Title: A single-center randomized double blind controlled clinical trial of intravenous fluid content in children with diabetic ketoacidosis admitted to the pediatric intensive care unit (NCT03066440)

Study protocol and statistical analysis plan to follow

Document date: 5/23/2019

University at Buffalo
The State University of New York
University at Buffalo Institutional Review Board (UBIRB)
Office of Research Compliance | Clinical and Translational Research Center Room 5018
875 Ellicott St. | Buffalo, NY 14203
UB Federalwide Assurance ID#: FWA00008824

Complete Research Protocol (HRP-503)

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Template Instructions

Sections that do not apply:

- *In several sections, the addition of checkboxes for **Not Applicable** have been added to the template as responses.*
    - *If an N/A checkbox is present, select the appropriate justification from the list.*
    - *If an N/A checkbox is not present, or if none of the existing checkboxes apply to your study, you must write in your own justification.*
- *In addition:*
    - *For research where the only study procedures are records/chart review: Sections 19, 20, 22, 23, 24, 25, 31, and 32 do not apply.*
    - *For exempt research: Sections 31 and 32 do not apply.*

Studies with multiple participant groups:

- *If this study involves multiple participant groups (e.g. parents and children), provide information in applicable sections for each participant group. Clearly label responses when they differ. For example:*

  Response:

  Intervention Group: Children with DKA who receive DKA management with intravenous fluids primarily containing lactated ringers

  Control Group: Children with DKA who receive DKA management with intravenous fluids primarily containing normal saline

Formatting:

- *Do not remove template instructions or section headings when they do not apply to your study.*

If you are pasting information from other documents using the "Merge Formatting" Paste option will maintain the formatting of the response boxes.

Amendments:

- *When making modifications or revisions to this and other documents, use the **Track Changes** function in Microsoft Word.*
- *Update the version date or number **on Page 3.***

PROTOCOL TITLE:

Include the full protocol title.

Response:

A single-center randomized double blind controlled clinical trial of intravenous fluid content in children with diabetic ketoacidosis admitted to the pediatric intensive care unit

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Department
Telephone Number
Email Address

Response:

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VERSION:

Include the version date or number.

Response:

Protocol version number: 3.0 Version date: May 23, 2019

GRANT APPLICABILITY:

Indicate whether this protocol is funded by a grant (e.g. NIH, foundation grant). For a grant with multiple aims, indicate which aims are covered by this research proposal.

NOTE: This question does not apply to studies funded by a sponsor contract.

Include a copy of the grant proposal with your submission.

Response:

This study is funded by a Wildermuth Foundation

The grant application will be included with this submission.

RESEARCH REPOSITORY:

Indicate where the research files will be kept, including when the study has been closed. The repository should include, at minimum, copies of IRB correspondence (approval, determination letters) as well as signed consent documents. This documentation should be maintained for 3 years after the study has been closed.

Response:

All data files will be entered electronically in the REDCap database. Paper documents will be stored in the Research Document Store Office (room 5154), Conventus Building, 1001 Main Street, Buffalo, NY 14203

1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives of this research.

Response:

Aim 1: To compare the duration of acidosis after admission in children randomized to receive intravenous fluids containing normal saline (NS) to those receiving intravenous fluids containing lactated ringers (LR) during the treatment of diabetic ketoacidosis in the pediatric intensive care unit.

Aim 2: To correlate the duration of acidosis with the length of hospitalization and intensive care unit stay after admission in children randomized to receive intravenous fluids containing normal saline to those receiving intravenous fluids containing lactated ringers during the treatment of diabetic ketoacidosis in the pediatric intensive care unit.

1.2 State the hypotheses to be tested, if applicable.

NOTE: A hypothesis is a specific, testable prediction about what you expect to happen in your study that corresponds with your above listed objectives.

Response:

Primary hypothesis: Children with diabetic ketoacidosis (DKA) who are treated with intravenous fluids containing lactated ringers will have a shorter duration of metabolic acidosis after hospital admission than those treated with intravenous fluids containing normal saline.

Secondary hypothesis: The duration of acidosis after hospital admission in children with DKA will be positively associated with length of stay in the intensive care unit and hospital.

2.0 Scientific Endpoints

2.1 Describe the scientific endpoint(s), the main result or occurrence under study.

NOTE: Scientific endpoints are outcomes defined before the study begins to determine whether the objectives of the study have been met and to draw conclusions from the data. Include primary and secondary endpoints. Some example endpoints are: reduction of

*symptoms, improvement in quality of life, or survival. Your response should **not** be a date.*

Response:

The **primary** study outcome will be the duration of metabolic acidosis after hospital admission.

Resolution of metabolic acidosis will be defined in three ways to delineate the iatrogenic effect from intravenous fluids from that of the primary pathology in diabetic ketoacidosis:

1. Serum ketone level <1mmol/L;
2. Venous pH > 7.3;
3. Serum bicarbonate level > 15mmol/L.

Secondary outcomes: Length of stay in the pediatric intensive care unit and length of stay in the hospital.

3.0 Background

3.1 Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute to existing knowledge. Describe any gaps in current knowledge. Include relevant preliminary findings or prior research by the investigator.

Response:

Diabetic Ketoacidosis occurs in approximately 30% of children with new onset type 1 diabetes mellitus (T1DM) and 5-10% of newly diagnosed children with type 2 diabetes [1]. DKA is a decompensated metabolic state resulting from insulin deficiency. DKA is characterized by acidosis, ketonemia, ketonuria, and hyperglycemia. Mortality from DKA in the United States is about 0.15%. Morbidity related to DKA is caused by shock, intestinal ischemia, cardiac arrhythmias, thrombosis, and cerebral edema [2, 3]. Clinically significant cerebral edema occurs in just 0.3-1% of all DKA, but results in 55-87% of all deaths related to DKA. The exact etiology of cerebral edema in DKA remains unclear, but it is consistently associated with osmotic shifts, hypoventilation, cerebral hypoperfusion, and administration of bicarbonate. With the intent to prevent shock, ischemia, and the thrombotic state, providers tend to administer large amounts of intravenous fluids in the form of 0.9% saline, also called normal saline, to patients in the initial treatment of DKA. Aggressive fluid administration has been shown to increase the risk of cerebral edema and does not reverse the primary metabolic deficiency driving the acidosis [4, 5].

During the treatment and recovery phases of DKA, the continued use of aggressive amounts of NS may be the mechanism by which patients develop a hyperchloremic metabolic acidosis (HMA) as NS contains a higher chloride concentration than serum. The detrimental clinical consequences of a high chloride load from intravenous fluids have been demonstrated in patients after trauma, in acute kidney injury, and in certain shock states [6, 7]. During HMA in

DKA, the anion gap and ketosis have resolved, but acidosis persists due to an abnormally high chloride level caused by large volumes of NS coupled with the increased absorption of chloride by the kidney as less bicarbonate is generated due to the excretion of ketones in urine [8-10]. In retrospective data, the occurrence of HMA in DKA was correlated with a delayed resolution of acidosis and prolonged hospital stay. A prolonged hospital stay is associated with preventable financial burden, overutilization of health care resources, and missed days of work and school.

Lactated Ringers is an intravenous fluid that not only has lower chloride content than NS but also buffers acidosis by generating bicarbonate from lactate. By mitigating the rates of or severity of HMA, use of LR could potentially shorten length of stay and the morbidity of prolonged hospitalization.

There have been limited prospective clinical studies in pediatric patients examining the association of the chloride content of intravenous fluids and outcome in DKA. This prospective randomized controlled trial is being performed to compare the duration of acidosis and hospital length of stay in children with DKA who are admitted to a pediatric intensive care unit and are treated with intravenous fluids containing NS or LR. The primary study hypothesis is that use of LR will be associated with decreased duration of hyperchloremic metabolic acidosis and, therefore, shorter hospitalization than use of NS in the treatment of pediatric DKA.

3.2 Include complete citations or references.

Response:

1. Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, et al. Trends in the Prevalence of Ketoacidosis at Diabetes Diagnosis: The SEARCH for Diabetes in Youth Study. Pediatrics. 2014;133(4):e938-e45.

2. Wolfsdorf JI, Allgrove J, Craig ME, Edge J, Glaser N, Jain V, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Pediatr Diabetes. 2014;15 Suppl 20:154-79.

3. Wolfsdorf JI. The International Society of Pediatric and Adolescent Diabetes guidelines for management of diabetic ketoacidosis: Do the guidelines need to be modified? Pediatr Diabetes. 2014;15(4):277-86.

4. Glaser NS, Ghetti S, Casper TC, Dean JM, Kuppermann N, Pediatric Emergency Care Applied Research Network DKAFSG. Pediatric diabetic ketoacidosis, fluid therapy, and cerebral injury: the design of a factorial randomized controlled trial. Pediatr Diabetes. 2013;14(6):435-46.

5. Wolfsdorf J, Glaser N, Sperling MA. Diabetic ketoacidosis in infants, children, and adolescents: A consensus statement from the American Diabetes Association. Diabetes Care. 2006;29(5):1150-9.

6. Langer T, Santini A, Scotti E, Van Regenmortel N, Malbrain ML, Caironi P. Intravenous balanced solutions: from physiology to clinical evidence. Anaesthesiol Intensive Ther. 2015;47 Spec No:s78-88.

7. Yunos N, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. ASsociation between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308(15):1566-72.

8. Van Zyl DG, Rheeder P, Delport E. Fluid management in diabetic-acidosis--Ringer's lactate versus normal saline: a randomized controlled trial. QJM. 2012;105(4):337-43.

9. Mahler SA, Conrad SA, Wang H, Arnold TC. Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis. Am J Emerg Med. 2011;29(6):670-4.

10. Adrogue HJ, Wilson H, Boyd AE, 3rd, Suki WN, Eknoyan G. Plasma acid-base patterns in diabetic ketoacidosis. N Engl J Med. 1982;307(26):1603-10.

4.0 Study Design

4.1 Describe and explain the study design (e.g. case-control, cross-sectional, ethnographic, experimental, interventional, longitudinal, and observational).

Response:

This is a single center, double blinded, randomized controlled trial with two treatment arms to be performed at a single tertiary care children's hospital. Patients will be randomized within 2 hours of initiation of care to receive DKA management using intravenous fluids containing primarily normal saline or lactated ringers. All other aspects of DKA management will be the same in each arm, per the institution protocol.

5.0 Local Number of Subjects

5.1 Indicate the total number of subjects that will be enrolled or records that will be reviewed locally.

Response:

We plan to enroll 104 subjects in the study with 52 in each arm.

5.2 If applicable, indicate how many subjects you expect to screen to reach your target sample (i.e. your screen failure rate).

Response:

All children with Diabetic ketoacidosis presenting to the John R. Oishei Children's Hospital (OCH) emergency department (ED) or transferred directly from outside facility to the pediatric intensive care unit (PICU) will screened for eligibility. Patients who are directly admitted to the PICU will represent 10% of the study sample with the remainder coming from the ED. As not all children in DKA are admitted to the PICU from the ED, it is estimated that approximately an additional 200 patients will be screened in the ER to achieve the target study size. In total, we anticipate screening approximately 310 patients with DKA for this study.

5.3 Justify the feasibility of recruiting the proposed number of eligible subjects within the anticipated recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Response:

Using historical patient volume data, it is estimated that approximately 2 years will be required to reach the target enrollment number.

6.0 Inclusion and Exclusion Criteria

*6.1 Describe the criteria that define who will be **included** in your final study sample.*

NOTE: This may be done in bullet point fashion.

Response:

Inclusion criteria:

1. Age between 0 and 18 years
2. Diagnosis of DKA from Type I DM:
   a. Venous pH less than 7.25
   b. Ketonuria as confirmed on urine point-of-care testing or urinalysis
   c. Hyperglycemia (Serum glucose > 200 mg/dl)
   d. Serum bicarbonate <15 mmol/L
3. Need for PICU admission based on clinical discretion

*6.2 Describe the criteria that define who will be **excluded** from your final study sample.*

NOTE: This may be done in bullet point fashion.

Response:

Exclusion criteria:

1. Physician discretion for any reason not listed here
2. Septic or hypovolemic shock
3. Signs of life-threatening cerebral edema or multi-organ failure upon presentation to the emergency room or pediatric intensive care unit
4. More than 2 hours since arrival to the PICU or from first provider contact in the emergency room
5. Pregnancy
6. Type II DM
7. Elevated anion gap metabolic acidosis from another source other than ketoacidosis

6.3 Indicate specifically whether you will include any of the following special populations in your study using the checkboxes below.

NOTE: Members of special populations may not be targeted for enrollment in your study unless you indicate this in your inclusion criteria.

Response:

☐ Adults unable to consent

☒ Individuals who are not yet adults (infants, children, teenagers)

☐ Pregnant women

☐ Prisoners

6.4 Indicate whether you will include non-English speaking individuals in your study. ***Provide justification if you will exclude non-English speaking individuals.***

In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may ***not*** *be routinely excluded from research as a matter of convenience.*

In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English. Some examples include pilot studies, small unfunded studies with validated instruments not available in other languages, studies with numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.

Response:

Non-English speaking individuals will not be enrolled in this study. Spanish, Burmese, Somalian, Chinese, Russian, Arabic are the languages most likely to be spoken by the prospective subjects' legal guardian.

We expect to encounter a diverse group of non-English speaking legal guardians. The above list of languages does not include all non-English languages that we may encounter during our study recruitment phase.

We will not enroll non-English speaking subjects in this study as it is impractical for us to translate the consent documents in all conceivable languages. Meanwhile, it is impractical for us to have two people who speak the same non-English language during the recruitment phase with one being the person who obtains the consent and one being the witness per our IRB request at any given time.

By not including non-English speaking subjects in this study, we are not withholding any benefit from these patients. Meanwhile, we do not anticipate that we add any burden to the patients enrolled in the study.

The main purpose of this study is to compare the duration of acidosis after admission in children randomized to receive intravenous fluids containing normal saline to those receiving intravenous fluids containing lactated ringers during the treatment of DKA in the pediatric intensive care unit.

Treating a DKA patient with normal saline or lactated ringers are currently both the standard of care at this institution. For a patient who is eligible and enrolled in the study, he/she will be randomized to receive either normal saline or lactated ringers in a controlled setting. For patients who meet study criteria that are not enrolled in the study, they will also receive either normal saline or lactated ringers or a mixture of both, depending on the treating physician's discretion. So regardless of whether a child with DKA is enrolled in the study or not, he/she will receive similar treatment.

Thus, we will exclude subjects whose legal guardians do not speak English from the study due to the above mentioned reasons. We believe that we will not withhold any benefit from non-participants, nor add undue burden to the participants by not enrolling non-English speaking patients in the study.

7.0 Vulnerable Populations

If the research involves special populations that are considered vulnerable, ***describe the safeguards included to protect their rights and welfare.***

NOTE: You should refer to the appropriate checklists, referenced below, to ensure you have provided adequate detail regarding safeguards and protections. You do not, however, need to provide these checklists to the IRB.

7.1 For research that involves ***pregnant women,*** *safeguards include:*
NOTE CHECKLIST: Pregnant Women (HRP-412)

Response:

☒ **N/A**: This research does not involve pregnant women.

7.2 For research that involves ***neonates of uncertain viability or non-viable neonates,*** *safeguards include:*
NOTE CHECKLISTS: Non-Viable Neonates (HRP-413), or Neonates of Uncertain Viability (HRP-414)

Response:

☒ **N/A:** This research does not involve non-viable neonates or neonates of uncertain viability.

7.3 For research that involves ***prisoners****, safeguards include:*
NOTE CHECKLIST: Prisoners (HRP-415)

Response:

☒ **N/A:** This research does not involve prisoners.

7.4 For research that involves ***persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children")****, safeguards include:*
NOTE CHECKLIST: Children (HRP-416)

Response:

We will obtain consent from legal guardians.

☐ **N/A:** This research does not involve persons who have not attained the legal age for consent to treatments or procedures ("children").

*7.5 For research that involves **cognitively impaired adults**, safeguards include: NOTE CHECKLIST: Cognitively Impaired Adults (HRP-417)*

Response:

☒ **N/A:** This research does not involve cognitively impaired adults.

*7.6 Consider if other specifically targeted populations such as students, employees of a specific firm, or educationally or economically disadvantaged persons are vulnerable. **Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.***

Response:

No other specially targeted populations will be enrolled in this study.

8.0 Eligibility Screening

*8.1 Describe **screening procedures** for determining subjects' eligibility. Screening refers to determining if prospective participants meet inclusion and exclusion criteria.*

Include all relevant screening documents with your submission (e.g. screening protocol, script, and questionnaire).

Response:

The screening will be performed 7 days a week and 14 hours a day by the research assistants and coordinator in the emergency department. If a patient is admitted directly to the PICU, the PICU physicians will actively screen patient for eligibility on a 24-hour basis. There will be a screening form to facilitate the screening (attached with this submission).

☐ **N/A:** There is no screening as part of this protocol.

9.0 Recruitment Methods

☐ **N/A:** This is a records review only, and subjects will not be recruited. NOTE: If you select this option, please make sure that all records review procedures and inclusion/exclusion screening are adequately described in other sections.

9.1 Describe when, where, and how potential subjects will be recruited.

NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study. Include specific methods you will use (e.g. searching charts for specific ICD code numbers, Research Participant Groups, posted advertisements, etc.).

Response:

Most subjects will be recruited in the ED of John R. Oischei Children's Hospital. A research assistant (RA) or the study coordinator will actively screen potential

eligible patients by checking the ED patients' chart in the Kaleida health electronic PowerChart system. A patient with chief complains such as "DKA, hyperglycemia, high blood glucose, fast breathing, weight loss, excessive thirst or peeing" will be screened for eligibility. If a patient is suspected to be eligible for the study, the RA or the coordinator will approach the treating physician, and ask him/her to identify the eligibility of this patient by going over the screening form.

If a patient is directly admitted to the PICU from outside facility, the bedside clinician will screen eligibility by using the screening form.

The screening form is readily available in the PICU and ED for use.

9.2 Describe how you will protect the privacy interests of prospective subjects during the recruitment process.

NOTE: Privacy refers to an individual's right to control access to him or herself.

Response:

If a patient is identified to be eligible for the study in the ED, one of the study PIs or coordinator, or an ED fellow physician will approach the potential subject and his/her legal guardian in the patient's room in the ED and introduce the study to them when no other people are around.

If a patient is identified to be eligible in the PICU, one of the study PIs or the coordinator, or a PICU fellow will approach the potential subject and his/her legal guardian in the patient's room in the PICU and introduce the study to them when no other people are around.

9.3 Identify any materials that will be used to recruit subjects.

NOTE: Examples include scripts for telephone calls, in person announcements / presentations, email invitations.

For advertisements, include the final copy of printed advertisements with your submission. When advertisements are taped for broadcast, attach the final audio/video tape. NOTE: You may submit the wording of the advertisement prior to taping to ensure there will be no IRB-required revisions, provided the IRB also reviews and approves the final version.

Response:

No recruitment materials will be used for this study.

10.0 Procedures Involved

*10.1 Provide a description of **all research procedures or activities** being performed and when they are performed once a subject is screened and determined to be eligible. Provide as much detail as possible.*

NOTE: This should serve as a blueprint for your study and include enough detail so that another investigator could pick up your protocol and replicate the research. For studies that have multiple or complex visits or procedures, consider the addition of a schedule of events table in in your response.

Response:

Upon consenting, a copy of the signed informed consent document with the subject name and medical record number will be sent to our inpatient pharmacy by an ED research assistant if the subject is enrolled in the ED. If a subject is enrolled in the PICU, the signed consent will be faxed to the inpatient's pharmacy. Meanwhile, the study protocol will be placed using an electronic order set containing the study DKA management protocol that is identical to the routine management of DKA with the exception of the fluid content per arm. Please refer to study protocol schematic shown in supplement 1.

After receiving the copy of the consent, patients will be randomly assigned a treatment arm (group A or B) and a study ID by the pharmacy following a randomization table generated by a statistician. Each group correlates with a treatment arm assignment visible on a randomization table available only to the inpatient pharmacy personnel. Pharmacy personnel will then provide the appropriate content to the intravenous fluids with a generic label "DKA study fluids with dextrose" and "DKA study fluids without dextrose." The fluids look identical as the bags will be labeled with standardized labelling as "DKA Study fluid with dextrose" or "DKA study fluid without dextrose." **The study ID will also be labeled on the bags and typed into the electronic orders by pharmacy.** The bags will be properly covered by the labels to ensure complete blinding of the subject and the medical treatment team. The intravenous fluids will be transported to the patients per the regular system used in the ER and PICU.

We anticipate that the eligible patients will be consented within 2 hours of arrival to the PICU or after the first provider makes contact in the ED and shortly thereafter started on continuous infusions of intravenous fluids and insulin per the study protocol.

After admission to the PICU, DKA fluid management uses a two-bag system to maintain glucose levels between 100 and 300 mg/dL. Once the patient's glucose concentration falls below 300 mg/dL, the intravenous fluids containing dextrose are started and the fluids without dextrose are titrated downward. In addition to containing necessary electrolytes, the study intravenous fluids will contain either lactated ringer's or normal saline based on the assigned treatment arm.

Study fluid management of the two-bag system will follow the same guidelines for rate of fluid delivery and amount of dextrose used currently in the routine management of patients in DKA. Bedside healthcare personnel will treat all study subjects identically regardless of treatment arm. To provide blinding to all bedside staff, intravenous fluid bags will be labelled as "DKA study fluid with dextrose" or "DKA study fluid without dextrose." The fluid bags will be covered with an opaque black bag to mask any visible description of the fluid content.

Fluids will be adjusted using the study protocol as outlined here:

Serum Glucose	DKA study fluids without dextrose	DKA study fluids with dextrose
>300mg/dL	100% of the hourly rate	0%

200-300 mg/dL	50% of the hourly rate	50% of the hourly rate
<200 mg/dL	0%	100% of the hourly rate

Study participants will not receive any additional laboratory tests other than those that are already involved in standard DKA management. Currently, routine DKA management involves hourly finger-stick or laboratory glucose levels, every 2-hour serum electrolytes and blood gases, every 6-hour serum beta-hydroxybutyrate levels, and urine ketones with every void. This will be the same for all study participants on both treatment arms.

The study fluids will be used until the acute management of DKA using the continuous insulin infusion and two-bag fluid system is stopped. This will occur when the venous pH is equal to or greater than 7.30, the serum bicarbonate level is equal to or greater than 15 mmol/L and serum ketone levels are less than 1mmol/L.

10.2 Describe what data will be collected.

NOTE: For studies with multiple data collection points or long-term follow up, consider the addition of a schedule or table in your response.

Response:

Baseline demographic data that will be collected including age, sex, race, co-morbid conditions, vital signs, number of hospitalizations for DKA in the preceding 12 months, and date and time of transfer to the PICU.

ED lab data that will be collected include all laboratories obtained in the ED, intravenous fluid volume and type administered, time to start of insulin and PRISM score.

PICU lab data that will be collected include all pH, bicarbonate, anion gap, chloride and beta-hydroxybutyrate levels, sodium, potassium, BUN, creatinine, glucose etc. If the patient remains in DKA after 32 hours after initial ED labs, PICU lab data will be collected until the closest to 36 hours after the initial ED labs were obtained.

Outcomes to be collected include length of stay in the hospital and ICU, resolution of acidosis including time to a serum pH>7.30, bicarbonate >15mg/dl, and normal anion gap.

10.3 List any instruments or measurement tools used to collect data (e.g. questionnaire, interview guide, validated instrument, data collection form).

Include copies of these documents with your submission.

Response:

Please find the attached (1) Demographic data form, (2) ER laboratory data form, (3) Outcomes data form, (4) PICU laboratory data form, (5) Screening form

10.4 Describe any source records that will be used to collect data about subjects (e.g. school records, electronic medical records).

Response:

All the data will be collected from the electronic medical records of enrolled subjects using the Kaleida Health Powerchart system.

*10.5 Indicate whether or not **individual** subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.*

Response:

No individual subject results will be shared with subjects or his or her primary care physician.

*10.6 Indicate whether or not **study** results will be shared with subjects or others, and if so, describe how these will be shared.*

Response:

No study results will be shared with subjects or others. Final results of this study may be presented at a conference or published in a peer-reviewed journal, but only group data will be published in these circumstances; no individual data will be shared.

11.0 Study Timelines

11.1 Describe the anticipated duration needed to enroll all study subjects.

Response:

The study will enroll children with DKA for an estimated period of 2 years or as long as needed to reach the target study size of 104 patients. If the number is reached in earlier than anticipated time-period, the enrollment will stop.

11.2 Describe the duration of an individual subject's participation in the study. Include length of study visits, and overall study follow-up time.

Response:

Study participation begins from randomization to hospital discharge. The study intervention will cease once acute DKA management is stopped in the PICU prior to floor transfer. The choice of intravenous fluid, if any needed, will then be left to the discretion of the managing team.

11.3 Describe the estimated duration for the investigators to complete this study (i.e. all data is collected and all analyses have been completed).

Response:

We plan to complete patient recruitment with 2 years of time based on the volume seen in a previously completed chart review study. With an additional 6 to 9

months needed for data analysis and manuscript preparation, a total of 33 months will span study initiation to completion.

12.0 Setting

12.1 Describe all facilities/sites where you will be conducting research procedures. Include a description of the security and privacy of the facilities (e.g. locked facility, limited access, privacy barriers). Facility, department, and type of room are relevant. Do not abbreviate facility names.

NOTE: Examples of acceptable response may be: "A classroom setting in the Department of Psychology equipped with a computer with relevant survey administration software," "The angiogram suite at Buffalo General Medical Center, a fully accredited tertiary care institution within New York State with badge access," or, "Community Center meeting hall."

Response:

This study will be performed in the private patient's room in Emergency Department and the Pediatric Intensive Care Unit of John R Oishei Children's Hospital. It is a fully accredited, free-standing children's hospital with academic and tertiary care services.

12.2 For research conducted outside of UB and its affiliates, describe:

- *Site-specific regulations or customs affecting the research*
- *Local scientific and ethical review structure*

NOTE: This question is referring to UB affiliated research taking place outside UB, i.e. research conducted in the community, school-based research, international research, etc. It is not referring to multi-site research. UB affiliated institutions include Kaleida Health, ECMC, and Roswell Park Cancer Institute.

Response:

☒ **N/A:** This study is not conducted outside of UB or its affiliates.

13.0 Community-Based Participatory Research

13.1 Describe involvement of the community in the design and conduct of the research.

NOTE: Community-Based Participatory Research (CBPR) is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

Response:

☒ **N/A:** This study does not utilize CBPR.

13.2 Describe the composition and involvement of a community advisory board.

Response:

☒ **N/A:** This study does not have a community advisory board.

14.0 Resources and Qualifications

*14.1 Describe the qualifications (e.g., education, training, experience, expertise, or certifications) of the Principal Investigator **and** staff to perform the research. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research.*

NOTE: If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify a person by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that the person meets the qualifications described to fulfill their roles.

Response:

This study is a multidisciplinary study involving fellow and attending physicians in the divisions of pediatric critical care, emergency medicine, and endocrinology in the Department of Pediatrics.

The principal investigator is Dr. Amanda Hassinger, a clinical associate professor of pediatrics and an attending physician in PICU. She has a Master's of Science in Epidemiology. She was the site PI for several NIH-funded multi-center trials and has active ongoing research in pediatric critical care and pediatrics. She also serves as research mentor for numerous residents and fellows.

The following physicians will be co-investigators for this study.

Dr. Ryan Breuer, a clinical assistant professor of pediatrics and an attending physician in the PICU. He has a MPH as well as has participated in several NIH-funded and multi-center trials. He is the assistant program director for the pediatric critical care fellowship and is a mentor to pediatric residents and fellows.

Dr. Jill Fennell, a third year fellow in pediatric emergency medicine program, she has been a PI and co-PI for other clinical and quality improvement studies.

Dr. Kathleen Bethin is an attending physician in Pediatric Endocrinology at OCH. She has been involved in many NIH and pharmaceutical funded clinical studies in the past. She also has been and is a research mentor for numerous residents and fellows.

Dr. Michelle Penque is an attending physician in pediatric emergency medicine and the medical director of the OCH Emergency Medicine Division. She has been actively involved in clinical research studies and serves as a research mentor for residents and fellows.

Haiping Qiao is the study coordinator at OCH. She has 14 years of clinical research experience. She has been involved in numerous clinical research projects in the Department of Pediatrics including but not limited to randomized drug trials, device studies, chart reviews, surveys, and observational studies. She will be responsible for IRB submission, obtaining informed consents as well as training the ED RAs for this project.

The statistician, Dr. Brian Wrotniak, has extensive expertise in study design and data analysis. He is responsible for study design and data analysis for this study.

The ED and PICU fellows will assist to obtain informed consents when the PIs and study coordinator are not available. They have been trained and updated every 6 months on the progress and detail of this study.

Describe other resources available to conduct the research.

Response: A group of research assistants in the ED will help us to screen potential eligible patients seven days a week.

14.2 Describe the time and effort that the Principal Investigator and research staff will devote to conducting and completing the research.

NOTE: Examples include the percentage of Full Time Equivalents (FTE), hours per week. The question will elicit whether there are appropriate resources to conduct the research.

Response:

The study PIs will share the duties of study maintenance, surveillance and data collection. This could represent upwards of 5-10 hours per week depending on study enrollment volume.

The PI, Dr. Hassinger, will be offsite for one year starting in July 2019. Dr. Breuer will be responsible for daily supervision of the project while she is gone. This is estimated to represent 2-3 hours per week over the course of the project.

14.3 Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the human research, if applicable.

NOTE: One example includes: on-call availability of a counselor or psychologist for a study that screens subjects for depression.

Response:

There is no need for medical or psychological resources for subjects of this project, since this study involves no more than minimal risk. Patients enrolled in this study will receive either normal saline or lactated ringer intravenous fluids; both of which are used by physicians per clinical discretion as a part of routine DKA care. Being in the study does not add extra risk for subjects.

14.4 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Response:

The PI, co-PIs, and study coordinator have been involved in the study protocol development. They know the study aims, design, and procedures very well. The PI will train the co-PIs on data collection prior to subject enrollment.

In addition, the PI and co-PIs will present the study at the PICU and ED faculty and research meetings to inform them of the study protocol and procedures, to ensure compliance and update on changes. For those who miss the training at the faculty meetings, the PI and co-PI will offer individual training to them. In addition, the PI, co-PI or the study coordinator will offer training to the PICU and ED fellows on how to obtain consent. The refresh training will be done every 12 months or when new personnel start in each division. All the training procedures will be documented on the training log as part of regulatory documents.

Our research assistants (RA) in the ED are directly working under the supervision of the study coordinator. The RAs' job duties include: screening potential eligible patients and assisting subject enrollment. The study coordinator will provide training to all RAs before the start of recruitment. In addition, RA re-training will be done every 12 months during the subject recruitment period. All training process will be documented on training logs.

The training will focus on the following aspects:

1. Review study protocol by presenting the materials to the RAs with a slide show. The RAs are required to understand the study aims/purpose and the detail study procedures.

2. Review subject screening form. The RAs are required to know the inclusion and exclusion criteria for the study and know what kind of patients are potentially eligible and need to screen for the study.

3. Training the RAs on the post consenting procedures including sending the consent to pharmacy, and transferring the fluid bag back to the ED.

The trainer and trainees' names will be documented in the training log. The training log will be kept as one of the regulatory documents for this study.

All our study team members are CITI trained.

15.0 Other Approvals

15.1 Describe any approvals that will be obtained prior to commencing the research (e.g., school, external site, funding agency, laboratory, radiation safety, or biosafety).

Response:

☒ **N/A:** This study does not require any other approvals.

16.0 Provisions to Protect the Privacy Interests of Subjects

16.1 Describe how you will protect subjects' privacy interests during the course of this research.

NOTE: Privacy refers to an individual's right to control access to him or herself. Privacy applies to the person. Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.

Examples of appropriate responses include: "participant only meets with a study coordinator in a classroom setting where no one can overhear", or "the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."

Response:

The study team will approach patients and their legal guardians in the private patient rooms in the ED or PICU to introduce the study to them when no other people are around.

16.2 Indicate how the research team is permitted to access any sources of information about the subjects.

NOTE: Examples of appropriate responses include: school permission for review of records, consent of the subject, HIPAA waiver. This question ***does apply*** *to records reviews.*

Response:

All study personnel are active physicians or researchers at OCH and have been granted privileges by Kaleida Health IST to access the medical records in Powerchart for carrying out their duties as clinician or researchers. In addition, we are asking for a partial HIPAA waiver from our IRB for patient screening purposes.

17.0 Data Management and Analysis

17.1 Describe the data analysis plan, including any statistical procedures. This section applies to both quantitative and qualitative analysis.

Response:

Univariate analysis will be used to determine if the subjects in each treatment arm differ at baseline through t-test or Wilcoxon Rank Sum testing for continuous data and Chi-square testing for categorical data. Any differences will be controlled for in the analysis of the primary outcome (length of acidosis) using linear regression. All outcomes will be correlated with the overall chloride load given via intravenous fluids during DKA management. All analyses will be performed using IBM SPSS software, version 25 (Chicago, IL) and SAS (SAS Institute Inc., Cary, NC) with significance set at $p<0.05$.

17.2 If applicable, provide a power analysis.

NOTE: This may not apply to certain types of studies, including chart/records reviews, survey studies, or observational studies. This question is asked to elicit

whether the investigator has an adequate sample size to achieve the study objectives and justify a conclusion.

Response:

Our retrospective chart review of 55 pediatric patients admitted to the PICU with DKA found that it took a median of 8 hours (IQR 1-3, 4-8) for the anion gap to normalize and an additional 8 hours (IQR 1-3, 3-14) for overall acidosis to resolve. A power calculation using these data found that a total of 104 patients (52 patients in each arm) are required to attain 80% power to detect a difference in the median duration of acidosis of 8 hours at a significance level of $p<0.01$.

If an interim data analysis at 50% enrollment shows a trend toward inadequate power, additional subjects may be added to ensure successful hypothesis testing can be performed. If the inverse is true, the study may be stopped early.

17.3 Describe any procedures that will be used for quality control of collected data.

Response:

All data will be reviewed for outliers and queried using established data validation methods by the PI.

18.0 Confidentiality

A. Confidentiality of Study Data

Describe the local procedures for maintenance of confidentiality of ***study data and any records that will be reviewed for data collection****.*

18.1 A. Where and how will all data and records be stored? Include information about: password protection, encryption, physical controls, authorization of access, and separation of identifiers and data, as applicable. Include physical (e.g. paper) ***and*** *electronic files.*

Response:

The signed consent documents and screening form with patient ID sticker will be placed in locked data boxes in the ED and PICU. The study coordinator will collect these documents on a daily basis, and store them in a locked file cabinet in Conventus building, Room 5154, 1001 Main Street, Buffalo, NY 14222.

All study associated data will be collected by Dr. Breuer and co-PI, Dr. Jill Fennell at their offices located in the PICU attending and ED fellow offices. Both offices, Room 5281 and 5238, are located on the 5th floor in Conventus building. They will collect data by logging in password protected Kaleida electronic Powerchart system.

Study data will be entered into a password protected UB online secure database, REDcap by Drs. Hassinger or Fennell. If data is collected at any time using paper forms, these forms will be discarded into a HIPAA bin once entered into REDcap.

PHI including ED admission date, PICU admission and discharge date, and hospital discharge date will be collected in data form. Each subject's data will be identified using an assigned study ID. The study ID number will be used to label the subject's data forms and will also be the code key to link the subjects' identities and their data. The PI and co-PI will be fully responsible to protect the confidentiality of the data in the process of collecting data.

Subject's study ID number, randomization group, medical record number Record ID and enrollment date will be documented on a subject enrollment log, the Record ID is generated by REDCap when a subject data is entered in the database. The subject enrollment log will be saved on a secure online drive in the study coordinator, PI and Co-PI (Dr. Jill Fennell)'s password-protected computers.

18.2 A. How long will the data be stored?

Response:

The electronic database saved in REDCap will be stored online indefinitely. Enrollment logs will be stored for three years after study is closed by IRB, then it will be deleted from the online secure drive. Signed informed consent and screening forms will be stored in locked file cabinet for three years after study is closed.

18.3 A. Who will have access to the data?

Response:

The PI, co-PIs will have access to the data. The statistician will have access to the de-identified data for data analysis purposes, but will not have access to any PHI. The study coordinator will have access to the signed consent documents and the screening forms.

18.4 A. Who is responsible for receipt or transmission of the data?

Response:

The study coordinator will be responsible for transmission of the signed consent, screening form and the subject enrollment log.

18.5 A. How will the data be transported?

Response:

Data will be entered in password protected electronic database REDCap. The study coordinator will manually collect informed consent and screening forms from ED and PICU. In addition, the coordinator will send the subject enrollment log to the PI and co-PI via secure email system.

B. Confidentiality of Study Specimens

*Describe the local procedures for maintenance of confidentiality of **study specimens**.*

☒ **N/A:** No specimens will be collected or analyzed in this research. *(Skip to Section 19.0)*

18.6 B. Where and how will all specimens be stored? Include information about: physical controls, authorization of access, and labeling of specimens, as applicable.

Response:

18.7 B. How long will the specimens be stored?

Response:

18.8 B. Who will have access to the specimens?

Response:

18.9 B. Who is responsible for receipt or transmission of the specimens?

Response:

18.10 B. How will the specimens be transported?

Response:

19.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

NOTE: Minimal risk studies may be required to monitor subject safety if the research procedures include procedures that present unique risks to subjects that require monitoring. Some examples include: exercising to exertion, or instruments that elicit suicidality or substance abuse behavior. In such cases, N/A is not an acceptable response.

19.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Response:

Subjects enrolled in this study will receive intravenous fluid containing normal saline or lactated ringer's; both fluids are considered standard of care in the treatment of DKA. There is no other intervention for this study, we believe this study does not involve more than minimum risk to the participants. However, interim outcome analysis will be performed every 6 months to identify any problems that may associate with the study.

19.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response:

In the interim analysis, patient outcomes will be reviewed as will any adverse events. An adverse event will be defined as any clinically important untoward medical occurrence in a child enrolled in this study different from what is expected in the clinical course of a child with DKA.

The investigator will evaluate any changes in laboratory values and physical signs and will determine if the change is clinically important and different from what is expected in the clinical course patients with DKA. Expected events for DKA are untoward clinical occurrences that are perceived by the investigator to occur with reasonable frequency in the day-to-day care of patients with DKA treated in an intensive care unit. Examples of expected events that may occur during treatment of DKA include cerebral edema, thrombotic events, acute kidney injury, hypokalemia, hypomagnesemia, hypophosphatemia, hypernatremia, hyponatremia, hyperchloremia, hyperglycemia and hypoglycemia.

Expected events will be evaluated monthly by the investigators and will not be considered reportable unless the event is considered by the investigator to be associated with the study procedures such as unexpectedly severe or more frequent than usually seen in the treatment of DKA. Organ failures related to DKA or an underlying condition will not be reported as adverse events. These will be captured in the data collection form but are routine occurrences during the treatment and recovery phase of DKA.

19.3 Describe the frequency of safety data collection.

Response:

As there is minimal risk related to this study, no regular safety data will be collected.

19.4 Describe who will review the safety data.

Response:

As there is minimal risk related to this study, no regular safety data will be collected nor will need review.

19.5 Describe the frequency or periodicity of review of cumulative safety data.

Response:

The aggregate study data will be analyzed every 6 months. The frequency of all expected complications from DKA will be analyzed at that time.

19.6 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response:

Observed rates of expected events will be statistically compared using one-sided t-tests to previously reported rates of known complications associated with DKA to ensure that participants do not have a significantly higher rate of complications.

19.7 Describe any conditions that trigger an immediate suspension of the research.

Response:

As the study protocol does not vary from the standard treatment, there is no obvious trigger or possible event that can be anticipated to lead to immediate suspension of the research.

20.0 Withdrawal of Subjects

☐ **N/A:** This study is not enrolling subjects. This section does not apply.

*20.1 Describe **anticipated** circumstances under which subjects may be withdrawn from the research without their consent.*

Response:

If there are any concerns from the managing team at any time, the patient can be withdrawn from the study and intravenous fluids can be ordered open-label at any time.

20.2 Describe any procedures for orderly termination.

NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.

Response:

After termination of study protocol, managing physicians can order any intravenous fluids if needed based on clinical scenario. No additional follow up with the subject is planned after withdrawn from the study.

20.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.

Response:

After withdrawal of subjects, outcomes data will still be collected until hospital discharge with the permission of the guardian and participant.

21.0 Risks to Subjects

21.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks. Include a description of the probability, magnitude, duration, and reversibility of the risks.

NOTE: Breach of confidentiality is always a risk for identifiable subject data.

Response:

This study involves use of intravenous fluids which are part of the standard of care. Therefore, this study provides minimal risk. Breach of confidentiality is the only potential risk.

21.2 Describe procedures performed to lessen the probability or magnitude of risks, including procedures being performed to monitor subjects for safety.

Response:
Please refer to section 18 for protecting the confidentiality about study data. In summary, signed informed consent and patient screening form will be stored in locked study boxes in the ED and PICU and collected daily by the study coordinator, and then stored in locked file cabinet in research document room in the Conventus building. Data will be collected by PI and co-PIs (Drs. Ryan Breuer and Jill Fennell) in their offices and entered directly in password protected online secure database RedCap. Subject enrollment log will be sent by the coordinator to the PI and co-PI via secure email system and stored in password protected UPA online secure drive.

*21.3 If applicable, indicate **which procedures** may have risks to the subjects that are currently unforeseeable.*

Response:

None

21. 4 If applicable, indicate which research procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Response:

None

21.5 If applicable, describe risks to others who are not subjects.

Response:

None

22.0 Potential Benefits to Subjects

22.1 Describe the potential benefits that individual subjects may experience by taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit.

*NOTE: Compensation **cannot** be stated as a benefit.*

Response:
There is no direct benefit associated with participating in this study. The results of this study are intended to improve the outcomes of children with DKA in the future by shortening the length of stay and decreasing the incidence of iatrogenic hyperchloremic acidosis.

23.0 Compensation for Research-Related Injury

☒ **N/A:** The research procedures for this study do not present risk of research related injury (e.g. survey studies, records review studies). This section does not apply.

23.1 ***If the research procedures carry a risk of research related injury,*** *describe the available compensation to subjects in the event that such injury should occur.*

Response:

23.2 Provide a copy of contract language, if any, relevant to compensation for research related injury.

NOTE: If the contract is not yet approved at the time of this submission, submit the current version here. If the contract is later approved with ***different language regarding research related injury****, you must modify your response here and submit an amendment to the IRB for review and approval.*

Response:

24.0 Economic Burden to Subjects

24.1 Describe any costs that subjects may be responsible for because of participation in the research.

NOTE: Some examples include transportation or parking.

Response:

There is no financial burden on subjects because of participation in this study.

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

25.0 Compensation for Participation

25.1 Describe the amount and timing of any compensation to subjects, including monetary, course credit, or gift card compensation.

Response:

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

☒ **N/A:** There is no compensation for participation. This section does not apply.

26.0 Consent Process

26.1 Indicate whether you will be obtaining consent.

NOTE: This does not refer to consent documentation, but rather whether you will be obtaining permission from subjects to participate in a research study. Consent documentation is addressed in Section 27.0.

☒ ***Yes*** *(If yes, Provide responses to each question in this Section)*
☐ ***No*** *(If no, Skip to Section 27.0)*

26.2 Describe where the consent process will take place. Include steps to maximize subjects' privacy.

Response:

To protect patient privacy, the consent process will take place in the patient's room in the ED or PICU when no other people are around except the legal guardian and patient.

26.3 Describe how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study.

NOTE: It is always a requirement that a prospective subject is given sufficient time to have their questions answered and consider their participation. See "SOP: Informed Consent Process for Research (HRP-090)" Sections 5.5 and 5.6.

Response:

The treatment for DKA needs to be started as soon as possible upon detection of the condition with the goal of study enrollment within 2 hours of first provider contact. Although we do not have a long period of time for consenting, no pressure will be given to the patient and their legal guardian for consent. A study team member will introduce the study to patient and the legal guardian, and give them enough time to think and make a complete informed decision. The consent will be signed after all questions are answered.

26.4 Describe any process to ensure ongoing consent, defined as a subject's willingness to continue participation for the duration of the research study.

Response:

When a subject is on the study, the PI or the study coordinator will check with the patient on a daily basis and communicate with the legal guardian and address their concerns about the study. The legal guardians can withdraw their children from the study at any time during the study process. They will be informed about their right to take part in the study or withdraw from the study in the very beginning when they are being approached for consent.

26.5 Indicate whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, or if there are any exceptions or additional details to what is covered in the SOP, describe:

- *The role of the individuals listed in the application who are involved in the consent process*
- *The time that will be devoted to the consent discussion*
- *Steps that will be taken to minimize the possibility of coercion or undue influence*
- *Steps that will be taken to ensure the subjects' understanding*

Response:

☒ We have reviewed and will be following "SOP: Informed Consent Process for Research (HRP-090)."

Non-English Speaking Subjects

☒ **N/A:** This study will not enroll Non-English speaking subjects. *(Skip to Section 26.8)*

26.6 Indicate which language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

NOTE: The response to this Section should correspond with your response to Section 6.4 of this protocol.

Response:

26.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

NOTE: Guidance is provided on "SOP: Informed Consent Process for Research (HRP-090)."

Response:

Cognitively Impaired Adults

☒ **N/A**: This study will not enroll cognitively impaired adults. *(Skip to Section 26.9)*

26.8 Describe the process to determine whether an individual is capable of consent.

Response:

Adults Unable to Consent

☒ **N/A**: This study will not enroll adults unable to consent. (*Skip to Section 26.13)*

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent (Sections 26.9 and 26.10) ***and, where possible, assent of the individual should also be solicited*** *(Sections 26.11 and 26.12).*

26.9 Describe how you will identify a Legally Authorized Representative (LAR). Indicate that you have reviewed the "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" for research in New York State.

NOTE: Examples of acceptable response includes: verifying the electronic medical record to determine if an LAR is recorded.

Response:

☐ We have reviewed and will be following "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

26.10 ***For research conducted outside of New York State****, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response:

26.11 Describe the process for ***assent of the adults****:*

- *Indicate whether assent will be obtained from all, some, or none of the subjects. If some, indicate which adults will be required to assent and which will not.*

Response:

- *If assent will not be obtained from some or all subjects, provide an explanation of why not.*

Response:

26.12 Describe whether ***assent of the adult*** *subjects will be documented and the process to document assent.*

NOTE: The IRB allows the person obtaining assent to document assent on the consent document using the "Template Consent Document (HRP-502)" Signature Block for Assent of Adults who are Legally Unable to Consent.

Response:

Subjects who are not yet Adults (Infants, Children, and Teenagers)

☐ **N/A**: This study will not enroll subjects who are not yet adults. *(Skip to Section 27.0)*

26.13 Describe the criteria that will be used to determine ***whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research*** *under the applicable law of the jurisdiction in which the research will be conducted* ***(e.g., individuals under the age of 18 years)****. For research conducted in NYS, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."*

NOTE: Examples of acceptable responses include: verification via electronic medical record, driver's license or state-issued ID, screening questionnaire.

Response:

We will conduct this study in NY State. We will use the SOP HRP-013 as the criteria to determine if a subject is not yet an adult. We will check medical records for subject's birthdate.

26.14 ***For research conducted outside of New York State****, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response:

26.15 Describe whether parental permission will be obtained from:

Response:

☒ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

☐ Parent permission will not be obtained. A waiver of parent permission is being requested.

NOTE: The requirement for parent permission is a protocol-specific determination made by the IRB based on the risk level of the research. For guidance, review the "CHECKLIST: Children (HRP-416)."

26.16 Describe whether permission will be obtained from individuals ***other than parents****, and if so, who will be allowed to provide permission. Describe your procedure for determining an individual's authority to consent to the child's general medical care.*

Response:

Permission will be obtained from a legal guardian, who may not be the parent of the potential subject. In this case, the legal guardian must provide the legal documentation of his/her status at the time of signing the informed consent, or this legal documentation must be readily available in the patient's medical record.

26.17 Indicate whether assent will be obtained from all, some, or none of the ***children****. If assent will be obtained from some children, indicate which children will be required to assent.*

Response:

Assent will not be obtained from all of the subjects who are between 7 and 17 years of age as it is impractical in the setting of DKA. Children are often sleepy and incapable of providing informed assent while in DKA from a medical standpoint.

26.18 When assent of children is obtained, describe how it will be documented.

Response:

Not applicable

27.0 Waiver or Alteration of Consent Process

Consent will not be obtained, required information will not be disclosed, or the research involves deception.

☒ **N/A:** A waiver or alteration of consent is not being requested.

27.1 If the research involves a waiver or alteration of the consent process, please review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure that you have provided sufficient information for the IRB to make the determination that a waiver or alteration can be granted.

NOTE: For records review studies, the first set of criteria on the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" applies.

Response:

27.2 If the research involves a waiver of the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response:

This is not a planned emergency research.

28.0 Process to Document Consent

☐ **N/A:** A Waiver of Consent is being requested.
(Skip to Section 29.0)

28.1 Indicate whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not or if there are any exceptions, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

NOTE: If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent. This is sometimes referred to as 'verbal consent.' Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information.

If you will document consent in writing, attach a consent document with your submission. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)". If you will obtain consent, but not document consent in writing, attach the script of the information to be provided orally or in writing (i.e. consent script or Information Sheet).

Response:

☒ We will be following "SOP: Written Documentation of Consent" (HRP-091).

29.0 Multi-Site Research (Multisite/Multicenter Only)

☒ **N/A:** This study is not an investigator-initiated multi-site study. This section does not apply.

*29.1 If this is a multi-site study **where you are the lead investigator**, describe the processes to ensure communication among sites, such as:*

- *All sites have the most current version of the IRB documents, including the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.*

Response:

29.2 Describe the method for communicating to engaged participating sites:

- *Problems*
- *Interim results*
- *Study closure*

Response:

29.3 Indicate the total number of subjects that will be enrolled or records that will be reviewed across all sites.

Response:

29.4 If this is a multicenter study for which UB will serve as the IRB of record, and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods.

Response:

30.0 Banking Data or Specimens for Future Use

☒ **N/A:** This study is not banking data or specimens for future use or research outside the scope of the present protocol. This section does not apply.

*30.1 If data or specimens will be banked (stored) for **future use, that is, use or research outside of the scope of the present protocol**, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.*

NOTE: Your response here must be consistent with your response at the "What happens if I say yes, I want to be in this research?" Section of the Template Consent Document (HRP-502).

Response:

30.2 List the data to be stored or associated with each specimen.

Response:

30.3 Describe the procedures to release banked data or specimens for future uses, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Response:

31.0 Drugs or Devices

☐ **N/A:** This study does not involve drugs or devices. This section does not apply.

31.1 If the research involves drugs or devices, list and describe all drugs and devices used in the research, the purpose of their use, and their regulatory approval status.

Response:

This study involves commonly used intravenous fluid (0.9% Normal saline, lactated ringer's solution with additives potassium acetate and potassium phosphate), both fluids are considered by the FDA to be drugs. These fluids and medications are approved by FDA and are routinely used in the hospital as part of the standard DKA management protocol; they are not considered study drugs.

31.2 Describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

Response:

All fluids and medications used in this study are stored in inpatient pharmacy at OCH. Hospital-based and universal standard regulations are used by hospital pharmacy to store and deliver the drugs and intravenous fluids.

After obtaining consent, a copy of the signed consent will be sent to the inpatient pharmacy, and the ED or PICU physician will also place a DKA study order set electronically through the PowerChart system. Upon receiving the signed consent and the order set, the Pharmacy personnel will assign a randomization number to each subject. Each number will correlate with a treatment arm assignment visible on a randomization table available only to pharmacy personnel. They will provide the appropriate content to the intravenous fluids with a generic label "DKA study fluids with dextrose" and "DKA study fluids without dextrose." As the fluids look identical, they would only differ visually in labelling, so standardized labelling as described here will allow all treating physicians to be blinded to treatment arm assignment.

The IV fluid bag will be sent to the ED or PICU using the current delivery system in place for all patients. No special arrangements are necessary.

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

31.3 Identify the holder of the IND/IDE/Abbreviated IDE.

Response:

No investigational drug or device will be used for this project.

31.4 Explain procedures followed to comply with FDA sponsor requirements for the following:

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

Response:

32.0 Humanitarian Use Devices

☒ **N/A:** This study does not involve humanitarian use devices. This does not apply.

32.1 For Humanitarian Use Device (HUD) uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

Response:

32.2 For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.

Response: