

Final Statistical Analysis Plan

for

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

(The EvK Clinical Trial, UTSW IRB# STU022015-023, NCT02643381)

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Prepared by:
Gerald Matchett, M.D.


G. Matchett
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This document is seven (7) pages in length, including title page.

Summary

The purpose of this document is to confirm the clinical definitions and statistical plan for the EvK Clinical Trial. This document was finalized prior to the conclusion of enrollment in the clinical trial. For each topic below the original plan in the IRB-approved protocol from April 2016 is presented, followed by the updated plan from August 2020.

(1) Trial Profile Diagram

April 2016:

Not fully described in original protocol.

August 2020:

We will summarize the movement of patients through the trial using a CONSORT Diagram (typically “Figure 1” of clinical trial manuscripts), with allowances for the pragmatic design of enrollment used in this trial.

(2) Primary Endpoint and Statistical Testing

April 2016:

The primary endpoint is survival at Day 7. 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 QA/QI data, 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% dropout rate, 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. At the mid-way point of the study, an interim analysis will be performed to assess futility using O’Brien-Fleming approach.

August 2020:

Unchanged from original.

(3) Secondary Endpoints

April 2016:

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)

August 2020:

Survival at 28 days following emergency endotracheal intubation
Sequential Organ Failure Assessment (SOFA) scores
-Calculated on d1, d2, d3 and d4

- Maximum SOFA Score
- Delta SOFA (Maximum SOFA – Initial SOFA)
- Immediate outcomes of endotracheal intubation
 - Vital Signs (heart rate, blood pressure)
 - Presence or absence of cardiovascular collapse (as defined by Halliday et al 2020 and Janz et al 2019, new SBP < 65 mmHg, addition of vasopressors, or cardiac arrest or death within 1 hour)
 - Other Complications (descriptive, including trauma, surgical airway, aspiration).
- Duration of mechanical ventilation
 - Days
- Duration of catecholamine therapy
 - Days and type(s) and dose, including aggregate usage by group (vasopressor days)
 - Peak norepinephrine dose
- Length of stay in ICU / hospital
 - Days in ICU, survivors. Partial days will be rounded up to full days. Hospital LOS is being omitted as a secondary endpoint.
- New diagnoses
 - Will assess for both confirmed and suspected adrenal insufficiency based on EMR documentation from the clinical team.
- Outcomes related to patients with a diagnosis of Sepsis
 - Survival at Day 7 and Day 28.
 - SOFA scores, with the same analysis as above.

(4) Plan for Assessment of Quality of Randomization

April 2016:

Not fully described in the original protocol.

August 2020:

We will use post-hoc statistical testing of all baseline variables to assess the quality of randomization between the two groups. This will include data typically placed in Table 1 of clinical trial manuscripts. Table 1 will include age, gender, demographics, weight / BMI, co-existing conditions, in-hospital location of enrollment (example: MICU vs SICU), Knaus chronic health status score, reason for intubation, vital signs at randomization, laboratory values at randomization. The specific statistical tests used will be at the recommendation of the study statistician.

(5) Plan for potential early stoppage of enrollment between the interim analysis (n=375) and full study enrollment (n=825) (April 2016):

April 2016:

Not addressed in original protocol.

August 2020:

At any point after the interim analysis the DSMB may elect to stop the trial if the number of enrollments relative to the number of drop-outs merits stoppage. For example, if substantially fewer patients drop out than originally estimated, the trial may be stopped

before n=825. This decision will be made in consultation with the study statistician. This plan was submitted to the IRB with the 2020 Continuing Review.

(6) Definitional Matters Regarding Sepsis

April 2016:

“Sepsis” was extensively considered but not explicitly defined in the original trial protocol.

August 2020:

“Sepsis” is based on a clinician-defined diagnosis, which exists (or not) at the moment of randomization or earlier, based on time-stamped documentation in the EMR. This diagnosis is made by the treating medical or surgical ICU team, not the study team, and identified by physician manual chart review. The EMR is assessed for the presence or absence of this diagnosis. A post-randomization diagnosis of sepsis will not be considered sepsis for purposes of this analysis.

As an exploratory (tertiary) endpoint subjects with a pre and/or post-randomization clinician-defined diagnosis of sepsis will be considered as a group.

“Septic Shock” is based on clinician-defined diagnosis as above, in addition to the need for catecholamine therapy.

“Sepsis-3 Sepsis” is a tertiary endpoint will be made based on Singer et al 2016, the Third Consensus Definition. This will include

- suspected infection (based on the prescription of sustained antibiotic therapy),
- AND
- SOFA > or = 2.

“Sepsis-3 Septic Shock” as a tertiary endpoint will include the above in addition to

- Vasopressors required to maintain MAP > or = 65 mmHg, AND
- Serum lactate > 2 mmol/L.

(7) Definitional Matters Regarding Adrenal Insufficiency

April 2016:

“Adrenal Insufficiency” was extensively considered but not explicitly defined in the original trial protocol.

August 2020:

“Adrenal Insufficiency” (or “Confirmed Adrenal Insufficiency”) for purposes of this secondary analysis will be a clinician-defined syndrome which is assessable in the EMR after randomization by physician manual chart review. This diagnosis may (or may not) be made based on laboratory testing which is performed and interpreted by the treating team.

“Suspected Adrenal Insufficiency” will include any critically ill ICU patient who is

- persistently hypotensive despite vasopressor therapies, AND
- is prescribed “stress dose” IV hydrocortisone intravenously (repeated doses) by the medical or surgical ICU teams for the explicit purpose of treating this hypotension.

Other steroids such as methylprednisolone, dexamethasone or others will not be considered for purposes of this definition.

We plan to perform statistical calculations using the combined endpoint of “Confirmed or Suspected Adrenal Insufficiency.”

References

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