The “two bag” system for treatment of adults with diabetic ketoacidosis: a prospective randomized trial

Protocol Number: 18-00025

National Clinical Trial (NCT) Identified Number: NCT03660189

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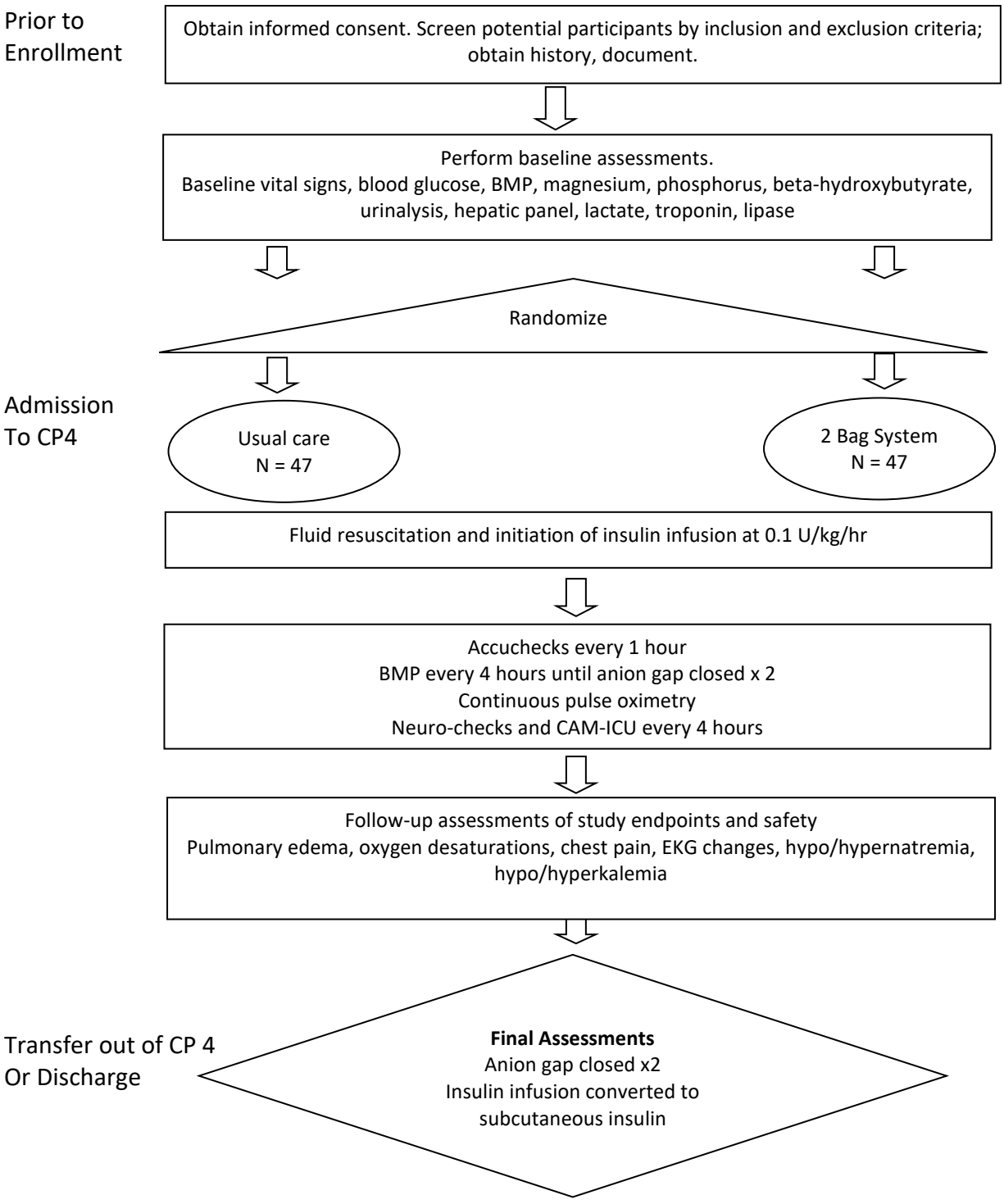
9 October 2018

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	The "two bag" system for treatment of adults with diabetic ketoacidosis: a prospective randomized study
Study Description:	Patients with diabetic ketoacidosis (DKA) will be randomized to the "two bag" system group or the usual care group using the one bag system. Patients treated with the two bag system of intravenous (IV) fluids for DKA will have a significantly shorter time to anion gap closure when compared to the traditional one bag system.
Objectives:	This is a prospective randomized controlled trial to determine whether the "two bag" system of administering IV fluids for the treatment of adults with DKA results in decreased time to anion gap closure and decreased length of stay in the hospital, when compared to usual care with a "one bag" system of IV fluids.
Endpoints:	The primary endpoint is time to anion gap closure. Secondary endpoints include hypoglycemic episodes, clinical signs of dyspnea, pulmonary edema, hypoxemia events, chest pain with EKG changes, hyponatremia events, hypokalemia events, ICU/hospital length of stay, and total volume of intravenous fluids administered.
Study Population:	Sample size of 150 patients, between the age of 18-85, admitted for diabetic ketoacidosis.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	The study will be performed at a single center, at MetroHealth Medical Center in Cleveland, Ohio.
Description of Study Intervention:	The two bag system of IV fluids for DKA management.
Study Duration:	12 months
Participant Duration:	Subjects will participate in the study for the duration of their hospitalization while in the intensive care unit or the stepdown unit. On average this may range from 1-5 days.

1.2 SCHEMA


Prior to Enrollment
Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Perform baseline assessments.
Baseline vital signs, blood glucose, BMP, magnesium, phosphorus, beta-hydroxybutyrate, urinalysis, hepatic panel, lactate, troponin, lipase
Randomize
Admission To CP4
Usual care
N = 47
2 Bag System
N = 47
Fluid resuscitation and initiation of insulin infusion at 0.1 U/kg/hr
Accuchecks every 1 hour
BMP every 4 hours until anion gap closed x 2
Continuous pulse oximetry
Neuro-checks and CAM-ICU every 4 hours
Follow-up assessments of study endpoints and safety
Pulmonary edema, oxygen desaturations, chest pain, EKG changes, hypo/hypernatremia, hypo/hyperkalemia
Transfer out of CP 4 Or Discharge
Final Assessments
Anion gap closed x2
Insulin infusion converted to subcutaneous insulin

2 INTRODUCTION

2.1 STUDY RATIONALE

The “two bag” system of IV fluids for management of DKA is used widely in the pediatric intensive care unit. The benefits of the two bag system from the pediatric literature include: decreased response time to IV fluid changes, decreased time to correction of bicarbonate and ketones, and decreased total IV fluid volume administered. There was one retrospective study of the two bag system in adults, which showed decreased time to anion gap closure and decreased hypoglycemic events. To this date, there are no prospective randomized trials to evaluate the efficacy of the two bag system in adults.

2.2 BACKGROUND

Diabetic ketoacidosis (DKA) remains an ongoing problem in the United States, with up to 500,000 hospitalizations per year (1). The incidence of this life threatening disorder has been increasing over the last several years. Most patients with DKA have Type 1 diabetes, but up to one third of DKA cases are seen in adults with Type 2 diabetes. Dehydration resulting in hypovolemia and electrolyte abnormalities are significant causes of morbidity and mortality in this patient population.

The management of DKA requires frequent monitoring of the patient’s blood glucose, fluid status, and electrolytes which usually requires intensive care level of monitoring. The recommendations for DKA management are based on the American Diabetes Association (ADA) Consensus Statement guidelines from 2009 (1), which uses a one bag system. The ADA guidelines recommend an insulin infusion to be initiated at 0.1 units/kg/hour. The initial bag of fluid is either 0.9% saline or 0.45% saline depending on the patient’s corrected sodium level. Once the blood sugar decreases to 200 mg/dl, the insulin infusion is decreased to 0.02 to 0.05 U/kg/hr and 5% dextrose is added to the fluid bag being administered. The rate of the fluids is determined by the patient’s estimated level of dehydration. One of the challenges with the one bag system is that there is an intrinsic delay in changes to IV fluids since the new fluid bag must be prepared by the pharmacy prior to administration, which may lead to hypoglycemia while waiting for the new fluid bag containing dextrose to arrive. It is also more likely to waste IV fluid bags, if a new fluid bag is started prior to the completion of the current fluid bag, and multiple changes may be necessary throughout their hospital stay depending on the patient’s electrolyte levels.

The “two bag” system involves two bags of identical fluids with electrolytes, except one bag has 0% dextrose and the other has 10% dextrose. The two fluid bags run simultaneously into a Y-connector and into a single IV catheter. The rates of the two fluid bags are adjusted depending on the patient’s blood sugar. For example, if the blood sugar is greater than 500 mg/dl, the 0% dextrose bag will run at the full rate of 200 ml/hr (determined by the patient’s degree of dehydration) and the 10% dextrose bag will run at 0 ml/hr. As the blood sugar falls, the rate of the 10% dextrose bag increases according to pre-determined rates, while the rate of the 0% dextrose bag decreases to keep the total fluid rate constant. Since the hyperglycemia in DKA typically corrects before the ketosis, this provides a more efficient method of titrating the dextrose concentration based on the patient’s needs, while continuing to infuse the insulin drip at a constant rate to prevent further ketogenesis. The two bag system has been studied in pediatric patients with Type 1 diabetes and used frequently in pediatric intensive care units for the treatment of DKA.

The two bag system was first studied in the pediatric population when Grimberg, et al performed a retrospective chart review in 1999. This study concluded that when compared to the traditional one bag system, the two bag system used a significantly less amount of total IV fluids (from 8.6 L to 4.5 L) which resulted in decreased hospital costs (2). There was also a shorter response time for IV fluid changes and the protocol was well liked by the nursing and house staff. Another retrospective chart review in pediatrics (by So, et al in 2009) revealed that the two bag system had a faster rate of serum bicarbonate and ketone correction which was statistically significant (3). However, the rate of pH and blood glucose correction was no different in the two groups. In contrast, a prospective study in pediatrics from 2004 showed no significant differences in serum bicarbonate correction, glucose correction, or total number of IV fluid bags used (4). Nevertheless, there was a significant decrease in time to make changes to the IV fluids, as seen in previous studies. Although the overall results of these pediatric studies together were somewhat inconclusive, all of them were limited by small sample sizes of around 30 patients and no randomized controlled trials have been performed.

There is one study in the literature that introduced the two bag system into the care of adult patients with diabetic ketoacidosis. Munir, et al performed a retrospective cohort study in 2015 involving adult patients who were treated with the two bag system compared to conventional treatment with the one bag system (a retrospective before/after study) with a larger sample size of 383 patients. They found the two bag system to be beneficial, with decreased time to anion gap closure (from 13.56 hours to 10.94 hours), decreased hypoglycemic events, and faster time to blood glucose normalization to less than 250 mg/dl (5). There was no difference in improvement in serum bicarbonate or hospital length of stay. The two groups were similar in severity of DKA and Charlson Comorbidity Index.

To this date, there are no prospective studies to evaluate the potential benefits of the two bag system in adult patients with DKA.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

- Shortness of breath – uncommon
- Pulmonary edema due to fluid overload – uncommon
- Desaturations to less than 89% or new oxygen requirement – uncommon
- Chest pain with acute EKG changes not on admission EKG – rare
- Hypo/hypernatremia - uncommon
- *Hypo/hyperkalemia - uncommon*

2.3.2 KNOWN POTENTIAL BENEFITS

The literature demonstrates that when using the set protocol of the two bag system for IV fluid administration during the treatment of DKA, there is the potential for faster time to resolution of DKA. Resolution of DKA is defined as normalized blood glucose with the cessation of ongoing ketogenesis, which is marked by the closure of the anion gap on two sequential blood tests. Using the two bag system may lead to decreased ICU stay and potentially decreased hospital length of stay. In addition, with a set protocol of IV fluids, there may be less confusion between physicians and nurses regarding

fluid management based on each hourly blood glucose value. For society in general, there is potential benefit of decreased hospitalization costs for patients admitted with DKA.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The main risks of the two bag system is concern for developing fluid overload or electrolyte abnormalities while on a continuous infusion of IV fluids. However, the same risks are present in the "usual care" group and during the aggressive fluid resuscitation phase.

The potential benefits outweight the risks, which can be minimized. In order to minimize the patient's exposure to these risks, the patients will be monitored continuously by pulse oximetry to watch for developing hypoxemia which may result from pulmonary edema (this is usual care for all DKA patients). The electrolytes will be monitored every 4 hours to ensure that any abnormalities are treated in a timely manner, and the concentration of electrolytes will be repleted as needed. Confidentiality of patient data will be emphasized to all research staff during regular research meetings. Patient data will be de-identified using a numbering system in RedCap.

3 OBJECTIVES AND ENDPOINTS

This is a prospective randomized controlled trial to determine whether the "two bag" system of administering intravenous (IV) fluids for the treatment of adults with diabetic ketoacidosis (DKA) results in decreased time to anion gap closure and decreased length of stay in the hospital, when compared to usual care with a "one bag" system of IV fluids.

The primary endpoint is time to anion gap closure. Secondary endpoints include hypoglycemic episodes, clinical signs of dyspnea, pulmonary edema, hypoxemia events, chest pain with EKG changes, hyponatremia events, hypokalemia events, ICU/hospital length of stay, and total volume of intravenous fluids administered.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study will be performed at a single center, at MetroHealth Medical Center in Cleveland, OH.
This a prospective, randomized trial comparing the "two bag" system for DKA compared to the traditional "one bag" system. The duration of participation will vary, as it will be based on the time the patient requires treatment with the insulin infusion.

- The on-call fellow physician (a co-investigator of the study) will screen all patients admitted with DKA to CP4 West and CP4 East and determine if they qualify for enrollment by the inclusion and exclusion criteria.
- Informed consent will be obtained by the fellow from either the patient, healthcare power of attorney, next of kin, or legal guardian depending on the patient's mental status and competency
- Subjects will be fluid resuscitated with IV fluids based on usual care

- Insulin infusion will be ordered at 0.1 U/kg/hr for all subjects
- Home diabetic medications will be held until DKA is resolved
- Neurologic checks and CAM-ICU scores will be performed every 4 hours
- Laboratory orders:
    - Basic metabolic panel STAT every 4 hours.
    - Admission EKG, troponin, lipase, magnesium, phosphorus, and hepatic function panel (to calculate the expected anion gap based on the albumin).
    - Finger stick blood glucose every 1 hour
- Subjects will be randomized into two groups of "usual care" and "two bag system" for IV fluids
- The randomization process will be performed by assigning patients to a random number after enrolling in the study, using an online "random number generator." Patients with odd numbers will be assigned to the control group and patients with even numbers will be assigned to the experimental group. The randomization will be performed on a 1:1 basis for the two groups.
- The "usual care" group is the control group
    - This group will be treated with one bag of IV fluid at a time, and the algorithm is based on the American Diabetes Association Consensus Statement guidelines from 2009 (1).
    - The initial bag of fluid is usually either 0.9% saline or 0.45% saline depending on the patient's corrected sodium level
    - Once the blood sugar reaches 200 mg/dl, the insulin infusion is decreased to 0.02 to 0.05 U/kg/hr and 5% dextrose is added to the fluid bag being used
    - The rate of the fluids is determined by the patient's estimated dehydration
- The "two bag system" group is the experimental group
    - One bag will be saline (either normal saline (NS) or half normal saline depending on patient's sodium level) and the second bag will be normal saline with 10% dextrose (D10)
    - The protocol is as follows:
        - If blood sugar is > 300, run D10 solution at 0 ml/hr and saline solution at 200 ml/hr
        - If blood sugar is 250-299, run D10 solution at 50 ml/hr and saline solution at 150 ml/hr
        - If blood sugar is 200-249, run D10 solution at 100 ml/hr and saline solution at 100 ml/hr
        - If blood sugar is 150-199, run D10 solution at 150 ml/hr and saline solution at 50 ml/hr
        - If blood sugar is < 150, run D10 solution at 200 ml/hr and saline solution at 0 ml/hr
    - Normal saline infusion will be used if corrected Na is low
    - Half normal saline infusion may be used if corrected sodium is normal or high
    - Other fluids (such as lactated ringers) may be used depending on patient's hydration status and electrolytes
    - Potassium chloride (20 mEq/1 L fluid) will be added to the fluids if renal function is within normal limits and potassium is less than 5.2.
    - Potassium phosphate (20 mEq/1 L fluid) will be added to the fluids if phosphate is less than 1.0.
    - The primary team should replete the magnesium as needed for levels less than 2.0 mg/dl
    - The insulin infusion rate will not be adjusted until the anion gap has closed on 2 occurrences, unless patient develops hypoglycemia despite maximum D10 rate.
    - Transition to subcutaneous insulin when anion gap is closed on two occurrences.
    - The anion gap will be calculated by the equation:
        - Anion gap = Na – Cl – HCO3

- The expected anion will be adjusted for low albumin by a calculation of 1g/dl decrease in albumin correlates with +2.5 points in the anion gap

- The investigators performing the data collection will be blinded to the treatment groups
- For patients in the experimental group, if the subject develops hypo/hypernatremia, hypo/hyperkalemia, shortness of breath, pulmonary edema, oxygen desaturations < 89%, or chest pain with new EKG changes, the provider/house staff may temporarily suspend the two bag system protocol in order to treat the complication appropriately. It will remain up to the primary team whether or not it is appropriate to restart the protocol. All protocol deviations will be documented and measured.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A randomized prospective trial has not yet been performed to evaluate efficacy of the two bag system in adults.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study. This occurs when the anion gap is closed and the patient is transitioned to subcutaneous insulin.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 18-85
4. Diagnosis of diabetic ketoacidosis defined as:
    a. Blood sugar greater than 250 mg/dl
    b. Venous pH less than 7.25
    c. Bicarbonate less than 18
    d. Evidence of ketone formation with either positive urine ketones or elevated beta-hydroxybutyrate > 3
    e. Anion gap greater than 10 +/ - 2 (or higher than expected anion gap corrected for albumin)

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnancy
2. Hyperglycemic hyperosmolar state

3. Ketosis from other etiology such as starvation or alcoholic ketosis
4. Acute exacerbation of congestive heart failure
5. Acute coronary syndrome or non-ST elevation MI
6. Pulmonary edema from other cause such as decompensated liver failure or acute renal failure
7. Renal failure requiring renal replacement therapy (hemodialysis)
8. Septic shock

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

All patients admitted to CP4 with a diagnosis of DKA will be screened for participation in the study. No other forms of recruitment will be performed.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The "two bag system" group is the experimental group

- One bag will be saline (either normal saline (NS) or half normal saline depending on patient's sodium level) and the second bag will be normal saline with 10% dextrose (D10)
- The protocol is as follows:
    - If blood sugar is > 300, run D10 solution at 0 ml/hr and saline solution at 200 ml/hr
    - If blood sugar is 250-299, run D10 solution at 50 ml/hr and saline solution at 150 ml/hr
    - If blood sugar is 200-249, run D10 solution at 100 ml/hr and saline solution at 100 ml/hr
    - If blood sugar is 150-199, run D10 solution at 150 ml/hr and saline solution at 50 ml/hr
    - If blood sugar is < 150, run D10 solution at 200 ml/hr and saline solution at 0 ml/hr
- Potassium will be added to the fluids if the patient has normal renal function and potassium value is less than 5.2.
- The insulin infusion rate will not be adjusted until the anion gap has closed on 2 occurrences, unless patient develops hypoglycemia despite maximum D10 rate.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The subjects will be randomized into the two groups using a random number generator. Odd numbers will be assigned to the control group and even numbers will be assigned to the experimental group. Randomization will be performed on a 1:1 basis for the two groups. The providers/house officers are not able to be blinded, since they will be responsible for the IV fluid orders for the patients. The patients and the investigators will be blinded.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If the subject develops any of the potential risks, the patient will still be included in the study. The complication will be treated appropriately. If necessary, protocol deviations will be allowed in order to treat the complication. Protocol deviations will be documented.

The patient may also withdraw from the study if they decide they no longer want to participate.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Will allow if patient withdraws from the study.

8 STATISTICAL CONSIDERATIONS

8.1 SAMPLE SIZE DETERMINATION

We are planning a study of a continuous response variable from independent control and experimental subjects with 1 control per experimental subject. In a previous study the response within each subject group was normally distributed with standard deviation 1.6. If the true difference in the experimental and control means is 1.082, we will need to study 47 experimental subjects and 47 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.9. The Type I error probability associated with this test of this null hypothesis is 0.05.

8.2 POPULATIONS FOR ANALYSES

Data will be analyzed using the intention to treat method.

8.3 STATISTICAL ANALYSES

8.3.1 GENERAL APPROACH

Patient characteristics will be compared using Student's t-test or chi-squared tests, as appropriate. The time to anion gap closure between the traditional one bag system and the two bag system will be compared by the Student's t-test to determine if there is a statistically significant difference between the two groups. Secondary outcomes will be evaluated using chi-squared tests, bivariate and multivariable logistic regressions. The two group's time to anion gap closure can be compared graphically using a Kaplan Meier curve. The difference in time to anion gap closure between the two groups can be further analyzed using a multivariable Cox regression analysis to control for confounding

factors. All analyses will be performed using STATA 11.0 software. A p-value of <0.05 will be considered statistically significant.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

9.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

If the patient has altered mental status and is unable to consent, the next of kin or power of attorney will be approached for consent.

9.1.1.3 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 4 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending

or contemplated marketing applications in an ICH region or until at least 4 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations.

9.1.2 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the MetroHealth IRB has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

REFERENCES

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