Memorial Hospital where

[redacted]

patients require emergency endotracheal intubation, including the hospital floors (medical and surgical), specialty and sub-specialty areas, operating rooms, procedural areas, emergency department, intensive care units, and elsewhere in Parkland Memorial Hospital. The sources of research material are the patient lists maintained and used by the supervising medical and surgical teams. After enrollment in the EvK Trial, data will be gathered retrospectively through the EPIC electronic medical records system. No new clinical data will be generated in the patient's chart, other than documentation related to notification of study enrollment, which is mandated by the FDA. Eligible patients will be identified by the treating medical and surgical teams who are collaborating in the EvK Trial (see Page 1 and Appendix 2), as well as their colleagues who have been briefed on trial procedures, inclusion/exclusion criteria, and other aspects of the trial. An initial list of list of Co-Investigators is included on the front page of this protocol, and a list of study liaisons is attached in Appendix 2. The final list of Co-Investigators is likely to include additional individuals who work at Parkland Memorial Hospital and are employed by either Parkland Memorial Hospital or UT-Southwestern Medical Center.

10. Recruitment Methods and Consenting Process:

Study subjects will be recruited by the supervising medical and surgical teams, including the Anesthesia Code Team. Eligible patients will be screened using the inclusion and exclusion criteria. The patients enrolled in the study may include individuals under the direct care of the study investigators. For this clinical trial it is not possible to obtain written informed consent prior to patient enrollment. The U.S. Food and Drug Administration (FDA) published regulations regarding this type of research. These regulations are available in FDA 21 CFR 50.24. We will formally request to waive pre-enrollment consent. Based on FDA 21 CFR 50.24, we have crafted a comprehensive Community Consultation Plan and Post-Enrollment Notification Plan, which is

[redacted]

attached in Appendix 5. For participants who are screened but found not eligible for the study: No data will be collected on these individuals. For participants who are screened and then enrolled in the study: The essential documents will be filed with each individual's research file, which will be maintained in secure storage.

11. Potential Risks:

The principal medical risks of this study relate to the side effect profiles of ketamine and etomidate. Both etomidate and ketamine are standard-of-care medications for emergency endotracheal intubation (Jabre et al., 2009). Each drug does have the potential for side effects, which include the effects listed below.

Common adverse reactions to etomidate

A) Transient venous pain on injection

B) Transient skeletal movements

C) Hypoventilation

D) Hypertension (uncommon) or hypotension (uncommon). Significant changes in blood pressure are relatively uncommon with etomidate.

E) Nausea and/or vomiting

F) Suppression of adrenal function

Common Adverse reactions to Ketamine

A) Hallucinations, delirium

B) Hypertension (more common, tends to be relatively minor changes) or hypotension (rare)

C) Hypoventilation

D) Tachycardia (usually minor)

E) Nystagmus (involuntary eye movements)

[redacted]

As with any clinical research trial, there is a risk of loss of privacy with this study. We have a comprehensive strategy to mitigate that risk. That strategy is discussed below in Section 13.

12. Subject Safety and Data Monitoring:

Study oversight will include a Data Safety and Monitoring Board (DSMB). The DSMB will include specialists from several different specialties including anesthesiology, critical care medicine, surgery and pharmacy (Appendix 2). The DSMB will meet quarterly or monthly as needed to review all patient enrollments. If necessary the DSMB will meet more often than that to review specific study subjects. All study subjects will be reviewed by the DSMB for any study-related adverse outcomes. A written record of DSMB meetings will be generated. The IRB will be notified in writing of any adverse study-related outcomes, using the existing IRB reporting forms.

13. Procedures to Maintain Confidentiality:

Study data will be collected and stored at Parkland Memorial Hospital. Dr. [redacted] office in the Department of Anesthesiology will serve as the central node of the study. Her office is locked, and a locked storage cabinet will be used to store study-related materials. Her office is New Parkland Hospital, Rm# [redacted].

While the study is ongoing, electronic study data will be stored on a password-protected laptop computer, and on a password-protected flash drive(s). Study data itself will be maintained on a Microsoft spreadsheet file(s) that are maintained on secured computer devices, and on handwritten worksheets. The spreadsheet itself will include the study subject's medical record number and birthdate, along with other data relevant to the primary and secondary study endpoints. The study worksheets will include a patient demographic sticker. Appendix 3 contains

[redacted]

a sample data collection spreadsheet. Appendix 4 contains a sample study worksheet. These worksheets will be used to ensure proper follow-up with each study subject. Each subject will be given a study number, for example Subject001. Prior to public disclosure of data (for example publication of study results), all protected health information including medical record number and birthdate will be removed. For the sake of posterity, a confidential file will be maintained that links subject number to medical record number. This information will not be disclosed publicly. Study data will also be stored on a secured RedCap Database, a sample of which appears in Appendix 3.

Paper records that are generated during the study will include individual study subject worksheets (Appendix 4) which we will retain in secure storage, and also formal notification letters that will be placed in the medical record and/or mailed to enrolled patients and/or their families or next of kin (Appendix 13 and 14). Other paper documentation will include records of DSMB meetings. Paper records will be stored temporarily in [redacted] office in the locked storage cabinet.

Long-term storage of study data and forms will be in the Department of Anesthesiology storage locker. This locker is located [redacted]. The locker is climate controlled. The physical address is [redacted]. The key to the storage locker is maintained in the lock box in the Chairperson's Office Suite. This locker is used for long-term storage of clinic records, confidential files and other sensitive documents. We have used this storage locker for long-term storage of other research documents (with IRB approval). Once the mandatory storage time has elapsed (historically 6 years), study records will be destroyed.

[redacted]

The research team will have access to the study records and data. No one outside the research team will have access to protected health information, with the exception UT-Southwestern IRB, Parkland Hospital OCR, and any applicable state and federal oversight agencies. We anticipate publishing the results of our study in a medical or scientific journal, and/or on the internet. Anonymous study data, for example survival curves, study outcomes, and anonymous demographic data will be published as part of the report of study results. No PHI will be disclosed. We will also publish our methodology, including the methodology used for emergency research (Appendix 5). There will likely be several publications that arise from this research project.

14. Potential Benefits:

The purpose of this study is to define which agent, etomidate or ketamine, is associated with a greater chance of survival after emergency endotracheal intubation. We believe that the increase in the usage of ketamine that will happen as a result of this study is likely to benefit the patients at Parkland Hospital directly. In our recent QA/ QI project of emergency endotracheal intubations done by the Anesthesia Code Team (ACT) we found that etomidate is commonly used for sedation during this procedure. Propofol is also relatively commonly used by the ACT. However, in our review of cases we found that etomidate seems to be associated with lower long-term survival compared to other agents (Figure 3). In our QA/QI project we also observed that propofol is associated with the phenomenon of immediate post-administration cardiac arrest, more than any other sedative agent. Thus, we believe that increase in usage of ketamine that will happen as a result of this study is likely to benefit the patients at Parkland Hospital directly. There are many other potential benefits to patients outside the study, and to society in general. Presently etomidate is frequently used for emergency intubation, locally, nationally and

[redacted]

internationally. The EvK Trial may clarify if this practice is best for patients, or if the use of etomidate should be restricted.

15. Biostatistics:

The study is designed and powered to have 80% power with 0.05 level of significance to detect a 10% difference in proportions survived at 7-days post endotracheal intubation. Based on the data from our QA/QI project, the proportions of patients survived are assumed to be 85% and 95% for the etomidate and ketamine groups, respectively. With these assumptions, n = 750 patients (etomidate n=375, ketamine n=375) will be needed to have 80% power. Assuming a 10% screen failures (individuals who were randomized, but then never intubated for clinical reasons), we anticipate n = 825 will be needed.

Study subjects will be analyzed in an "intent to treat" manner regardless of what agent(s) they receive, as long as they receive an induction agent and are intubated. The primary hypothesis of no – difference in proportions survived at 7 days post-intubation will be tested using a chi-square test for proportions. Results for the primary study aim will be summarized as p-value and 95% confidence interval for difference in proportions survived. Chi-square tests, Fisher's exact test, Student's t-test and log-rank test will be used to test hypotheses related to secondary end-points. All analyses will be done with a 0.05 level of significance.

Using data from a recent QA/QI project, we estimate that the Anesthesia Code Team performs approximately 34 emergency endotracheal intubations per month, or approximately 400 per year. [redacted], our collaborator in the Emergency Department, has estimated that the emergency department performs approximately 10-20 emergency endotracheal intubations per month, or approximately 120 per year. In the operating rooms and related procedural areas, we estimate that the department of anesthesia performs approximately 10-20 emergency endotracheal intubations per month, or approximately 120 per year. These number combined could provide approximately 640

candidate patients that could be enrolled per year. We estimate that it will take up to three years to reach a goal of 750 patients enrolled in the study. At the mid-way point of the study, an interim analysis will be performed to assess futility using O'Brien-Fleming approach.

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[redacted]

Figure 1: Quality Assessment / Quality Improvement (QA/QI) data from emergency endotracheal intubations performed by the Anesthesia Code Team (ACT) at Parkland Memorial Hospital over the last calendar year (July 2014 – May 2015). June 2015 is omitted. The ACT performs, on average, 34 emergency endotracheal intubations each month.

[redacted]

Figure 2: Quality Assessment / Quality Improvement (QA/QI) data from emergency endotracheal intubations performed by the Anesthesia Code Team (ACT) at Parkland Memorial Hospital over the last calendar year (July 2014 – May 2015). June 2015 is omitted. The ACT frequently uses etomidate for emergency endotracheal intubations. This is consistent with local and national standards of care. Prior reports have suggested etomidate is used approximately 60% of the time for emergency endotracheal intubation.

[redacted]

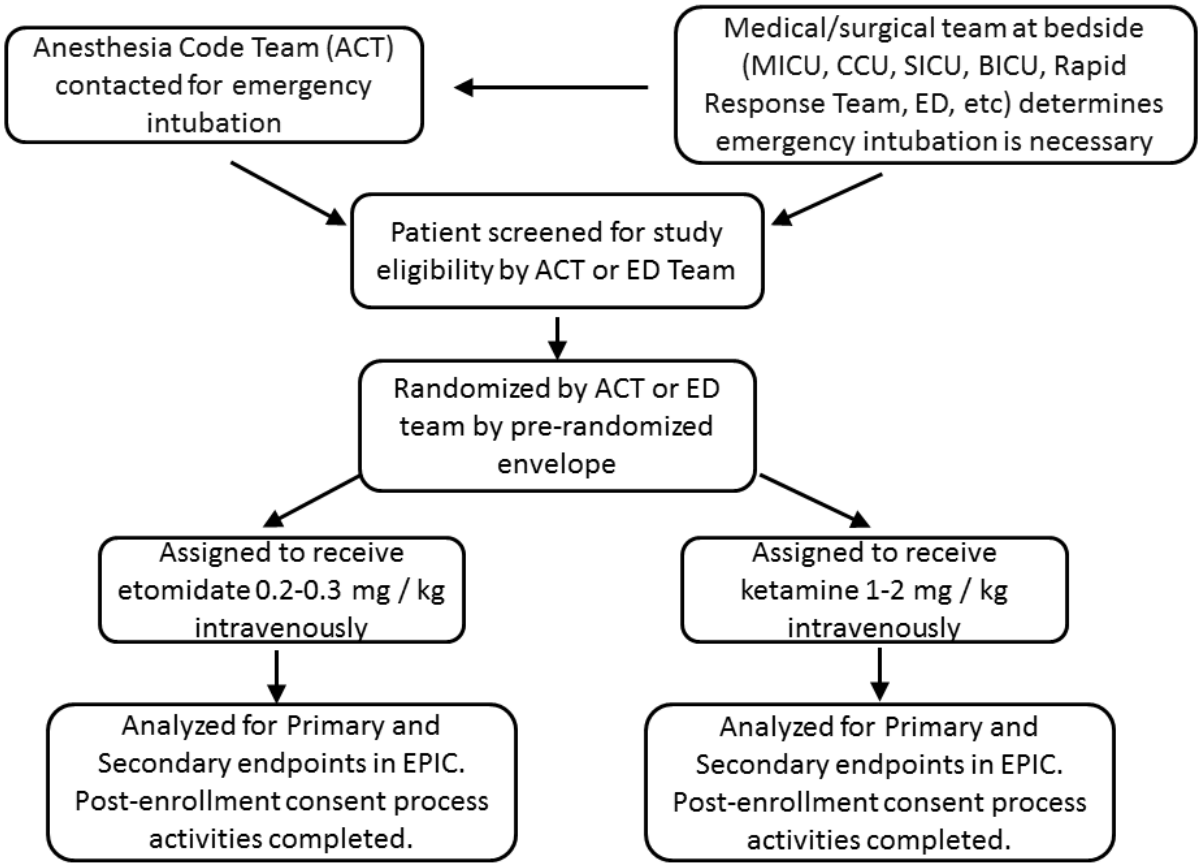
Figure 3: Quality Assessment / Quality Improvement (QA/QI) data from emergency endotracheal intubations performed by the Anesthesia Code Team (ACT) at Parkland Memorial Hospital over the last calendar year (July 2014 – May 2015). June 2015 is omitted. Etomidate is associated with lower rates of survival in both historical time periods analyzed.

[redacted]

Figure 4: Quality Assessment / Quality Improvement (QA/QI) data from emergency endotracheal intubations performed by the Anesthesia Code Team (ACT) at Parkland Memorial Hospital from July – December 2014. Sequential Organ Failure Assessment (SOFA) scores, segregated by type of sedative medication used for emergency endotracheal intubation. Higher SOFA scores are associated with lower predicted survival. The mean initial SOFA scores in patients receiving etomidate are only slightly higher than those receiving propofol, suggesting that the starting health status in this analysis is similar. Patients receiving no drug for sedation (for example, patients in cardiac arrest), have substantially higher SOFA scores. (S.D. = Standard Deviation).

[redacted]

Figure 5: Proposed Study Workflow



[redacted]

Appendix 1: Primary and Secondary Endpoints

Primary Endpoint
Survival at Day 7 following emergency endotracheal intubation

Secondary Endpoints
Survival at 28 days following emergency endotracheal intubation
Sequential Organ Failure Assessment (SOFA) scores
Immediate outcomes of endotracheal intubation
Duration of mechanical ventilation
Duration of catecholamine therapy
Length of stay in ICU / hospital
New diagnoses (for example, a diagnosis of adrenal insufficiency)

[redacted]

Appendix 2: Provisional Study Liaison Assignments

Data / Informatics Security and Storage Liaison
[redacted]

Dept. of Anesthesiology – MD Liaisons
[redacted]

Dept. of Anesthesiology – CRNA Liaisons
[redacted]

Dept. of Emergency Medicine Liaisons
[redacted]

Dept. of Internal Medicine / Critical Care Medicine Liaison
[redacted]

Dept. of Surgery Liaisons
[redacted]

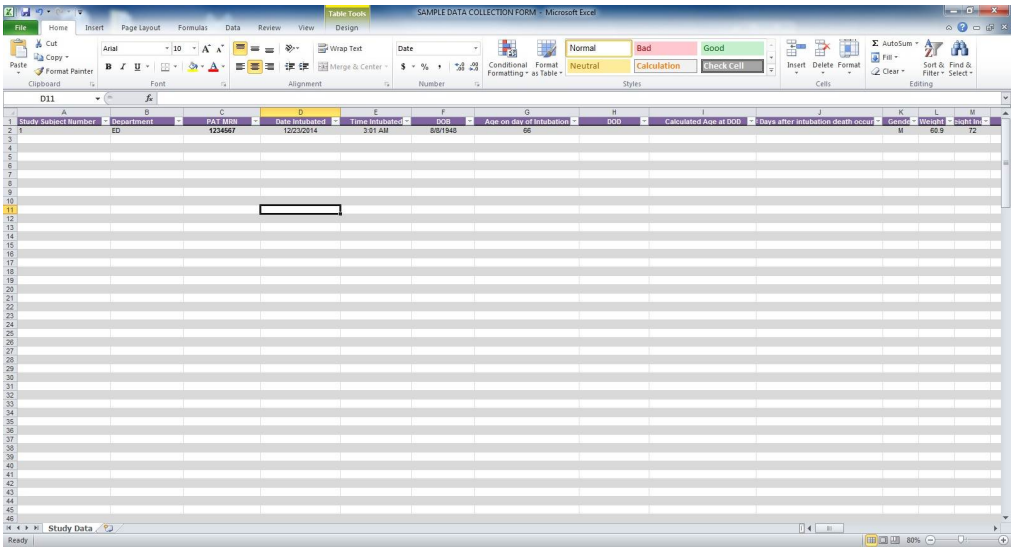
Parkland Hospital Pharmacy Liaisons
[redacted]

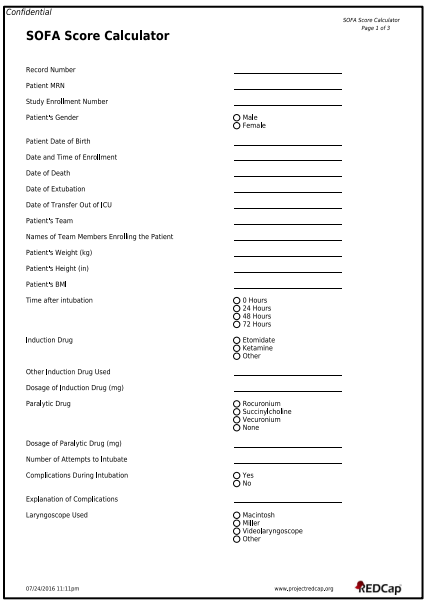
Statistical Design and Oversight
[redacted]

Data Safety and Monitoring Board (DSMB)
[redacted]

[redacted]

Appendix 3: Draft Data Collection Form (Excel Top, RedCap Bottom)





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SOFA Score Calculator

Page 1 of 3

SOFA Score Calculator

Record Number

Patient MRN

Study Enrollment Number

Patient's Gender
- Male
- Female

Patient Date of Birth

Date and Time of Enrollment

Date of Death

Date of Extubation

Date of Transfer Out of ICU

Patient's Team

Names of Team Members Enrolling the Patient

Patient's Weight (kg)

Patient's Height (in)

Patient's BMI

Time after intubation
- 0 Hours
- 24 Hours
- 48 Hours
- 72 Hours

Induction Drug
- Etomidate
- Ketamine
- Other

Other Induction Drug Used

Dosage of Induction Drug (mg)

Paralytic Drug
- Rocuronium
- Succinylcholine
- Vecuronium
- None

Dosage of Paralytic Drug (mg)

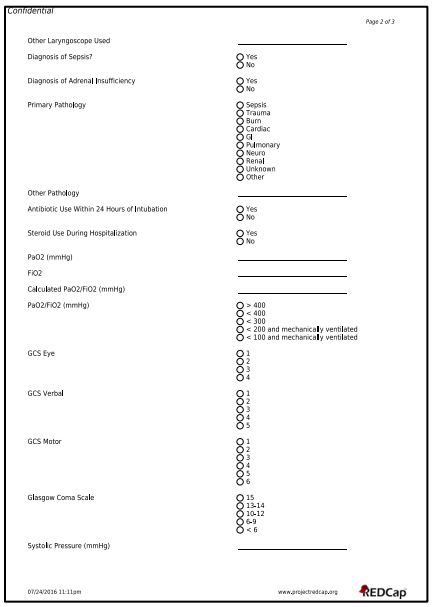
Number of Attempts to Intubate

Complications During Intubation
- Yes
- No

Explanation of Complications

Laryngoscope Used
- MacIntosh
- Miller
- Videolaryngoscope
- Other

07/24/2016 11:11pm www.projectredcap.org REDCap



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Other Laryngoscope Used

Diagnosis of Sepsis?
- Yes
- No

Diagnosis of Adrenal Insufficiency
- Yes
- No

Primary Pathology
- Sepsis
- Trauma
- Burn
- Cardiac
- GI
- Pulmonary
- Neuro
- Renal
- Unknown
- Other

Other Pathology

Antibiotic Use Within 24 Hours of Intubation
- Yes
- No

Steroid Use During Hospitalization
- Yes
- No

PaO2 (mmHg)

FiO2

Calculated PaO2/FiO2 (mmHg)

PaO2/FiO2 (mmHg)
- > 400
- < 400
- < 300
- < 200 and mechanically ventilated
- < 100 and mechanically ventilated

GCS Eye
- 1
- 2
- 3
- 4

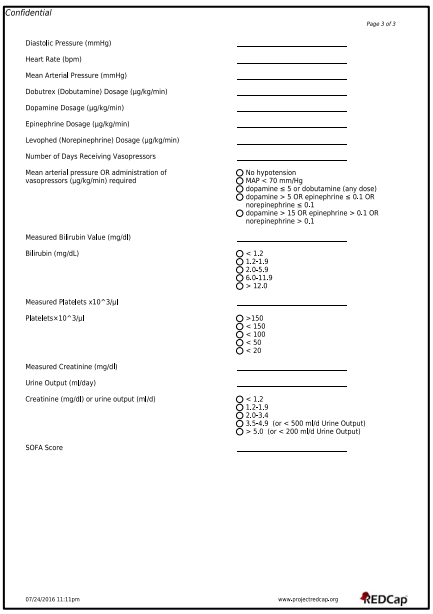
GCS Verbal
- 1
- 2
- 3
- 4
- 5

GCS Motor
- 1
- 2
- 3
- 4
- 5
- 6

Glasgow Coma Scale
- 15
- 13-14
- 10-12
- 6-9
- < 6

Systolic Pressure (mmHg)

07/24/2016 11:11pm www.projectredcap.org REDCap



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Diastolic Pressure (mmHg)

Heart Rate (bpm)

Mean Arterial Pressure (mmHg)

Dobutrex (Dobutamine) Dosage (µg/kg/min)

Dopamine Dosage (µg/kg/min)

Epinephrine Dosage (µg/kg/min)

Levophed (Norepinephrine) Dosage (µg/kg/min)

Number of Days Receiving Vasopressors

Mean arterial pressure OR administration of vasopressors (µg/kg/min) required
- No hypotension
- MAP < 70 mmHg
- dopamine ≤ 5 or dobutamine (any dose)
- dopamine > 5 OR epinephrine ≤ 0.1 OR norepinephrine ≤ 0.1
- dopamine > 15 OR epinephrine > 0.1 OR norepinephrine > 0.1

Measured Bilirubin Value (mg/dl)

Bilirubin (mg/dL)
- < 1.2
- 1.2-1.9
- 2.0-5.9
- 6.0-11.9
- > 12.0

Measured Platelets x10^3/µl

Platelets×10^3/µl
- >150
- < 150
- < 100
- < 50
- < 20

Measured Creatinine (mg/dl)

Urine Output (ml/day)

Creatinine (mg/dl) or urine output (ml/d)
- < 1.2
- 1.2-1.9
- 2.0-3.4
- 3.5-4.9 (or < 500 ml/d Urine Output)
- > 5.0 (or < 200 ml/d Urine Output)

SOFA Score

07/24/2016 11:11pm www.projectredcap.org REDCap

[redacted]

Appendix 4: Draft Study Worksheet.

Patient Name / MRN or Sticker

1. Study Number ___Subject#_____

2. Date / Time Enrolled: _____

3. Enrolling Team (names): _____

4. Agent Randomized To (circle): Etomidate Ketamine. Dose_____mg

5. Date 1st Attempt of Notification: _____. Method: Bedside Phone. Initials:_____
Notes:

6. Date 2nd Attempt of Notification:_____. Method: Bedside Phone. Initials:_____
Notes:

7. Date 3rd Attempt of Notification: _____. Method: Bedside Phone. Initials:_____
Notes:

8. If the patient is deceased, send Next-of-Kin Letter. Date:_____. Initials:_____

9. If the patient is alive, send Last-known-Address Letter. Date:_____. Initials:_____

10. Date of Data Safety and Monitoring Board Review:_____

11. Study-Related Adverse Outcome? Yes No

Notes:

12. I affirm that Study Enrollment Notification and DSMB Review are now COMPLETE.

Name, Signature and Date _____

[redacted]

Appendix 5: Community Consultation Plan and Post-Enrollment Notification Plan

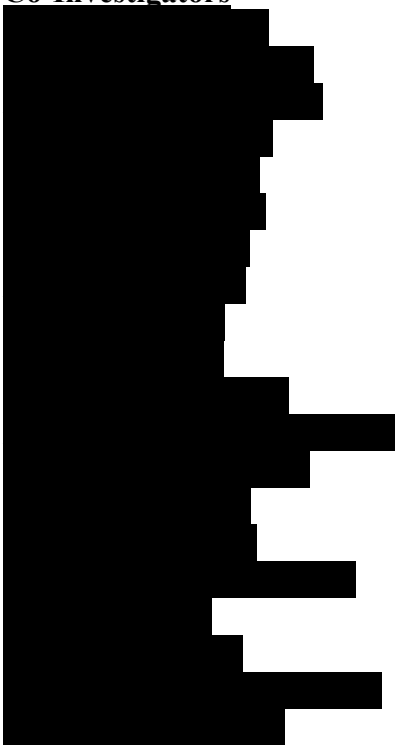
Community Consultation Plan for the EvK Trial*

**Etomidate versus ketamine for emergency endotracheal intubation: a prospective randomized clinical trial*

Principal Investigator

Gerald Matchett, MD
UT-Southwestern Dept. of Anesthesiology
5323 Harry Hines Blvd, MC 9068
Dallas, TX 75390-9068

Co-Investigators



Technical Consulting

[redacted]

[redacted]

Executive Summary

The EvK Trial will be conducted at Parkland Memorial Hospital by investigators in the Departments of Anesthesiology, Emergency Medicine, Medicine / Critical Care Medicine, Surgery, Pharmacy and Clinical Science. The study will randomize critically ill patients who require emergency endotracheal intubation to one of two groups: Etomidate or Ketamine. Because of the nature of this study – an emergency procedure on a critically ill patient – the study will require formal permission to bypass pre-enrollment written informed consent. The purpose of this Community Consultation Plan is to fulfill the community consultation requirements of the U.S. Food and Drug Administration Title 21 Code of Federal Regulations Section 50.24 (hereafter "FDA 21 CFR 50.24"), which governs research in emergency medical conditions. The Community Consultation Plan outlined in this document fulfills FDA 21 CFR 50.24 by outlining a plan to notify community leaders and the public at-large about this research study, provisions for study opt-out, and provisions for notification of study enrollment. This plan is based on FDA 21 CFR 50.24, and published expert recommendation (Holsti et al., 2015; Salzman et al., 2007).

Background and Rationale for a Community Consultation Plan

The EvK Trial is a study of the medications given to patients who require emergency endotracheal intubation. Study subjects will be randomized to receive one of two drugs immediately prior to emergency endotracheal intubation: etomidate or ketamine. Both etomidate and ketamine are currently standard-of-care for this procedure. Each drug has unique side effects. The EvK Trial will test the hypothesis that ketamine is associated with higher rates of survival after emergency endotracheal intubation. The proposed mechanism of this effect is that ketamine does not affect the adrenal glands, and therefore is safer for patients requiring

emergency endotracheal intubation. Etomidate is known to inhibit normal function of the adrenal glands, and may thereby be associated with lower survival rates.

Traditional medical research that involves human subjects is conducted with written informed consent prior to study enrollment. The rationale for obtaining written informed consent is to ensure that a patient who enrolls in the study fully understands the risks and benefits of participation in the study, and has been given an opportunity to have his/her questions answered. Written informed consent is a standard part of non-emergency research that involves human subjects. The requirement for pre-enrollment written informed consent is problematic for research studies that involve emergency medical care (Holsti et al., 2015; Salzman et al., 2007). In emergency situations it may be impractical or impossible to obtain proper written informed consent prior to treatment intervention(s). The U.S. Food and Drug Administration (FDA) has published guidelines for research that involves emergency medical care (FDA 21 CFR 50.24).The FDA has determined that pre-enrollment written informed consent *may be waived* for studies of emergency medical care, provided the stipulations outlined in FDA 21 CFR 50.24 are met. The EvK Trial qualifies to be conducted without pre-enrollment consent outlined in FDA 21 CFR 50.24 because it meets the following requirements:

I. The human subjects are in a life-threatening situation that necessitates urgent intervention.
II. Available treatments are unproven or unsatisfactory.
III. Collection of valid scientific evidence is necessary to determine the safety and effectiveness of the intervention.
IV. Obtaining informed consent is not feasible because the subjects are not able to give their informed consent as a result of their medical condition.

[redacted]

V. The intervention must be administered before consent can be obtained from the subject's legally authorized representative.

VI. There is no reasonable way to identify prospectively individuals likely to become eligible for participation.

VII. Participation in the research holds out the prospect of direct benefit to the subjects.

VIII. The clinical investigation could not practically be carried out without the waiver.

FDA 21 CFR 50.24 mandates that the following stipulations must be met for qualified research done under emergency conditions without pre-enrollment written informed consent:

I. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn.

II. Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits.

III. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results.

IV. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation.

V. If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's

[redacted]

participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

The purpose of this document is to outline the strategy for meeting requirements I-V. Prior to implementing any Community Consultation Plan we will obtain approval from the institutional review board. Appendix 6 lists a proposed timeline of outreach events for the EvK Trial. Appendix 7 shows a graphical representation of our proposed outreach plan. Appendix 8 lists more than 300 individuals and organizations that we will contact. This list was formulated based on local and regional governmental structure, and guided by 2010 census data detailing demographic information for the Dallas-Fort Worth area and published expert recommendations (Holsti et al., 2015; Salzman et al., 2007). Community outreach will be conducted bilingually (English and Spanish), reflecting the two most commonly used languages in Dallas-Fort Worth and in Parkland Hospital. Appendix 9 shows a draft letter Outreach to Community Leaders. Appendix 10 shows a draft EvK Clinical Trial Website. Appendix 11 shows a draft newpaper advertisement. Appendix 12 shows a draft flyer / poster advertisement. Appendices13 and 14 provide draft documentation related to post-enrollment notification to patients who have been enrolled in the study.

Section I. Consultation with community representatives and receipt of feedback

Initial community consultation will involve outreach to individuals who represent the larger population from which potential research candidates may be drawn. Community consultation will involve direct outreach to municipal, county and federal governmental officials, spiritual and other community leaders, media representatives, medical community representatives, and Parkland Hospital leadership. Direct outreach to these individuals (or their

[redacted]

representatives) will be made in writing. Appendix 8 contains a list of community leaders who will be invited to the initial outreach meeting. We plan to invite more than 300 individuals and organizations to the community meetings. This number compares favorably to prior reports of community notification plans, for example Salzman et al., 2007. In Salzman et al., 2007, a total of 127 individuals and organizations were invited to meetings, for a population zone of approximately 3.8 million (Minneapolis-St. Paul, the "Twin Cities"). We plan to invite more than 300 individuals and organizations for a population zone of approximately 6.5 million (Dallas-Fort Worth). In in addition to a formal meetings, the EvK Trial research team will also be available to meet with community leaders and community members on an as-needed basis. Appendix 9 shows a draft letter that will be sent to community leaders.

An initial outreach meeting will be scheduled with the aforementioned individuals or their representatives in Appendix 8. The background and rationale for the clinical trial will be discussed. The clinical trial feedback mechanisms will be presented. A written report of this meeting will be generated and sent to the UT-Southwestern IRB and the Parkland Memorial Hospital CRO.

EvK Trial Feedback Mechanisms

There will be multiple avenues for feedback during the community outreach prior to the start of enrollment. The web-based feedback mechanisms will continue for the duration of the study.

1. Telephone hotline and opt-out: 214-TBD-TTBD
2. Standard Mail: Dept. of Anesthesiology & Pain Management, University of Texas-Southwestern Medical Center MC 9068, 5323 Harry Hines Blvd, Dallas, TX 75390-9068

3. Email: tbd@evkclinicaltrial.org
4. Web-Site (online feedback form): www.evkclinicaltrial.org (or similar, yet to be established). A Spanish language version of this website will be created.

EvK Trial Opt-Out Provision

Any member of the community who wishes to "opt-out" of any possibility of participation in this clinical trial will be given a MedAlert bracelet. This will be provided free of charge. Individuals within the catchment area of Parkland Memorial Hospital wishing to formally opt-out may do so through the aforementioned feedback mechanisms.

General content of community notification (including meetings, advertisements, website)

The content presented in Section I will include broad information about the rationale, design, background and study procedures of the EvK Trial. Information will be available in both English and Spanish. Specific items to be presented / discussed include the following:

1. What is emergency endotracheal intubation, and why patients need emergency endotracheal intubation.
2. Current practices for emergency endotracheal intubation, locally and nationally
3. Background information for which drugs are commonly used for emergency endotracheal intubation, and the risks/benefits of common drugs.
4. An explanation of the EvK Trial study protocol
5. An explanation for why we cannot gain written informed consent prior to enrolling / randomizing patients in this trial
6. Contact information (feedback mechanisms above)

Section II. Public notification and receipt of feedback

[redacted]

FDA 21 CFR 50.24 mandates that the public be notified directly of the EvK Trial. This notification will be done using a three-pronged approach: Direct outreach by community meetings, formal advertising and press release in traditional media, posters and / or flyers, and formal advertising in online media. This outreach will be done bilingually (English and Spanish), which reflects the two most-common languages spoken at Parkland Memorial Hospital. Direct community outreach and notification will be guided by the geographic catchment area of Parkland Memorial Hospital. Generally this is Dallas County.

1. Direct Outreach to the Community

   Two community meetings will be scheduled prior to the start of the EvK Trial. There will be bilingual information at each meeting (English and Spanish). These meetings will be advertised through local news media, and through the study website (www.evkclinicaltrial.org, or similar, yet to be established). A draft version of the website is included in Appendix 8. The public at-large will be offered a chance to hear about the study and have their questions answered. A formal written report of these meetings will be generated and sent to the UT-Southwestern IRB and Parkland Hospital CRO. In in addition to a formal sit-down meeting, the EvK Trial research team will be available to meet with community leaders and members on an as-needed basis.

   There are several additional avenues of community outreach that may be pursued: Additional outreach may be conducted in conjunction with leadership of the Parkland Hospital COPCs. The Parkland Hospital COPCs have Advisory Groups that may be recruited to help facilitate outreach to the community about the study. Similarly, the UT-Southwestern Center for Patient Centered Outcomes Research has a Community Advisory Panel that may be contacted to help with dissemination of information about

the study. Finally, the UT-Southwestern Community Research Registry (a shared resource of the Center for Translational Medicine) maintains a database of community volunteers who are non-patients, but have agreed to be contacted about research projects. Pending budget and availability this database may be enlisted to help with dissemination of information.

2. Formal advertising in traditional media

The EvK Trial will be advertised by one print advertisement in the Dallas Morning News, and in Al Dia Dallas, one of the local Spanish language publications. The advertisement will list the study website and feedback mechanisms listed above, and will likely appear in both the print and online version of the newspapers. The advertisement will notify the public of the community meetings. A draft advertisement is provided in Appendix 11. Additionally, [redacted], the Senior Vice President of Communications & External Relations at Parkland Memorial Hospital has offered to allow the EvK Trial to participate in some of the local advertising that Parkland Memorial Hospital already does through other local newspapers, budget and space permitting. These newspapers include the Dallas Weekly, Dallas Examiner, El Heraldo News, Dallas Voice, and Southern Dallas Magazine. A formal written report of these efforts will be generated and sent to the UT-Southwestern IRB and Parkland Hospital CRO.

3. Formal advertising in online media

The EvK Trial and study website will be advertised via google charge-per-click advertising. These ads will direct the user to the study website, which will provide a feedback mechanism listed above. The online advertising will continue as long as the study is actively enrolling patients. These advertisements will be directed to the

geographic catchment area of Parkland Hospital. Charge-per-click advertising will be conducted in both English and Spanish. Additional online media outreach and / or advertising will include establishment of a Facebook® page for the trial, and a Twitter® page for the trial. A draft of the study website is provided in Appendix 8. The online community outreach portions of this protocol are guided by recent published reports that support the utility, generally speaking, of online outreach efforts (Bond et al., 2012; Ryan 2012; Broockman and Green 2013). Additional outreach efforts will include a notification submission to the Parkland Memorial Hospital website (www.parklandhospital.com), and a similar submission to the UT-Southwestern Medical Center website (www.utsouthwestern.edu), and a submission to the weekly "Campus Update" email newsletter.

EvK Trial Feedback Mechanisms

There will be multiple avenues for feedback during the community outreach prior to the start of enrollment. The web-based feedback mechanisms will continue for the duration of the study.

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4. Web-Site (online feedback form): www.evkclinicaltrial.org (or similar, yet to be established). A Spanish language version of this website will be created.

EvK Trial Opt-Out Provision

[redacted]

Any member of the community who wishes to "opt-out" of any possibility of participation in this clinical trial will be given a MedAlert bracelet. This will be provided free of charge. Individuals within the catchment area of Parkland Memorial Hospital wishing to formally opt-out may do so through the aforementioned feedback mechanisms.

General content of community notification (including meetings, advertisements, website)

The content presented to in Section I will include broad information about the rationale, design, background and study procedures of the EvK Trial. Information will be available in both English and Spanish language versions. Specific items to be presented / discussed include the following:

1. What is emergency endotracheal intubation, and why patients need emergency endotracheal intubation.
2. Current practices for emergency endotracheal intubation, locally and nationally. Specifically which drug(s) are commonly used for this procedure.
3. Background information for which drugs are commonly used for emergency endotracheal intubation, and the risks/benefits of common drugs.
4. An explanation of the EvK Trial study protocol.
5. An explanation for why we cannot gain written informed consent prior to enrolling / randomizing patients in this trial.
6. Contact information (feedback mechanisms above).

Assessment of Feasibility of Providing In-Hospital Handouts to Elective Hospital Admission patients and ED patients regarding the study

We assessed the feasibility of providing a handout to every single ED patient and hospital patient as a means of providing broad notification about the study, with contact number for

[redacted]

questions, to provide an indication of the willingness of subjects at-risk for emergency intubation to participate in the study. In theory it would be good to identify patients at high-risk for needing emergency intubation. However, we believe that it is very difficult to identify a group of patients who are stable enough on admission to read and comprehend a form, but who are at subsequent risk of being intubated. Clinically speaking we believe that this group of patients is likely to be vanishingly small. What's far, far more common is that a patient comes into the ED in a critically ill "unstable" medical state, in no position to reasonably read and comprehend a form, and shortly thereafter requires emergency intubation. Based on this workflow we do not believe it is feasible to identify and notify patients who are especially at-risk for needing emergency endotracheal intubation.

Assessment of Results of Community Consultation Plan

Throughout the study we will track the results of our Community Consultation Plan. Based on published expert opinion, we estimate that attendance at our community meetings may be approximately10 attendees for every 100 invitations (Salzman et al., 2007) based on direct invitation by mail alone. We will send direct invitation by mail to more than 300 individuals and organizations listed in Appendix 6, which suggests about 30 individual attendees from this effort alone. The print advertisements will appear in Al Dia Dallas (circulation 225,000) and the Dallas Morning News (circulation 400,000) will likely push this number upward, as will the direct outreach to the Parkland Hospital and UT-Southwestern Medical Center communities. Charge-per-click advertising will also likely push the number of attendees upward.

Online charge-per-click advertising through www.google.com will begin prior to patient enrollment, and continue on a continuous basis until enrollment for the study is complete. Google advertising tracks metrics such as "ad impressions," "click through rate," and other

[redacted]

quantitative metrics which we will be able to report in the continuing reviews of this study. Similarly, Facebook and Twitter accounts will offer quantitative metrics that we will report and follow. We will also be able to report total number of website visits to our trial website, provisionally www.evkclinicaltrial.org. We expect that ad impressions through google will number in the hundreds or thousands over the life of the study, and possibly more than that.

Budget permitting we plan to purse polling of individuals in Dallas County to test the impact of our community outreach, using an approach based on research published previously (Bond et al., 2012; Ryan 2012; Broockman and Green 2013). In constructing the study we evaluated both online and telephone dialing protocol we solicited bids for both online polling and telephone polling. We received written bids from four companies: Google Consumer Surveys, WinningConnections Polling, PremiereReporting Polling, and AAM Political Polling. Telephone polling is outside of our financial means for the study, and so we will focus on online polling.

Internet-based online polling has been validated compared to Random Digit Dialing (RDD) telephone poling in at least one study to date (Chang and Krosnick 2009). Online polling is heavily used in National Science Foundation (NSF)-Funded projects, for example the American National Election Study (http://www.electionstudies.org/). Recent work by the Pew Research Center from 2012 has reported that "Both African Americans and English-Speaking Latinos are as likely as whites to own any sort of mobile phone, and are more likely to use their platform for a wider range of activities (Zikuhr and Smith 2012)." In the opinion of our consulting political scientist [redacted], online survey-based polling without RDD is a reasonable approach for evaluating our CCP (Personal Communication from [redacted] 11/9/2015).

[redacted]

Section III. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study

The EvK Trial will be registered with the US federal government at www.clinicaltrials.gov. Results from the study will be published on that website in accordance with federal law. Additionally, following completion of the EvK Trial, we intend to make our findings publically known through one of the following mechanisms: publishing study results in a medical journal and/or publishing study results in news releases and news reports. The study website (provisionally www.evkclinicaltrial.org) will provide a link to www.clinicaltrials.gov, and will provide links to study results and may list study results directly.

Section IV. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation

The EvK Trial will be overseen by a Data Safety Monitoring Board (DSMB) that is chaired or co-chaired by an individual(s) other than the principal investigator. This committee will meet quarterly or monthly, or more often if needed, to evaluate progress of the study and review individual cases for any adverse study events. Specific items that the DSMB will review include study accrual rate, the global experience of study participants, study attrition rate, patterns of study-related Adverse Events, patterns of protocol deviations and/or violations, and any changes in the risks or benefits of the study. Appendix 2 contains a provisional list of members of the DSMB.

Section V. Subsequent Notification of Patient Enrollment

Per FDA 21 CFR 50.24, investigators must attempt to notify all patients that they have been enrolled in a research study. In the event the patient is unable to comprehend notification,

or is deceased, reasonable attempts at notification of the patient's surrogates, legal guardians or next-of-kin must be made. The EvK Trial will comply with these provisions.

Following enrollment in the study, the study team will assess for the patient's ability to discuss the clinical trail. Given the nature of this study (emergency endotracheal intubation), it is exceedingly unlikely that the patient will be able to participate in any meaningful discussion of research immediately after enrollment. In the rare circumstance that the individual patient is able to participate in a meaningful discussion in a timely way, then the study team will discuss the nature of the research project, its goals and objectives and the study protocols. The study team will give a letter notifying the patient of his/her enrollment into their medical record (Appendix 13). This will be documented in the patient's study worksheet (Appendix 4), and will complete the notification process.

For a large percentage of patients enrolled in this trial, we anticipate that the patients will not be able to have a meaningful discussion about the study immediately after enrollment, and possibly not for many days after enrollment. In this case, the study investigators will attempt to contact the patient's surrogates, legal guardians or next of kin, either in person at the patient's bedside or by telephone. If the aforementioned parties can be reached, the EvK Trial team will discuss the nature of the research project, its goals and objectives and the study protocols. If the family, surrogates, legal guardians or next-of-kin can be reached in person at the bedside or by telephone, the notification process will be considered complete.

If the family, surrogates, legal guardians or next-of-kin cannot be reached in person or by telephone, the EvK Trial team will send a letter to the patient's last known physical address (Appendix 14). The letter in Appendix 13 will be sent in the event that the patient is alive. In the

[redacted]

event that the patient is deceased, the research team will send the letter in Appendix 14. All of this will be documented in the patient's study worksheet on the Study Worksheet (Appendix 4).

During the notification process we will verbally request permission to use the patient's anonymous data. If verbal permission is granted, we will document that. If permission is denied, we will remove the patient's data from the study (from the point of denial of permission onward). Following these efforts, the EvK Trial team will do one of the following:

1. Document successful notification of the patient or family.
2. Document no response from attempts at bedside and telephone contact.

Summary of the Community Notification Plan for the EvK Trial

The EvK Trial is a prospective randomized study that will randomize patients under emergency circumstances to receive either etomidate or ketamine for emergency endotracheal intubation. Because of the nature of emergency intubation, obtaining written informed consent prior to enrollment in the EvK Trial is not possible. In order to comply with current FDA guidelines for non-consented emergency research (FDA 21 CFR 50.24), the Community Consultation Plan in this document presents a broad-based approach to notify community leaders and community members, using traditional media as well as online media and direct community meetings. Patients (or their next-of-kin) enrolled in the EvK Trial will be notified of enrollment in accordance with FDA guidelines. Individuals in the catchment area of Parkland Memorial Hospital who wish to avoid any possibility of participation in the EvK Trial will be given a free MedAlert bracelet indicating that wish.

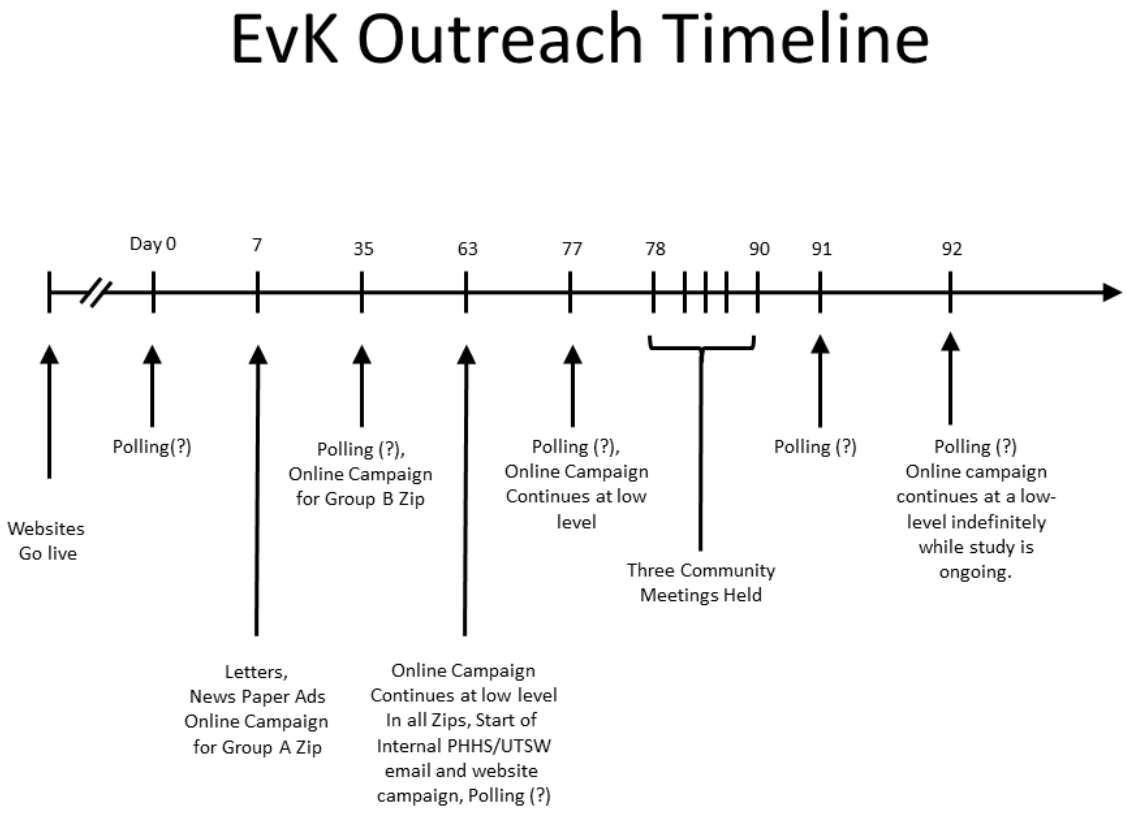
[redacted]

Appendix 6: Provisional Approximate Timeline of Community Consultation Plan Outreach

Start of Campaign: After IRB and Parkland Memorial Hospital CRO approval, the study website www.evkclinicaltrial.org , www.clinicaltrials.gov, Facebook Profile, and Twitter Profile will go live but are silent.
Day 0: Anonymous online polling within the zip-code catchment area (~$600): Sample potential question: *Have you heard of the EvK Clinical Trial at Parkland Hospital Y/N?*
Day 7: Letters go out, Handouts/Posters placed, Newspaper Ads Published, Websites "turned on." Online advertising starts for Zip codes in initial group (Group A)
Day 35: Anonymous online polling within the zip-code catchment area (~$600): Sample potential question: *Have you heard of the EvK Clinical Trial at Parkland Hospital Y/N?* Online advertising starts for Zip codes in secondary group (Group B).
Day 63: Anonymous online polling within the zip-code catchment area (~$600): Sample potential question: *Have you heard of the EvK Clinical Trial at Parkland Hospital Y/N?* Advertising online continues in all zip codes at low level going forward. Start of internal email campaign within UT/ PHHS systems. Internal website ads placed if approved.
Day 77: Anonymous online polling within the zip-code catchment area (~$600): Sample potential question: *Have you heard of the EvK Clinical Trial at Parkland Hospital Y/N?*
Day 78-90: Community & Leader Meetings
Day 91: Anonymous online polling within the zip-code catchment area (~$3000-4500): This may be more comprehensive polling with several questions about knowledge of the study, basic demographic information, measurements of how people feel about the study, measurements of opinion of potential benefit of the study.
Day 92 Onward: A website presence will be maintained, as will online outreach and advertising for the duration of active patient enrollment. The results of these efforts will be reported with CRs. Following the last community meeting, we will gather data from the community outreach, including number of advertising impressions, number of website clicks, metrics from Facebook and Twitter, direct website contacts, and direct data (budget permitting). A detailed report of the results of the will be created and submitted to the IRB. Enrollment begins if/when the IRB and Parkland Memorial Hospital CRO gives the formal go-ahead

[redacted]

Appendix 7: Graphical description of approximate timing of outreach events.



[redacted]

Appendix 8: Draft List of Community Leaders and Organizations for Community Consultation

Municipal Governmental Officials

1. [redacted], Mayor of Dallas, [redacted]
2. [redacted], District 6 Representative and Mayor Pro Tem, [redacted], [redacted]
3. [redacted], District 8 Representative and Deputy Mayor Pro Tem, [redacted], [redacted]
4. [redacted], District 1 Representative, [redacted]
5. [redacted], District 2 Representative, [redacted]
6. [redacted], District 3 Representative, [redacted]
7. [redacted], District 4 Representative, [redacted]
8. [redacted], District 5 Representative, [redacted],
9. [redacted] District 7 Representative [redacted]
10. [redacted], District 9 Representative, [redacted]
11. [redacted], District 10 Representative, [redacted],
12. [redacted] District 11 Representative, [redacted]
13. [redacted], District 12 Representative, [redacted]
14. [redacted], District 13 Representative, [redacted]
15. [redacted], District 14 Representative, [redacted],
16. [redacted], Dallas City Manager, [redacted]
17. [redacted], Chief Wellness Officer, [redacted]
18. [redacted], Dallas Ethics and Diversity Officer, [redacted],
19. [redacted], Mayor of Carrollton, [redacted], [redacted]
20. [redacted], Councilmember, [redacted]
21. [redacted], Councilmember and Carrollton Mayor Pro Tem, [redacted], [redacted]

[redacted]

22. [redacted], Councilmember and Carrollton Deputy Mayor Pro Tem, [redacted]
23. [redacted], Councilmember, [redacted]
24. [redacted], Councilmember, [redacted]
25. [redacted], Councilmember, [redacted]
26. [redacted], Councilmember, [redacted]
27. [redacted], Carrollton City Manager, [redacted]
28. [redacted], Mayor of Mesquite, [redacted]
29. [redacted], Councilmember, P[redacted]
30. [redacted], Councilmember, [redacted]
31. [redacted], Councilmember and Deputy Mayor Pro Tem, [redacted]
32. [redacted], Councilmember, [redacted]
33. [redacted], Councilmember and Mayor Pro Tem, [redacted]
34. [redacted], Councilmember, [redacted]
35. [redacted], Mesquite City Manager, [redacted]
36. [redacted], Mayor of Grand Prairie, [redacted]
37. [redacted], Councilmember, [redacted]
38. [redacted], Councilmember, [redacted]
39. [redacted], Councilmember, [redacted]
40. [redacted], Councilmember, [redacted],
41. [redacted], Councilmember, [redacted],
42. [redacted], Councilmember, [redacted],
43. [redacted], Councilmember, [redacted]
44. [redacted], Councilmember, [redacted]
45. [redacted], Mayor of Irving, [redacted]
46. [redacted], City Manager of Irving, [redacted]
47. [redacted], Councilmember, [redacted]
48. [redacted], Councilmember, [redacted]

[redacted]

49. [redacted], Mayor Pro Tem and Councilmember, [redacted]
50. [redacted], Councilmember, [redacted]
51. [redacted], Councilmember, [redacted]
52. [redacted], Deputy Mayor Pro Tem and Councilmember, [redacted].
53. [redacted], Councilmember, [redacted]
54. [redacted], Councilmember, [redacted]
55. [redacted], Mayor of DeSoto, [redacted]
56. [redacted], Councilmember, [redacted]
57. [redacted], Councilmember, [redacted]
58. [redacted], Councilmember, [redacted]
59. [redacted], Councilmember, [redacted]
60. [redacted], Councilmember, [redacted]
61. [redacted], Councilmember, [redacted]
62. [redacted], Mayor of Lancaster, [redacted]
63. [redacted], Councilmember, [redacted]
64. [redacted], Mayor Pro Tem and Councilmember, [redacted]
65. [redacted], Councilmember, [redacted]
66. [redacted], Deputy Mayor Pro Tem and Councilmember[redacted],
67. [redacted], Councilmember, [redacted]
68. [redacted], Councilmember, [redacted]
69. [redacted], Mayor of Garland, [redacted]
70. [redacted], Deputy Mayor Pro Tem and Councilmember, [redacted],
71. [redacted], Councilmember, [redacted]
72. [redacted], Councilmember, [redacted]
73. [redacted], Councilmember, [redacted]
74. [redacted], Councilmember, [redacted]
75. [redacted], Councilmember, [redacted]
76. [redacted], Councilmember, [redacted]
77. [redacted], Mayor Pro Tem and Councilmember, [redacted]
78. [redacted], Mayor of Richardson, [redacted]
79. [redacted], Mayor Pro Tem and Councilmember, [redacted]
80. [redacted], Councilmember, [redacted]
81. [redacted], Councilmember, [redacted]
82. [redacted], Councilmember, [redacted]

[redacted]

83. [redacted], Councilmember, [redacted]
84. [redacted], Councilmember, [redacted]
85. [redacted], Mayor of Plano, [redacted]
86. [redacted], Councilmember, [redacted]
87. [redacted], Councilmember and Deputy Mayor Pro Tem, [redacted]
88. [redacted], Councilmember, [redacted]
89. [redacted], Councilmember and Mayor Pro Tem, [redacted]
90. [redacted], Councilmember, [redacted]
91. [redacted], Councilmember, [redacted]
92. [redacted], Councilmember, [redacted]
93. [redacted], Mayor of Duncanville, [redacted]
94. [redacted], Councilmember, [redacted]
95. [redacted], Councilmember, [redacted]
96. [redacted], Councilmember, [redacted]
97. [redacted], Councilmember, [redacted]
98. [redacted], Councilmember, [redacted]
99. [redacted], Councilmember, [redacted]
100. [redacted], Mayor of Fort Worth, [redacted]
101. [redacted], Councilmember, [redacted]
102. [redacted], Councilmember, [redacted]
103. [redacted], Councilmember, [redacted]
104. [redacted], Councilmember, [redacted]
105. [redacted], Councilmember, [redacted]
106. [redacted], Councilmember, [redacted]
107. [redacted], Councilmember, [redacted]
108. [redacted], Councilmember, [redacted]
109. [redacted], Mayor of Arlington, [redacted]
110. [redacted], Councilmember, [redacted]
111. [redacted], Councilmember, [redacted]
112. [redacted], Councilmember, [redacted]
113. [redacted] Councilmember, [redacted]
114. [redacted], Councilmember, [redacted]
115. [redacted], Councilmember, [redacted]
116. [redacted], Councilmember, [redacted]
117. [redacted], Councilmember, [redacted]
118. [redacted], Mayor of Balch Springs, [redacted]
119. [redacted], Councilmember, [redacted]

[redacted]

120. [redacted], Mayor Pro Tem of Balch Springs, [redacted]
121. [redacted], Councilmember, [redacted]
122. [redacted], Councilmember, [redacted]
123. [redacted], Councilmember, [redacted]
124. [redacted], Councilmember, [redacted]
125. [redacted], City Manager of Balch Springs, [redacted]

County Governmental Officials

1. [redacted], Dallas County Judge, [redacted]
2. [redacted], District 1 County Commissioner, [redacted]
3. [redacted], District 2 County Commissioner, [redacted]
4. [redacted], District 3 County Commissioner, [redacted]
5. [redacted], District 4 County Commissioner, [redacted]
6. [redacted], Dallas County Health & Human Services Director, [redacted]

Federal Governmental Officials

1. [redacted], Texas 30th District, Dallas Area Congressperson, [redacted]
2. [redacted], Texas 32nd District, Dallas Area Congressperson, [redacted]

Media Representatives

1. [redacted], Fox Channel 4 TV News, [redacted]
2. [redacted], NBC Channel 5 TV News, [redacted]
3. [redacted], Telemundo Channel 39 TV News, [redacted]
4. [redacted], ABC Channel 8 TV News, [redacted]
5. [redacted], CBS Channel 11 TV News, [redacted]
6. [redacted], Dallas Morning News, [redacted]
7. [redacted], Al Dia Dallas, [redacted]
8. [redacted], KRLD News Radio 1080 AM, [redacted]
9. [redacted] KFLC Univision Radio America 1270 AM, [redacted]

Parkland Hospital Leadership

[redacted]

1. [redacted], Parkland Hospital Board Chair, [redacted]
2. [redacted], Parkland Hospital Board Member, [redacted]
3. [redacted], Parkland Hospital Board Vice Chair, [redacted]
4. [redacted], Parkland Hospital Board Member, [redacted],
5. [redacted], Parkland Hospital Board Member, [redacted],
6. [redacted], Parkland Hospital Board Member, [redacted],
7. [redacted], Parkland Hospital Board Member, [redacted],
8. [redacted], President and Chief Executive Officer of Parkland Health and Hospital System, [redacted]
9. [redacted], Executive Vice President and Chief Talent Officer, [redacted]
10. [redacted], Senior Vice President and Chief Compliance and Ethics Officer, [redacted]
11. [redacted], Executive Vice President and Chief Administrative Officer – Hospital Operations, [redacted]
12. [redacted], Executive Vice President and Chief Operating Officer, [redacted]
13. [redacted], Executive Vice President and General Council, [redacted],
14. [redacted], Executive Vice President and Chief Financial Officer, [redacted]
15. [redacted], Executive Vice President and Chief Administrative Officer – [redacted]
16. [redacted], Senior Vice President of Communications and External Affairs, [redacted]
17. [redacted], Interim Chief Medical Officer, [redacted]
18. [redacted], Executive Vice President and Chief Nursing Officer, [redacted]
19. [redacted] President of the Medical Staff, [redacted]
20. [redacted], Vice President of the Medical Staff, [redacted],

[redacted]

21. [redacted], Member of Medical Staff, [redacted]
22. [redacted], Member of Medical Staff, [redacted],
23. [redacted], Member of Medical Staff, [redacted]
24. [redacted], Member of Medical Staff, [redacted]
25. [redacted], Member of Medical Staff, [redacted]
26. [redacted], Member of Medical Staff, [redacted]
27. [redacted], Member of Medical Staff, [redacted]
28. [redacted], Member of Medical Staff, [redacted]
29. [redacted], Member of Medical Staff, [redacted]
30. [redacted], Member of Medical Staff, [redacted]
31. [redacted], Member of Medical Staff, [redacted]
32. [redacted], Member of Medical Staff, [redacted]
33. [redacted], Member of Medical Staff, [redacted]
34. [redacted], Member of Medical Staff, [redacted]
35. [redacted], Director of Trauma Services at Parkland Hospital, [redacted]
36. [redacted], Vice President for Clinical Research at Parkland Hospital, [redacted]
37. [redacted], Director of Research Services at Parkland Hospital[redacted]
38. [redacted], Vice President of Perioperative Services at Parkland Hospital, [redacted]

Medical Community Representatives

1. [redacted], President of the Dallas County Medical Society, [redacted]
2. [redacted], President-Elect of the Dallas County Medical Society, [redacted]
3. [redacted], Secretary/Treasurer of the Dallas County Medical Society, [redacted]
4. [redacted], Chairman of the Board of the Dallas County Medical Society, [redacted]

[redacted]

5. [redacted], Member of the Board of the Dallas County Medical Society, [redacted]
6. [redacted], Member of the Board of the Dallas County Medical Society, [redacted]
7. [redacted], Member of the Board of the Dallas County Medical Society, [redacted]
8. [redacted], Member of the Board of the Dallas County Medical Society, [redacted]
9. [redacted], Member of the Board of the Dallas County Medical Society, [redacted]
10. [redacted], Member of the Board of the Dallas County Medical Society, [redacted]
11. [redacted], Member of the Board of the Dallas County Medical Society, [redacted]
12. [redacted], Member of the Board of the Dallas County Medical Society, [redacted]
13. [redacted], Member of the Board of the Dallas County Medical Society, [redacted]
14. [redacted], Medical Director of Dallas County Health and Human Services, [redacted]
15. [redacted], Director of Dallas County Health and Human Services, [redacted]
16. [redacted], Dallas County Anesthesiology Society, [redacted]
17. [redacted], Dallas County Anesthesiology Society, [redacted]
18. [redacted] UT-Southwestern Medical Center, [redacted]
19. [redacted], UT-Southwestern Medical Center, [redacted]
20. [redacted], UT-Southwestern Medical Center, [redacted]
21. [redacted], UT-Southwestern Medical Center, [redacted]
22. [redacted], UT-Southwestern Medical Center, [redacted]
23. [redacted], UT-Southwestern Medical Center, [redacted]
24. [redacted], UT-Southwestern Medical Center, [redacted]

[redacted]

25. [redacted], UT-Southwestern Medical Center, [redacted],
26. [redacted], UT-Southwestern Medical Center, [redacted],
27. [redacted], UT-Southwestern Medical Center, [redacted]
28. [redacted], UT-Southwestern Medical Center, [redacted],
29. [redacted], UT-Southwestern Medical Center, [redacted],
30. [redacted], UT-Southwestern Medical Center, [redacted],
31. [redacted], UT-Southwestern Medical Center, [redacted],
32. [redacted], UT-Southwestern Medical Center, [redacted],
33. [redacted], UT-Southwestern Medical Center, [redacted],
34. [redacted], UT-Southwestern Medical Center, [redacted],
35. [redacted], UT-Southwestern Medical Center, [redacted],
36. [redacted], UT-Southwestern Medical Center, [redacted],
37. [redacted], UT-Southwestern Medical Center, [redacted],
38. [redacted], UT-Southwestern Medical Center, [redacted],
39. [redacted], UT-Southwestern Medical Center, [redacted]
40. [redacted], UT-Southwestern Medical Center, [redacted]
41. [redacted], UT-Southwestern Medical Center, [redacted],
42. [redacted], UT-Southwestern Medical Center, [redacted],
43. [redacted], UT-Southwestern Medical Center, [redacted],

Spiritual and Religious Leadership

[redacted]

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted]
8. [redacted]
9. [redacted]
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12. [redacted]
13. [redacted]
14. [redacted]
15. [redacted]
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37. [redacted]
38. [redacted]
39. [redacted]

Community Organizations

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]

[redacted]

6. [redacted]
7. [redacted]
8. [redacted]
9. [redacted]
10. [redacted]
11. [redacted]
12. [redacted]
13. [redacted]
14. [redacted]

Organizations Providing Emergency Social Services and Shelter

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted]
8. [redacted]
9. [redacted]
10. [redacted]
11. [redacted]
12. [redacted]
13. [redacted]
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15. [redacted]
16. [redacted]
17. [redacted]
18. [redacted]
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20. [redacted]
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22. [redacted]
23. [redacted]

[redacted]

24. [redacted]
25. [redacted]
26. [redacted]
27. [redacted]

Local Homeowners Associations

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted]
8. [redacted]

Local Hospitals

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]

Nursing Homes and Associations

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted]
8. [redacted]
9. [redacted]
10. [redacted]
11. [redacted]
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13. [redacted]
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16. [redacted]

[redacted]

17. [redacted], [redacted]
18. [redacted], [redacted]
19. [redacted]
20. [redacted]
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22. [redacted] [redacted]
23. [redacted] [redacted]
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25. [redacted] [redacted]
    [redacted]

[redacted]

Appendix 9: Draft Outreach Letter to Community Leaders (English/Spanish)

Dear (Community Leader),

I am one of the physicians at Parkland Memorial Hospital and UT-Southwestern Medical Center in Dallas, TX. The purpose of this letter is to inform you of an upcoming clinical research trial known as "Etomidate versus ketamine for emergency endotracheal intubation: a prospective randomized clinical trial (the EvK Trial)." This clinical trial will be done at Parkland Memorial Hospital, starting in 2016.

Why am I notifying you about this study?

The EvK Clinical Trial is a study of how to best take care of patients who require an emergency placement of a breathing tube. The purpose of the EvK Trial is to help us understand better which medication – etomidate or ketamine – is better for patients during this procedure. Because we are studying an emergency condition, it is not practical to obtain written informed consent prior to study enrollment. The U.S. Food and Drug Administration (FDA) requires that I notify community leaders, and the community broadly, before starting this type of study. These regulations are outlined in FDA 21 CFR 50.24. Our study is discussed in detail on our website, www.evkclinicaltrial.org, and is also registered on www.clinicaltrials.gov.

I would like to invite you, or your representative(s), to one of our community outreach meetings, listed below. Alternately I would be happy to speak with you in person, by phone, or by mail at one of the contact numbers listed above. The goal of these meetings is to answer any questions or concerns you might have about this study, and to ask for feedback.

Most sincerely yours,

Gerald Matchett, MD
Principal Investigator of the EvK Trial

Schedule for Public Meetings about the EvK Trial

Community Leader Meeting
Month, Date, Year, Room X, Parkland Memorial Hospital, X PM
Open to all community leaders and news media. Translator services available.
Please RSVP to XYZ@evkclinicaltrial.org

Open Community Meeting
Month, Date, Year, Room X, Parkland Memorial Hospital, X PM
Open to all community members and news media. Translator services available.
Please RSVP to XYZ@evkclinicaltrial.org

Open Community Meeting
Month, Date, Year, Room X, Parkland Memorial Hospital, X PM
Open to all community members and news media. Translator services available.
Please RSVP to XYZ@evkclinicaltrial.org

Clinical Trial Contact Information
Telephone hotline: 214-TBD-TTBD
Standard Mail: Dept. of Anesthesiology & Pain Management, University of Texas-Southwestern Medical Center MC 9068, 5323 Harry Hines Blvd, Dallas, TX 75390-9068
Email: tbd@evkclinicaltrial.org
Web-Site:www.evkclinicaltrial.org

[redacted]

Appendix 10: Draft EvK Trial Website (English/Spanish)

Etomidate versus Ketamine for Emergency Endotracheal Intubation: A prospective randomized clinical trial (the EvK Trial)

Brief Summary
Patients who are having problems breathing sometimes require placement of a breathing tube in their mouth and windpipe. The purpose of this breathing tube is to save the patient's life. It is common to give the patient a medication to sedate him or her before the breathing tube is placed. For patients who are gravely ill two medications are commonly used: etmoidate or ketamine. Both medications have risks and benefits. We would like to do a study to figure out which one is better for our patients.

Detailed Summary
Critically ill individuals who require emergency endotracheal intubation (placement of a breathing tube in the patient's mouth) usually require sedation or anesthesia to make this process tolerable. There are several medication choices for anesthesia, including medications like etomidate, ketamine and propofol. Of these, etomidate and ketamine are frequently used for critically ill patients because they have minimal effects on the patient's vital signs (blood pressure and heart rate). Both etomidate and ketamine are standard-of-care medications, locally and nationally, and both are frequently used to sedate a patient for this procedure. Both etomidate and ketamine have side effects. One of the side effects of etomidate is that is suppresses the function of the adrenal glands. It is not known if this affects the patient's outcome in a significant way. Ketamine has other side effects, such as slightly increasing the patient's heart rate. It is not known if this affects the patient's outcome in a significant way.

The EvK Trial will be conducted at Parkland Memorial Hospital by investigators in the Departments of Anesthesiology, Emergency Medicine, Medicine / Critical Care Medicine, Surgery, and Pharmacy. The study will randomize critically ill patients who require emergency endotracheal intubation to one of two groups: Etomidate or Ketamine. We will observe the patients' outcomes. The only study intervention involves randomizing individual patients to one medication or the other. All study follow-up beyond that point is done by review of medical records.

Because of the nature of this study – an emergency procedure on a critically ill patient – the study will require formal permission to bypass pre-enrollment written informed consent. The purpose of this website is to notify the public of this research project, in accordance with rules set forth by the U.S. Food and Drug Administration (FDA 21 CFR 50.24).

Study Contact Methods

A. Telephone hotline and opt-out: 214-TBD-TTBD
B. Standard Mail: Dept. of Anesthesiology & Pain Management, University of Texas-Southwestern Medical Center MC 9068, 5323 Harry Hines Blvd, Dallas, TX 75390-9068
C. Email: tbd@evkclinicaltrial.org
D. Web-Site (online feedback form): www.evkclinicaltrial.org (or similar, yet to be established).

Link to study registration at www.clinicaltrials.gov

Links to Institutions
(Parkland Memorial Hospital Link)
(UT-Southwestern Medical Center Link)
(Dept. of Anesthesiology Link)
(Dept. of Medicine / CCM Link)
(Dept. of ED Link)
(Dept. of Surgery Link)
(Link to Parkland Memorial Hospital CRO)
(Link to UT-Southwestern IRB)

Link to Principal Investigator

[redacted]

http://profiles.utsouthwestern.edu/profile/120396/gerald-matchett.html

Links to FAQ's

1. **Are etomidate and ketamine used frequently for emergency endotracheal intubation?**
   Yes. Both are commonly used, and both are the "standard-of-care" locally and nationally.
2. **If both etomidate and ketamine are frequently used for this procedure, why are you doing the study?**
   There is considerable debate right now regarding which medication is better for patients. Each medication has side effects.
3. **What does it mean to "randomize" a patient?**
   This means that individual patients who are enrolled in the study will receive either etomidate or ketamine. Which medication they will receive will depend on random chance, similar to what happens with a coin toss.
4. **Besides receiving etomidate or ketamine, will patients in the study have any other study-related procedures?**
   No. The only intervention for the study is the choice of etomidate or ketamine, which will be done by random selection. Data will be gathered from the patient's medical record after they enter the study, but this will not have any effect on medical care.
5. **Why won't patients have a chance to sign a consent form before enrolling in the study?**
   The EvK Trial is a study of an emergency medical procedure. The patients who are eligible for the study are critically ill and require immediate medical care (placement of a breathing tube), and therefore cannot give informed consent. After a patient is enrolled in the study, the study team will notify the patient and / or family of study enrollment, in accordance with FDA rules governing emergency medical research (FDA 21 CFR 50.24).
6. **Is it legal to do a research study on a patient before he or she give written informed consent?**
   Yes, provided the study complies with the regulations governing this type of research. The U.S. Food and Drug Administration (FDA) has determined that in select cases of emergency research it is acceptable to do research without first obtaining written informed consent. Information about this can be obtained at the FDA website (linked here).
7. **Who is eligible to enroll in the study? Can patients volunteer for the study?**
   The EvK Trial will enroll patients who are critically ill, and specifically those who require emergency placement of a breathing tube. These patients are typically found in an emergency department, or intensive care unit, who are there under emergency circumstances. Because of this, individuals cannot volunteer for this study.
8. **How will the public be notified about the EvK Trial?**
   The U.S. Food and Drug Administration (FDA) requires that several specific measures be taken for research in emergency medical conditions. These measures are described in FDA 21 CFR 50.24, and include things like (A) A meeting with community leaders and (B) Outreach to the community at-large. The EvK Trial investigators have a comprehensive Community Outreach Plan that meets these requirements, and includes direct outreach to community leaders, media outreach, community outreach by meetings, and internet advertising and a study website (www.evkclinicaltrial.org).
9. **How many patients will enroll in the study?**
   Approximately 750 patients will enroll.
10. **Will the study investigators make money off the results of this study?**
    No. The EvK Trial collaborators do not have a financial stake in the outcome of the study. The study is primarily funded by the University of Texas-Southwestern Medical Center. Both medications used in the EvK Trial (etomidate and ketamine) are generic medications, and the study is not being done to market either medication. The EvK Trial is not a "for profit" study. No drug companies, or their agents or representatives, were involved in the design of this study, and none will be involved in the conduct of the study. Patients will not be billed or charged for study-related activities.

[redacted]

11. **How do I contact the research team if I have questions or concerns?**
    E. Telephone hotline and opt-out: 214-TBD-TTBD
    F. Standard Mail: Dept. of Anesthesiology & Pain Management, University of Texas-Southwestern Medical Center MC 9068, 5323 Harry Hines Blvd, Dallas, TX 75390-9068
    G. Email: tbd@evkclinicaltrial.org
    H. Web-Site (online feedback form): www.evkclinicaltrial.org (or similar, yet to be established).
12. **I would like to formally "opt-out" of the study. How do I do that?**
    Individuals who live in the catchment area of Parkland Memorial Hospital in Dallas, TX may "opt-out" of the study. To do this, please request to opt-out using the contact information above. You will be sent a custom MedAlert bracelet indicating this choice. The bracelet will be sent to you free of charge by mail.
13. **When and where are the community meetings?**

    Community Leader Meeting
    Month, Date, Year, Room X, Parkland Memorial Hospital, X PM
    Open to all community leaders and news media. Translator services available.
    Please RSVP to XYZ@evkclinicaltrial.org, or 214-TBD-TTBD

    Open Community Meeting
    Month, Date, Year, Room X, Parkland Memorial Hospital, X PM
    Open to the general public and news media. Translator services available.
    Please RSVP to XYZ@evkclinicaltrial.org, or 214-TBD-TTBD

    Open Community Meeting
    Month, Date, Year, Room X, Parkland Memorial Hospital, X PM
    Open to the general public and news media. Translator services available.
    Please RSVP to XYZ@evkclinicaltrial.org, or 214-TBD-TTBD

14. **Is this study approved by an Institutional Review Board (IRB)?**
    The IRB has reviewed the study, and has given us permission to begin the Community Notification Plan. The results of that plan will be reviewed by the IRB once the plan is completed. At that point the IRB may, or may not, permit us to begin enrolling patients.
15. **How long will this clinical trial take?**
    Approximately 2-3 years
16. **Will the results of this research be announced?**
    Yes. Results will be announced publically through various methods, including publication in a scientific journal. No Protected Health Information (PHI) will be published or publically disclosed.

[redacted]

Appendix 11: Draft Print Advertisements in Dallas Morning News and Al Dia Dallas

Announcing a New Clinical Trial at Parkland Memorial Hospital:

"Etomidate versus ketamine for emergency endotracheal intubation: a prospective randomized clinical trial (the EvK Trial)"

This clinical trial will be conducted at Parkland Memorial Hospital starting in 2016. In this trial we will study which medication (etomidate or ketamine) is better for patients who require emergency placement of a breathing tube in their mouth. Because the study is being done without pre-enrollment written informed consent, FDA 21 CFR 50.24 requires public notification and feedback.

For more information:

Community Leader Meeting
Month, Date, Year, Room X, Parkland Memorial Hospital, X PM
Open to all community leaders and news media. Translator services available.
Please RSVP to XYZ@evkclinicaltrial.org, or 214-TBD-TTBD

Open Community Meeting
Month, Date, Year, Room X, Parkland Memorial Hospital, X PM
Open to the general public and news media. Translator services available.
Please RSVP to XYZ@evkclinicaltrial.org, or 214-TBD-TTBD

Open Community Meeting
Month, Date, Year, Room X, Parkland Memorial Hospital, X PM
Open the general public and news media. Translator services available.
Please RSVP to XYZ@evkclinicaltrial.org, or 214-TBD-TTBD

Clinical Trial Contact Information
Telephone hotline: 214-TBD-TTBD
Standard Mail: Dept. of Anesthesiology & Pain Management, University of Texas-Southwestern Medical Center MC 9068, 5323 Harry Hines Blvd, Dallas, TX 75390-9068
Email: tbd@evkclinicaltrial.org
Web-Site:www.evkclinicaltrial.org

[redacted]

Appendix 12: Draft Poster / Flyer Advertisement (English/Spanish)

The **EvK Clinical Trial**

at Parkland Memorial Hospital

More Information:

The EvK Clinical Trial is a study of how to best take care of patients who require an emergency placement of a breathing tube. The purpose of the EvK Trial is to help us understand better which medication – etomidate or ketamine – is better for patients during this procedure. The full title of the study is "Etomidate versus ketamine for emergency endotracheal intubation: A prospective randomized clinical trial."

Because we are studying an emergency condition, it is not practical to obtain written informed consent prior to study enrollment. The U.S. Food and Drug Administration (FDA) requires notification of community leaders, and the community broadly, before starting this type of study.

Community Leader Meeting
Month, Date, Year, Room X, Parkland Memorial Hospital, X PM
Open to all community leaders and news media. Translator services available.
Please RSVP to XYZ@evkclinicaltrial.org, or 214-TBD-TTBD

Open Community Meeting
Month, Date, Year, Room X, Parkland Memorial Hospital, X PM
Open to the general public and news media. Translator services available.
Please RSVP to XYZ@evkclinicaltrial.org, or 214-TBD-TTBD

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MC 9068, 5323 Harry Hines Blvd, Dallas, TX 75390-9068
Email: tbd@evkclinicaltrial.org
Web-Site:www.evkclinicaltrial.org

[redacted]

Appendix 13: Draft Notice of Enrollment Letter (English/Spanish)

Dear (Enrolled Patient),

I am one of the researchers at UT-Southwestern Medical Center and Parkland Memorial Hospital in Dallas, TX. The purpose of this letter is to inform you that you were enrolled in a clinical trial during a recent hospitalization. The trial is known as "Etomidate versus ketamine for emergency endotracheal intubation: A prospective randomized clinical trial (The EvK Trial)," Institutional Review Board #STU022015-023.

In this clinical trial you received one of two medications during your medical or surgical care: etomidate or ketamine. These medications were used to help sedate you while a breathing tube was placed in your mouth. The purpose of the trial is to evaluate which medication (ketamine or etomidate) is associated with better outcomes following placement of a breathing tube. The clinical trial has no effect on medical care after the initial choice of medication. Both of the medications in the trial are commonly used for this procedure, both are approved by the U.S. Food and Drug Administration (FDA), and both are considered the "standard of care." Neither medication is considered experimental.

For this clinical trial my co-investigators and I obtained special permission from the Institutional Review Board to enroll patients prior to obtaining written consent. My co-investigators and I are obligated to inform you of the enrollment in person, by telephone or mail. My co-investigators and I would welcome the opportunity to speak with you or your family about this research trial. We would also like to ask permission to use your anonymous clinical data as part of the study. You have no obligations to contact us if you do not wish to do so. If you wish to contact me, please feel free to use any of the avenues listed below.

Most sincerely yours,

Gerald Matchett, MD
Principal Investigator
EvK Clinical Trial

Clinical Trial Contact Information
Telephone hotline: 214-TBD-TTBD
Standard Mail: Dept. of Anesthesiology & Pain Management, University of Texas-Southwestern Medical Center MC 9068, 5323 Harry Hines Blvd, Dallas, TX 75390-9068
Email: tbd@evkclinicaltrial.org
Web-Site:www.evkclinicaltrial.org

[redacted]

Appendix 14: Draft Notice of Enrollment Letter (English/Spanish) to Family / Next-of-Kin

Dear (Family and/or Next-of-Kin of Enrolled Patient)

I am one of the researchers at Parkland Memorial Hospital and UT-Southwestern Medical Center in Dallas, TX. The purpose of this letter is to inform you that your family member was recently enrolled in a clinical trial during his/her recent hospitalization. The trial is known as "Etomidate versus ketamine for emergency endotracheal intubation: A prospective randomized clinical trial (The EvK Trial)," Institutional Review Board #STU022015-023.

In this clinical trial your family member received one of two medications during the course of medical or surgical care: etomidate or ketamine. These medications were used to help sedate a patient while a breathing tube was placed in his or her mouth. The purpose of the trial is to evaluate which medication (ketamine or etomidate) is associated with better outcomes following placement of a breathing tube. The clinical trial has no effect on medical care after the initial choice of medication. Both of the medications in the trial are commonly used for this procedure, both are approved by the U.S. Food and Drug Administration (FDA), and both are considered the "standard of care." Neither medication is considered experimental.

For this clinical trial my co-investigators and I obtained special permission from the Institutional Review Board to enroll patients prior to obtaining written consent. My co-investigators and I are obligated to inform you of the enrollment in person, by telephone or mail. My co-investigators and I would welcome the opportunity to speak with you or your family about this research trial. We would also like to ask permission to use your relative's anonymous clinical data as part of the study. You have no obligations to contact us if you do not wish to do so. If you wish to contact me, please feel free to use any of the avenues listed below.

Most sincerely yours,

Gerald Matchett, MD
Principal Investigator
EvK Clinical Trial

Clinical Trial Contact Information
Telephone hotline: 214-TBD-TTBD
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