Fluid Therapy and Cerebral Injury in Pediatric Diabetic Ketoacidosis
Manual of Operations

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)
Pediatric Emergency Care Applied Research Network
Maternal and Child Health, Emergency Medical Services for Children (EMSC) Program

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Part I

The Network and Protocol

Chapter 1

Introduction

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1.1 PECARN Background

The EMSC Pediatric Emergency Care Applied Research Network (PECARN) consists of a team of Research Node Centers, each associated with a number of Hospital Emergency Department Affiliates (HEDA sites) and a data coordinating center (Central Data Management and Coordinating Center, CDMCC). PECARN is funded by the EMSC Program in the Maternal and Child Health Bureau at Health Resources and Services Administration (HRSA). The four Research Node Center principal investigators and their HEDA investigator colleagues have agreed to investigate problems in pediatric emergency care in a collaborative manner. Each investigator brings different research strengths to the PECARN. The Data Coordinating Center (CDMCC) was selected on the basis of experience with the coordination of multi-center clinical trials, and proven expertise in study design, data management and biostatistical analysis. The PECARN Central Data Management Coordinating Center (CDMCC) is located at the University of Utah.

1.2 Purpose of the Manual of Operations

After a PECARN study is approved for implementation by the Steering Committee, and the protocol is fully developed by the study Principal Investigator and the protocol subcommittee, the CDMCC will prepare a Manual of Operations (MOO). The MOO is to be used by the Principal Investigator (PI), Co-Investigators, Research Coordinators and data collectors at each participating Clinical Center to ensure that the study procedures are followed as uniformly as possible. The MOO includes details regarding patient eligibility and recruitment, informed consent, regulatory issues, data collection and flow, data entry, and procedures for reporting adverse medical events (when applicable). The MOO is produced as an operational, thorough, and adequately detailed document to be used as a reference by all Clinical Center personnel associated with a PECARN study. The MOO is distinct from the study protocol that has been approved by the PECARN for implementation. The MOO is much more detailed, and attempts to bridge the gap between designing the protocol and actually implementing the study. If the MOO and the study protocol are not in agreement, which will only occur in the event of error, the study protocol remains the definitive document. If readers of the MOO identify discrepancies between this MOO and the underlying study, they should contact the CDMCC so that the error may be fixed.

1.3 Project Summary

Our preliminary data strongly support the concept that diabetic ketoacidosis (DKA)-related cerebral injury and subsequent edema may occur in a spectrum of severities. The impact of variation in DKA treatment protocols on this cerebral injury is unknown and arguments for either slower or more aggressive fluid treatment protocols can be made. In this study, two rates of rehydration will be compared; a more rapid rate, designed to promote faster reperfusion of brain tissue and a slower rate, geared toward more gradual reperfusion. Within each of these two basic rehydration schemes, we will vary the type of rehydration fluid used (0.9% saline or 0.45% saline). We will compare treatment arms using a comprehensive set of assessments for neurological injury including measurements of subtle neurological dysfunction during DKA treatment (in addition to recording the frequency of acute, clinically-overt cerebral edema) and measures of long-term neurocognitive function. These studies will not only allow us to determine whether

variations in fluid treatment protocols affect acute neurological outcomes of DKA, but also will provide important additional data regarding the impact of DKA and DKA treatment on long-term neurocognitive function in children.

1.4 Role of Data Coordinating Center (CDMCC)

The Data Coordinating Center (CDMCC) is responsible for assisting PECARN investigators in the design and development of protocols, data management, providing biostatistical expertise and analysis of study data, and assistance with publication of research findings. In addition, the CDMCC is responsible to facilitate the logistics of study implementation. CDMCC staff work with the study PI, the study protocol subcommittee, the Steering Committee, and the Maternal and Child Health, Emergency Medical Services for Children (EMSC) Program staff throughout all phases of the research: planning, protocol development, peer review, patient recruitment, data collection, data management, data analyses, and publication.

1.5 Annual Institutional Review Board (IRB) Approval

It is required by law that all studies involving human subjects be reviewed at least annually by the Institutional Review Board (IRB) at each Clinical Center. Reviews may be conducted more frequently than yearly at the discretion of the local IRB. It is the responsibility of the Clinical Center investigator and the local Institutional Review Board to ensure that these yearly reviews occur.

For PECARN studies, the CDMCC staff will attempt to remind the investigators and research coordinators at each Clinical Center to renew their IRB application for the study, two to three months in advance of the anticipated deadline. Upon request, the CDMCC will also provide the investigators with material that may be requested by the Clinical Center IRB, such as a summary of adverse events or summarized patient accrual information. The IRB will not be provided with blinded outcome data, but for blinded studies, approval of the Data Safety Monitoring Board (DSMB) will be provided in writing for submission to the Clinical Center IRB.

The CDMCC must have a copy of the local IRB approval and renewal notices in order for a Clinical Center to participate in a PECARN study. The approval letter must be on institutional letterhead and include a statement

expressing that the yearly review has taken place, the date of the review, the expiration of the approval, and the outcome of the review. It is imperative that this letter indicate the *version* of the protocol that has been approved. This is critical because most study protocols undergo periodic revision, and IRB approval notices need to document that the approval refers to the most current version of the study protocol.

The University of Utah Institutional Review Board does not permit the CDMCC to accept data from a PECARN Clinical Center unless the CDMCC has documentation of local IRB approval, as described in the previous paragraphs. Data submission will be suspended until such documentation is submitted to the CDMCC.

To reiterate a crucial point, the CDMCC will make good faith efforts to remind PECARN investigators of their annual IRB review. However, the ultimate responsibility to ensure annual review rests with the Clinical Center investigator and the local clinical site IRB. There is no guarantee of CDMCC reminders, and failure to maintain local IRB approval will result in suspension from study participation in all instances.

Chapter 2

Study Protocol

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Abstract

Our preliminary data strongly support the concept that diabetic ketoacidosis (DKA)-related cerebral injury and subsequent edema may occur in a spectrum of severities. Although only a minority of children develop clinically-overt DKA-related cerebral injury of sufficient severity for obvious, profound neurological dysfunction, a much larger percentage may have subtle cerebral injury. The impact of variation in DKA treatment protocols on this cerebral injury is unknown and arguments for either slower or more aggressive fluid treatment protocols can be made. In the proposed study, we plan to conduct a factorial-design randomized controlled trial comparing four fluid treatment protocols for pediatric DKA. Two rates of rehydration will be compared; a more rapid rate, designed to promote faster reperfusion of brain tissue and a slower rate, geared toward more gradual reperfusion. Within each of these two basic rehydration schemes, we will vary the type of rehydration fluid used (0.9% saline or 0.45% saline). We will compare treatment arms using a comprehensive set of assessments for neurological injury including measurements of subtle neurological dysfunction during DKA treatment (in addition to recording the frequency of acute, clinically-overt cerebral edema) and measures of long-term neurocognitive function. These studies will not only allow us to determine whether variations in fluid treatment protocols affect acute neurological outcomes of DKA, but also will provide important additional data regarding the impact of DKA and DKA treatment on long-term neurocognitive function in children. In this way, we hope to identify a more ideal fluid management strategy for children with DKA.

2.1 Study Summary

2.1.1 Hypothesis

We hypothesize that in children:

1. Untreated DKA results in cerebral hypoperfusion and cytotoxic cerebral edema and the extent of cerebral injury may in part be determined by the duration of hypoperfusion.

2. During DKA treatment, reperfusion of previously hypoperfused cerebral tissue results in hyperemia and vasogenic cerebral edema, and the extent of injury caused by reperfusion may also be correlated with the duration of prior hypoperfusion.

3. More rapid rehydration protocols using higher sodium content fluids may promote more rapid reperfusion of hypoperfused brain tissue and result in decreased risk of neurological injury compared with slower rehydration protocols using lower sodium content fluids.

2.1.2 Specific Aims

Specific Aim 1. To determine the effects of variations in rates of administration and sodium content of intravenous fluids on the frequency of mental status abnormalities (abnormalities in Glasgow Coma Scale [GCS] scores and tests of working memory) during DKA treatment.

Specific Aim 2. To determine the effects of variations in rates of administration and sodium content of intravenous fluids on the frequency of overt, symptomatic cerebral edema during DKA treatment.

Specific Aim 3. To determine the effects of variations in rates of administration and sodium content of intravenous fluids during DKA treatment on long–term neurocognitive outcomes (3 months post discharge), particularly memory capacity and intelligence quotient (IQ).

2.1.3 Primary Endpoint

The primary endpoint of this study is the binary indicator that a subject's Glasgow Coma Score drops below 14 within the first 24 hours of treatment for DKA. The outcome will be analyzed by the two treatment factors of sodium concentration of rehydration fluid and the rate of rehydration.

2.1.4 Secondary Endpoints

Secondary endpoints of this study are:

1. frequency of clinically apparent cerebral edema during DKA treatment;

2. median scores on digit span testing during DKA treatment;

3. mean scores on tests of memory capacity 3 months after recovery from DKA;

4. mean scores on IQ tests 3 months after recovery from DKA.

2.1.5 Additional Analyses

The Child Behavior Checklist (CBCL)[1] for children between three and 18 years of age will be assessed during the acute hospitalization to obtain the parental baseline assessment of their child. The CBCL will be repeated at the three month follow up. While the CBCL does not relate to specific outcomes of the study, the Fluid Therapy in DKA study represents a unique opportunity to obtain behavioral information from a large population of pediatric DKA patients.

2.1.6 Patient Eligibility

Inclusion Criteria

To be included in this study, patients:

- must present or be transferred to a PECARN ED; AND
- are less than 18 years of age; AND
- have diagnosis of DKA (requires:
  - serum glucose or fingerstick glucose concentration >300 mg/dL AND
  - venous pH < 7.25 OR serum bicarbonate concentration < 15 mmol/L.)

Exclusion Criteria

The following patients will be excluded from the study:

- patients with pre-existing neurological disease that substantially impacts mental status or neurocongitive exam (e.g. cerebral palsy with developmental delay or autism); OR
- patients who present with concomitant alcohol or drug use, head trauma, meningitis or other conditions which might affect neurological function; OR
- patients transferred to one of the participating PECARN emergency departments after administration of IV fluid more than one 10cc/kg; OR
- patients who are known to be pregnant at time of ED evaluation; OR

- patients who have been enrolled in this study twice previously; OR
- patients for whom the treating physician believed a specific fluid and electrolyte regimen was warranted; OR
- patients that have been receiving IV fluids at a maintenance rate or greater (defined by the 4-2-1 rule) for more than two hours; OR
- patients for whom it has been more than four hours since DKA therapy (IV fluids, IV bolus, or IV insulin) began; OR
- patients who have been given hyperosmolar therapy (i.e. mannitol or 3% normal saline) prior to or since arriving at one of the participating PECARN emergency departments; OR
- patients for whom the treating physician intends to immediately administer hyperosmolar therapy (i.e. mannitol or 3% normal saline); OR
- patients whose baseline GCS is 11 or less

Repeat Enrollment of Subjects

Enrollment of children with multiple DKA episodes: Some children may present with multiple DKA episodes during the study period. To avoid excessively restricting the population available for enrollment, children previously enrolled in the study presenting with another episode of DKA will be eligible for enrollment. If a patient presents for a second enrollment before the completion of their first visit study follow-up or within 4 months of their first visit, data collection during the hospitalization phase for either episode would not be altered. In this case, the patient will complete the follow-up visit for the second enrollment episode only. To avoid bias resulting from very frequent enrollment of specific individuals, however, children will not be enrolled in the study more than twice.

2.1.7 Anticipated Recruitment and Study Duration

The total number that we plan to enroll in the study is 1510. The participating sites see $\approx$ 700 children per year with DKA in their respective emergency departments. However, $\approx$ 10% have had treatment initiated at an outside facility, and another 10% will not meet the other enrollment criteria, and will be excluded. Assuming a capture rate of 60-80% of the remaining patients, we will require 3-4 years of patient enrollment.

2.2 Background and Preliminary Studies

2.2.1 Background

Cerebral edema (CE) resulting from diabetic ketoacidosis (DKA) is the most frequent diabetes-related cause of death in children.[2–4] Clinically-overt CE occurs in approximately 1% of DKA episodes, and approximately 50% of affected children die or sustain permanent neurological injury.[5, 6] Although clinically overt CE occurs infrequently, several studies have shown that CE which is asymptomatic or associated with minor mental status disturbances, occurs in most children with DKA.[7–9] Neuroimaging studies of these children have shown that the severity of CE is greater in children who manifest subtle mental status abnormalities during DKA treatment compared to those whose mental status remains normal throughout therapy.[10] Thus, it appears that DKA-related CE may represent a continuum, with only the most severe cases manifesting substantial mental status abnormalities or signs of increased intracranial pressure. Frequent deficits in neurocognitive function have been demonstrated in children with type 1 diabetes,[11, 12] and recent data from studies by our group suggest that DKA may be an important factor associated with these deficits.[13] It is therefore essential to determine whether neurological injury can be prevented and long-term neurocognitive outcomes for children with diabetes improved by optimizing treatment for DKA.

The cause of DKA-related CE has been a topic of considerable debate for decades. Some investigators hypothesized that CE may result from osmotic shifts caused by rapid rehydration with intravenous fluids.[14–17] As a consequence, many protocols for managing DKA in children call for conservative fluid therapy. Although this hypothesis is intuitively appealing, data to show a clear association between aggressive fluid therapy and CE have been lacking. Instead, more recent data suggests that cerebral hypoperfusion may play a prominent role in the development of cerebral injury and CE.[6, 10, 18, 19] In the setting of DKA in children, the combination of severe dehydration and hypocapnia may lead to cerebral ischemia, particularly in more vulnerable areas of the brain. Hyperglycemia may also play a role in augmenting the degree of ischemic injury and edema formation.

If cerebral hypoperfusion during DKA is responsible for cerebral injury and edema formation, the optimal fluid treatment protocol under these circumstances is not obvious and needs to be identified. Conservative (slower) fluid resuscitation might serve to prolong the state of cerebral hypoperfusion, resulting in increased risk of cerebral injury. Furthermore, intravascular vol-

ume may decline during therapy as intravascular osmolality decreases with resolution of hyperglycemia. If fluid resuscitation is inadequate during this interval, cerebral hypoperfusion may be worsened. Use of low sodium content fluids could exacerbate this problem because less of the volume infused would be retained in the vascular space. Conversely, it could be argued that more conservative fluid therapy might help to decrease vasogenic CE later in the course of DKA treatment, and overly vigorous hydration may exacerbate edema formation. It is therefore unknown how fluid resuscitation protocols impact the risk of brain injury in children with DKA. This large, multicenter trial will provide the data necessary to definitively resolve this pressing clinical issue.

2.2.2 Preliminary Studies

Preliminary studies using MR imaging in a rat model show that untreated DKA is associated with cytotoxic cerebral edema (cell swelling) and reduced cerebral blood flow consistent with cerebral hypoperfusion. Rats with DKA also have low ATP/Pi ratios, low NAA/creatine (Cr) ratios and high lactate/Cr ratios on MR spectroscopy consistent with cerebral hypoperfusion. During DKA treatment in rats, a further decline in ATP/Pi, along with a decline in the NAA/Cr ratio is observed, suggesting injury caused by reperfusion or some other aspect of DKA treatment. In children with DKA, after several hours of treatment with insulin and intravenous fluids, we observed vasogenic edema and increased cerebral blood flow. These data are consistent with post-ischemic hyperemia similar to that typically observed in the setting of stroke and other ischemic states. High apparent diffusion coefficient (ADC) values during DKA treatment were significantly correlated with markers of dehydration and hypocapnia at presentation, again suggesting that cerebral hypoperfusion may be a causative factor. Children with DKA also have decreased NAA/Cr ratios during DKA treatment, suggesting subtle cerebral injury. Abnormalities in ADC measurements and alterations in cerebral ventricle size are more frequent in children with abnormal GCS scores during DKA treatment, suggesting that cerebral edema in these children may be associated with cerebral dysfunction. Children who have a history of DKA have decreased memory function and may show a trend toward lower verbal IQ scores than children with diabetes who have not had DKA. These data suggest that DKA may be associated with subtle long-term cerebral injury, regardless of whether clinically-overt cerebral edema develops.

2.3 Study Hypothesis and Design

The objective of this project is to determine whether variations in the rate of administration and sodium content of rehydration fluids during DKA treatment are associated with differences in neurological outcomes of DKA. We plan to conduct a prospective randomized control trial using a factorial design to compare the effect of rehydration strategies on neurological status during DKA treatment, the frequency of overt, symptomatic CE, and long-term neurocognitive outcomes.

We hypothesize that in children:

1. Untreated DKA results in cerebral hypoperfusion and cytotoxic cerebral edema and the extent of cerebral injury may in part be determined by the duration of hypoperfusion.

2. During DKA treatment, reperfusion of previously hypoperfused cerebral tissue results in hyperemia and vasogenic cerebral edema, and the extent of injury caused by reperfusion may also be correlated with the duration of prior hypoperfusion.

3. More rapid rehydration protocols using higher sodium content fluids may promote more rapid reperfusion of hypoperfused brain tissue and result in decreased risk of neurological injury compared with slower rehydration protocols using lower sodium content fluids.

The investigators have the following specific aims:

Specific Aim 1. To determine the effects of variations in rates of administration and sodium content of intravenous fluids on the frequency of mental status abnormalities (abnormalities in Glasgow Coma Scale [GCS] scores and tests of working memory) during DKA treatment.

Specific Aim 2. To determine the effects of variations in rates of administration and sodium content of intravenous fluids on the frequency of overt, symptomatic cerebral edema during DKA treatment.

Specific Aim 3. To determine the effects of variations in rates of administration and sodium content of intravenous fluids during DKA treatment on long–term neurocognitive outcomes (3 months post discharge), particularly memory capacity and intelligence quotient (IQ).

This trial will be analyzed as an intention-to-treat study.

2.4 Study Outcomes

2.4.1 Primary Endpoint

The primary endpoint of this study is the binary indicator that a subject's Glasgow Coma Score drops below 14 within the first 24 hours of treatment for DKA. The outcome will be analyzed by the two treatment factors of sodium concentration of rehydration fluid and the rate of rehydration.

2.4.2 Secondary Endpoints

Secondary endpoints of this study are:

1. frequency of clinically apparent cerebral edema during DKA treatment;
2. median scores on digit span testing during DKA treatment;
3. mean scores on tests of memory capacity 3 months after recovery from DKA;
4. mean scores on IQ tests 3 months after recovery from DKA.

2.4.3 Additional Analyses

The Child Behavior Checklist (CBCL)[1] for children between three and 18 years of age will be assessed during the acute hospitalization to obtain the parental baseline assessment of their child. The CBCL will be repeated at the three month follow up. While the CBCL does not relate to specific outcomes of the study, the Fluid Therapy in DKA study represents a unique opportunity to obtain behavioral information from a large population of pediatric DKA patients.

2.5 Patient Eligibility

2.5.1 Inclusion Criteria

To be included in this study, patients:

- must present or be transferred to a PECARN ED; AND
- are less than 18 years of age; AND
- have diagnosis of DKA (requires:

  - serum glucose or fingerstick glucose concentration >300 mg/dL AND
  - venous pH < 7.25 OR serum bicarbonate concentration < 15 mmol/L.)

2.5.2 Exclusion Criteria

The following patients will be excluded from the study:

- patients with pre-existing neurological disease that substantially impacts mental status or neurocongitive exam (e.g. cerebral palsy with developmental delay or autism); OR
- patients who present with concomitant alcohol or drug use, head trauma, meningitis or other conditions which might affect neurological function; OR
- patients transferred to one of the participating PECARN emergency departments after administration of IV fluid more than one 10cc/kg; OR
- patients who are known to be pregnant at time of ED evaluation; OR
- patients who have been enrolled in this study twice previously; OR
- patients for whom the treating physician believed a specific fluid and electrolyte regimen was warranted; OR
- patients that have been receiving IV fluids at a maintenance rate or greater (defined by the 4-2-1 rule) for more than two hours; OR
- patients for whom it has been more than four hours since DKA therapy (IV fluids, IV bolus, or IV insulin) began; OR
- patients who have been given hyperosmolar therapy (i.e. mannitol or 3% normal saline) prior to or since arriving at one of the participating PECARN emergency departments; OR
- patients for whom the treating physician intends to immediately administer hyperosmolar therapy (i.e. mannitol or 3% normal saline); OR
- patients whose baseline GCS is 11 or less

2.5.3 Repeat Enrollment of Subjects

Enrollment of children with multiple DKA episodes: Some children may present with multiple DKA episodes during the study period. To avoid excessively restricting the population available for enrollment, children previously enrolled in the study presenting with another episode of DKA will be eligible for enrollment. If a patient presents for a second enrollment before the completion of their first visit study follow-up or within 4 months of their first visit, data collection during the hospitalization phase for either episode would not be altered. In this case, the patient will complete the follow-up visit for the second enrollment episode only. To avoid bias resulting from very frequent enrollment of specific individuals, however, children will not be enrolled in the study more than twice.

2.5.4 Inclusion of Women and Minorities

The gender, ethnic and racial composition of patients enrolled this study is a function of the underlying referral population at each participating Clinical Center During this study, the Central Data Management Coordinating Center (CDMCC) will monitor patient accrual by race, ethnicity, and gender. If necessary, additional recruitment efforts will be made at specific centers to ensure that the aggregate patient sample contains appropriate gender and minority subsets.

2.6 Study Design and Methods

Overview and rationale: Our preliminary data strongly support the concept that DKA-related cerebral injury and subsequent edema may occur in a spectrum of severities. Although only a minority of children develop clinically-overt DKA-related cerebral injury of sufficient severity for obvious, profound neurological dysfunction, a much larger percentage may have subtle cerebral injury. The impact of variation in DKA treatment protocols on this cerebral injury is unknown and arguments for either slower or more aggressive fluid treatment protocols can be made. In the proposed study, we plan to conduct a factorial-design randomized controlled trial comparing four fluid treatment protocols for pediatric DKA. Two rates of rehydration will be compared; a more rapid rate, designed to promote faster reperfusion of brain tissue and a slower rate, geared toward more gradual reperfusion. Within each of these two basic rehydration schemes, we will vary the type of rehydration fluid used (0.9% saline or 0.45% saline). We will compare treatment arms using a comprehensive set of assessments for neurological injury including measurements of subtle neurological dysfunction during DKA treatment (in addition to recording the frequency of acute, clinically-overt cerebral edema) and measures of long-term neurocognitive function. These studies will not only allow us to determine whether variations in fluid treatment protocols affect acute neurological outcomes of DKA, but also will provide important additional data regarding the impact of DKA and DKA treatment on long-term neurocognitive function in children. In this way, we hope to identify a more ideal fluid management strategy for children with DKA.

2.6.1 Patient Evaluation During Acute DKA Treatment

In this section, we discuss study methods pertaining to Specific Aims 1 and 2:

Specific Aim 1. To determine the effects of variations in rates of administration and sodium content of intravenous fluids on the frequency of mental status abnormalities (abnormalities in Glasgow Coma Scale [GCS] scores and tests of working memory) during DKA treatment.

Specific Aim 2. To determine the effects of variations in rates of administration and sodium content of intravenous fluids on the frequency of overt, symptomatic cerebral edema during DKA treatment.

Enrollment and DKA Treatment Protocols

Upon arrival of a patient with suspected DKA in the ED, the treating emergency physician will begin standard fluid therapy using an initial intravenous

fluid bolus of 10cc/Kg of 0.9% saline, a volume and fluid type consistent with the initial fluid bolus in all of the study arms. During this initial therapy, the treating physician or other study personnel will review the study with the patients parents or guardians to obtain parental consent. Child assent will be obtained as required by local IRBs for children who are within the age range requiring assent and who are able to grant assent. After parental permission is obtained, children will be randomized to one of the four study arms. If consent cannot be obtained prior to completion of the initial 10cc/Kg fluid bolus, the treating physician can give fluids they would normally administer until consent is obtained. If consent cannot be obtained during this time (within two hours of receiving IV fluids at maintenance rate or greater or within four hours of beginning DKA therapy of any kind - IV fluid or IV insulin), patients will be considered ineligible. The fluid rate and fluid type will be changed to that specified by randomization as soon as consent is obtained. We anticipate based on experience from previous DKA studies, however, that these delays in consent will be infrequent.

Children will be randomized to one of the four fluid protocols (see Table 2.1 on the facing page). Protocol A1 will involve more rapid intravenous fluid treatment which will include a second 10cc/Kg bolus of 0.9% saline and assume a 10% fluid deficit. 0.45% saline used as the replacement fluid for protocol A1. Protocol A2 will be identical to A1 except that 0.9% saline will be used as the replacement fluid. Protocol B1 will involve slower rehydration (assumed 5% fluid deficit and no additional fluid bolus) with 0.45% saline used as the replacement fluid. Protocol B2 will be identical to B1 except that 0.9% saline will be used as the replacement fluid. In all regimens, the quantity of fluid given as boluses administered while awaiting consent, will be subtracted from the fluid deficit used to calculate the rate of fluid replacement.

For patients presenting with Glasgow Coma Scale (GCS) scores >13, randomization will be stratified by clinical center. A balanced randomization will be performed separately for those patients presenting with GCS scores <14, as these patients will not be included in the primary analysis. The CDMCC will prepare randomization schedules. The length of each randomization block will vary to reduce predictability, as the fluid therapy will be unblinded. Table 2.1 on the next page outlines the fluid treatment protocols.

Table 2.1: Fluid Treatment Protocol Summary

	Protocol A1	**Protocol A2**	**Protocol B1**	**Protocol B2**
Standard Initial Fluid Bolus	10 cc/kg bolus of 0.9% saline	10 cc/kg bolus of 0.9% saline	10 cc/kg bolus of 0.9% saline	10 cc/kg bolus of 0.9% saline
Additional IV fluid bolus	Additional 10 cc/kg of 0.9% saline	Additional 10 cc/kg of 0.9% saline	No additional bolus	No additional bolus
Assumed fluid deficit	10% body weight	10% body weight	5% body weight	5% body weight
Replacement of deficit	Replace half of fluid deficit + maintenance fluids over initial 12 hours, remaining deficit + maintenance fluids over next 24 hours	Replace half of fluid deficit + maintenance fluids over initial 12 hours, remaining deficit + maintenance fluids over next 24 hours	Replace deficit + maintenance fluids evenly over 48 hours	Replace deficit + maintenance fluids evenly over 48 hours
Fluid for deficit replacement	0.45% saline	0.9% saline	0.45% saline	0.9% saline

For all treatment protocols, initial fluid boluses of 0.9% saline may be repeated at the discretion of the treating physician if necessary to restore peripheral perfusion. With the exception of the initial fluid boluses, rehydration fluid in all treatment regimens will contain 20 mEq/L potassium chloride (KCl) and 20 mEq/L potassium phosphate initially. Subsequent potassium content of intravenous fluids will be adjusted to maintain serum potassium concentrations in the normal range. Although some previous DKA treatment guidelines suggest that physicians attempt to estimate the patient's percentage dehydration based on clinical signs, recent well-conducted studies have shown that physicians' clinical estimates of dehydration in children with DKA are inaccurate, and may either overestimate or underestimate the degree of dehydration.[20, 21] Based on these data, we chose to assign an assumed fluid deficit to each protocol, as per the table above, rather than relying on physicians' estimates. Assumed fluid deficits used in the protocols are either slightly above or slightly below the average deficit of 7% determined in recent investigations.[20, 21]

All 4 protocols will be identical in regard to other aspects of DKA treatment in the following respects: Insulin treatment will begin after the initial intravenous fluid boluses and restoration of peripheral perfusion. Insulin will be administered intravenously at a rate of 0.1 units/Kg/hour. Initial bolus or loading dosages of insulin will not be given. When the serum glucose concentration declines below 200-300 mg/dL, the intravenous fluids will be changed to a 5% dextrose solution based on the same solution (0.9% NS or 0.45% NS) to which the patient was randomized. The insulin infusion will be continued at the same rate. The concentration of dextrose in the intravenous fluids will be adjusted up to a maximum of 10% dextrose with a goal of maintaining the serum glucose concentration between 100 and 200 mg/dL. The insulin infusion rate will not be decreased unless the serum glucose concentration cannot be maintained within the desired range using a 10% dextrose solution.

2.6.2 Patient Evaluation At Follow Up

Specific Aim 3. To determine the effects of variations in rates of administration and sodium content of intravenous fluids during DKA treatment on long–term neurocognitive outcomes (3 months post discharge), particularly memory capacity and intelligence quotient (IQ).

Please refer to (Section 2.7.3 on page 26) for methods pertaining to Aim 3 neurocognitive assessments.

2.7 Data Collection

2.7.1 Baseline Data Collection

Baseline data recorded for all children will include age, gender, race and ethnicity, and any other chronic medical conditions in addition to diabetes mellitus. Household income and parental educational level will be recorded to assess socioeconomic status. At baseline, we will also record presence or absence of headache and severity (mild, moderate, severe), and assessment of peripheral perfusion (peripheral pulses, capillary refill time, blood pressure). For children with known diabetes, we will collect the duration of diabetes, number of previous episodes of DKA, number of previous episodes of severe hypoglycemia with loss of consciousness or seizures, most recent HbA_{1C} level and mean HbA_{1C} level during the preceding year. At presentation to the emergency department, we will collect serum glucose and electrolyte concentrations, serum calcium, serum phosphate, serum magnesium, blood pH and pCO_2, vital signs and age-appropriate GCS scores.

A rapid assessment of working memory (digit span recall) will be conducted at the time of enrollment, based on procedures that have been substantiated in decades of psychological research.[22–24] Participants will be asked to repeat a series of numbers heard aloud, in the same order as spoken (forward digit span) or backwards. The forward task measures the ability to maintain information on line, whereas the backward measures the additional ability to mentally manipulate information on line.[25] The examiner will increase the number of digits by one unit on each successive trial as long as the child repeats them correctly. The test will end when the child makes a mistake in two sequences of the same span in a row. Completion of this test should require 5-10 minutes. Children younger than 3 years of age are unable to cooperate with this testing, and this portion of the protocol will be omitted for children in this age group.

For children who are eligible for the study but decline to participate, as well as for those who were eligible but missed, we will record age, gender, race and ethnicity, new onset versus known diabetes, and initial blood glucose, blood pH, and blood urea nitrogen (BUN). This is to enable construction of the study CONSORT diagram, and to assess the possibility of bias in patient enrollment.

2.7.2 Data Collection during DKA Treatment

Data collection during management of DKA is summarized in Table 2.2 on the next page. After the initiation of treatment and recording of baseline

clinical and biochemical data, protocol procedures and ongoing data collection will continue for 24 hours or until resolution of DKA, defined as when the IV insulin drip is stopped, whichever comes first. All laboratory tests in Table 2.2 will be collected through hospital discharge - the frequencies of sampling indicated in Table 2.2 are the anticipated frequencies for 24 hours or until resolution of DKA. For example, all glucose values will be collected through hospital discharge, but it is not expected that glucose values will be sampled hourly following resolution of DKA. Clinical Center investigators and/or other assigned study personnel will conduct the digit span recall testing, or will train the nurses at each Clinical Center in the conduct of procedures related to the study (GCS and digit span recall testing) and review these procedures with nursing staff. Approximately 90% of children with DKA at the participating PECARN hospitals present between 7:00 AM and 10:00 PM, facilitating the enrollment of these patients.

Table 2.2: Summary of data collection during DKA management

DATA TO BE COLLECTED	FREQUENCY OF MEASUREMENT
Demographic and Historical Data	
Demographic data (age, gender, race/ethnicity)	At time of enrollment
Diabetes history for children with known DM (age at diagnosis of DM, mean HbA_{1C} over past year, most recent HbA_{1C}, number of previous DKA episodes, number of previous episodes of severe hypoglycemia)	At time of enrollment
Clinical data (medical conditions other than diabetes, presence and severity of headache, assessment of peripheral perfusion)	At time of enrollment
Biochemical Monitoring -	
Blood glucose concentration	At presentation and hourly
Electrolytes (Na, K, Cl, HCO_3, BUN, Cr)	At presentation and every 2-4 hours
Blood pH and pCO_2	At presentation and every 2-4 hours
Serum Ca, Phos, Mg	At presentation and every 4-8 hours
Assessment of Neurological Function	
Mental status assessment (GCS)	At enrollment and hourly
Brief memory assessment (digit span recall)	At enrollment and every 4 hours during normal waking hours

GCS scores will be assessed and recorded every hour throughout the study period. If any of the hourly GCS scores fall below 14, repeat GCS assessment will be done 15 minutes later for reassessment and/or confirmation of the GCS score. If the repeat GCS assessment confirms a score below 14, the patient will be classified as having abnormal mental status during the DKA episode. Abnormal GCS scores will be reported to the attending physicians per usual hospital protocol.

If the GCS returns to 14 and then drops below 14 again, it will not be necessary to do a confirmatory reassessment 15 minutes later. In this event, the hourly recording of the GCS is sufficient.

The digit span recall test (for children older than 3 years of age) will be assessed every 4 hours during normal waking hours (approximately 7AM and 10PM). Digit span recall will not be assessed during usual sleep hours because the patients cooperation during these hours is likely to be limited. At each testing session, new digit permutations will be presented to prevent children's performance from reflecting, in part, memorization from earlier testing sessions.

Additional patient monitoring that is already standard of care for children with DKA will occur according to the guidelines at each Clinical Center, which follow international guidelines for the management of DKA in children.[26, 27] This standard monitoring will include serum glucose concentrations and vital signs measured and recorded every hour, and serum sodium, chloride, potassium, bicarbonate (HCO_3), BUN and creatinine concentrations and blood pH and pCO_2 measured and recorded every 2-4 hours for the first 24 hours of DKA therapy or until resolution of DKA (when the IV insulin drip is stopped). Serum calcium, magnesium and phosphate concentrations will be measured every 4-8 hours. Fluid intake and urine output will also be recorded, as per Clinical Center protocols.

Data from previous studies demonstrate that nearly all neurological injuries caused by DKA occur within the first 24 hours of treatment, and the large majority within the first 12 hours.[6] Therefore extending the monitoring period beyond this time frame is unlikely to be useful. Patient monitoring and laboratory testing after the first 24 hours of treatment will proceed according to the usual protocols of each institution. Treatment of suspected cerebral edema will be at the discretion of the attending physician, per Clinical Center protocol. Monitoring data required by this study protocol will be recorded by the Clinical Center investigator, Research Coordinator, or other delegated staff. Data pertaining to the initial patient assessment will be recorded by a physician (the ED physician, or the Clinical Center investigator, if available).

The Child Behavior Checklist (CBCL) will be obtained for subjects who are three to 17 years of age. The CBCL will be filled out by the parents prior to hospital discharge. The parents will answer the CBCL with their assessment of their child *prior* to the current hospitalization.

2.7.3 Post-recovery Neurocognitive Assessment

Patients 3-17 years of age will return for an outpatient follow-up visit approximately 3 months after recovery from the DKA episode. Visits will be arranged to occur within a time frame of 3 months ± 4 weeks from the date of hospital discharge. Because children younger than 3 years are unable to cooperate with the kinds of tests designed for the proposed research, children who are younger than 3 years at the time of the 3 month visit will not participate in this portion of the study.

Appropriate conduct of the testing procedures will be verified through practice sessions at the initial training meeting and, when feasible, by review of a videotaped testing session at intervals after initiation of the study (Section 2.11.3 on page 50).

The standardized neurocognitive testing will include initial glucose screening to verify that the subject is appropriate for cognitive testing, and age appropriate cognitive testing. These are detailed in the following sections. Table 2.3 summarizes the neurocognitive assessment to be conducted.

Table 2.3: Summary of neurocognitive testing at 3 month visit

Age of subject	Testing Procedures
Six to 18 years	IQ assesment with WASI, Memory assessment with color task, spatial location task, digit span test
Three to 5 years	IQ assessment with abbreviated WPPSI-III, Memory assessment with abbreviated color task, spatial location task, digit span test
Younger than 3 years	No neurocognitive evaluation

Scores on neurocognitive testing will not be disclosed to parents/guardians or participants. Parents/ guardians of children with an IQ score below 85 (1 SD below mean) will be notified via a letter that testing indicated "possible learning problems." It will be stated, however, that this testing is not definitive, the testing was done within a research study by non-neuropsychologists,

and that follow up with the child's school and/or a psychologist for definitive testing is recommended.

Glucose screening

Immediately prior to neurocognitive testing, a fingerstick blood glucose concentration will be measured. Fingerstick glucose will be measured by patient or parent using his/her own glucose meter. Patients with hypoglycemia (blood glucose less than 70 mg/dL) will receive treatment for the hypoglycemic episode (oral glucose-containing beverage) and the neurocognitive testing will be rescheduled as soon as feasible. Patients with glucose concentrations above 350 mg/dL will be evaluated for ketosis via urine dipstick. Patients with positive tests for ketones will have neurocognitive testing rescheduled, and the family will be instructed to contact the child's endocrinologist for further management advice. Parents will also be queried about the occurrence of severe hypoglycemia (with loss of consciousness or mental status changes) between the time of hospital discharge and the three-month follow-up visit and these data will be recorded.

Cognitive testing children $\geq$ 6 years of age

Intelligence Quotient (IQ). IQ will be tested with the Wechsler Abbreviated Scale of Intelligence (WASI).[28] The WASI is a rapid, yet reliable measure of intelligence in clinical, educational, and research settings. The WASI has been standardized nationally and yields the three traditional IQ scores: Verbal, Performance and Full Scale IQ. The WASI requires approximately 30 minutes to administer.

The IQ assessment includes 4 subtests. Although each of them stands alone, it is important that the participant completes all of them in one session as the test norms are based on them being administered this way.

Memory Tasks. We will test memory with two tasks: the color task and the spatial-position task. Both tasks will evaluate two aspects of memory function: familiarity and recollection of contextual detail. The child will be asked to evaluate not only whether they are familiar with the item by recognizing whether or not they have seen the item before, but also whether they recall the specific contextual detail about those items (e.g. "I saw this item before, and it was presented with a red border"; "I saw this item before, and it was presented on the upper part of the screen"). Together, the

administration of the two memory tasks will last approximately 50 minutes. A break will be included between the two tasks.

For the two tasks, a set of unambiguous line drawings will be used.[29] These materials are normed with child participants for familiarity, visual complexity, and name agreement. An age-appropriate number of stimuli will be used for the color task, spatial-position task, and as non-studied distracters.

Figure 2.1 shows a schematic summary of these testing procedures.

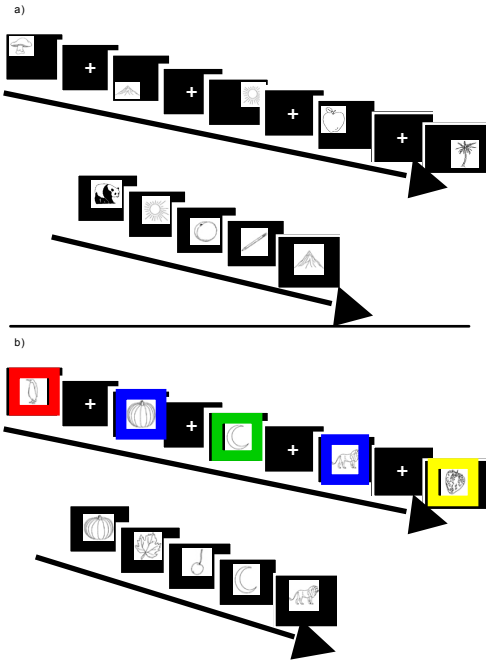

Figure 2.1: Memory task schematic

If a memory task is interrupted during study of the pictures, then we may not be able to re-administer the task on a different day, because memory for these items may interfere with subsequent performance. If a memory task is interrupted towards the end (i.e. the pictures have been viewed and we have most but not all of the responses), then it may be possible to use these data. If such interruptions occur, the Clinical Center coordinator should notify the CDMCC and the determination of whether to reschedule the patient will be made on a case-by-case basis after discussion with the primary study investigators.

Color task. An age-appropriate number of pictures will be presented in black ink surrounded by a border which will be either green, red, yellow or blue. Participants will be instructed to say aloud the name of the object being depicted in the drawing, and to try to remember the color of its border. The items will be presented in randomized sequences, such that the order of item of presentation and the association between item and color will vary across participants. Each drawing will be shown for 2 seconds, followed by a 2 second interval during which a fixation point will be presented on the screen. Then, participants will be given a self-paced recognition test including an age-appropriate number of studied drawings and new drawings presented in random order. Participants will first determine whether they have seen the drawing before (i.e. old/new recognition judgment) and then, if an item is recognized as previously seen, participants will be asked to recall the color in which it had been presented.

Spatial position task. This task will be identical to the color task, except that the items will be associated with a spatial position in which they will appear instead of the color of their border (i.e. one of the 4 quadrants of the computer screen). Participants will be instructed to say aloud the name of the object being depicted in the drawing, and try to remember its spatial position.

Digit span test. The digit span recall test was conducted during hospitalization, and will be repeated at the follow-up visit. Participants will be asked to repeat a series of numbers heard aloud, in the same order as spoken (forward digit span), or backwards. The examiner will increase the number of digits by one unit on each successive trial as long as the child repeats them correctly. The test will end when the child makes a mistake in two sequences of the same span in a row. Completion of this test should require 5-10 minutes.

Child Behavior Checklist (CBCL) At the three month evaluation, the CBCL will be filled out by the parents of children who are older than three years of age. The information from the CBCL will be compared with the CBCL filled out during the acute hospitalization.

Cognitive testing children 3 to 5 years of age

Children in this younger age group will undergo both IQ and memory testing, similar to the older children, but modified versions of the testing pro-

cedures will be used to accommodate the typical neurocognitive capacities and shorter attention span of these younger children.

Intelligence Quotient (IQ). The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III[30]) will be used as the instrument for IQ assessment in the 3-5 year old age group. IQ will be estimated from 7 subtests in 4-5-year-olds (Block Design, Information, Matrix Reasoning, Vocabulary, Picture Concepts, Word Reasoning, and Coding). For 3 year-olds, a short form of the test including 4 of the 12 subtests (Receptive Vocabulary, Block Design, Information, and Object Assembly) will be employed to shorten the duration of IQ testing. This abbreviated version of the WPPSI will allow assessment of IQ while avoiding excessive fatigue which might compromise the child's cooperation with memory testing. Previous research validated this approach.[31, 32]

Memory Tasks. Children in this younger age group will undergo memory task testing using modified versions of the testing procedures to accommodate the typical neurocognitive capacities and shorter attention span of these younger children. The digit span test will also be conducted for these younger children as described in Section 2.7.3 on the previous page.

Child Behavior Checklist (CBCL) At the three month evaluation, the CBCL will be filled out by the parents of children who are older than three years of age. The information from the CBCL will be compared with the CBCL filled out during the acute hospitalization.

2.8 Data Analysis

2.8.1 Primary Endpoint

The primary outcome is the binary indicator that a patient's GCS score drops below 14 (i.e. abnormal score) within the first 24 hours of treatment of DKA. There will be two treatment factors: sodium concentration of rehydration fluids and rate of rehydration. The interaction between these is expected to be small-to-moderate in relation to the expected treatment effect. Regardless of the presence of an interaction, tests for each of the two main effects remain valid. These effects will be tested separately, using the Mantel-Haenszel χ-square test, stratified by hospital, and by the other main factor. For example, the test for effect of sodium concentration will

be stratified by rate of rehydration. Each test will have a two-sided Type I error probability of 0.025, following a Bonferroni adjustment to guarantee an overall Type I error probability of less than 0.05. Patients presenting with abnormal GCS scores (GCS<14) will not be included in this primary analysis.

In addition to evaluating the statistical significance of effects, we will report observed differences in the primary outcome and the corresponding 95% confidence intervals using the summary statistic found to be most appropriate. The interaction between the two factors (saline concentration and rate of rehydration) will also be studied in a post hoc analysis.

2.8.2 Secondary Endpoints

GCS scores and overt cerebral edema

GCS scores between the 4 groups will be compared using a Wilcoxon rank-sum test or a Van Elteren test, stratified by hospital. Patients presenting with GCS scores < 14 will be included in this analysis. The outcome will be difference between GCS score at presentation and lowest recorded GCS score, with death as the worst possible ranking. In an additional sub-analysis, we will compare the severity of mental status abnormalities among patients in the study arms by computing scores based on the number of hours that each patient's GCS score remains below 14. Clinically overt CE will be treated as binary and analyzed with Mantel-Haenszel tests.

We will perform another secondary analysis of the GCS score outcome by assessing the treatment effect after adjustment for covariates that we have previously demonstrated to be associated with CE. The covariates that we will include are initial BUN, pCO_2, pH, and serum sodium concentration. A logistic regression model will be used for the indicator outcome of GCS score < 14. In order to incorporate covariates in the analysis of the magnitude of GCS drop, we will consider drops as being in one of three categories: 0 to 1, 2 to 3, and 4 or greater. These ordinal categories will be used as the response in a proportional-odds model.

Digit span scores during DKA treatment

Digit span scores are measured as the longest span correctly recited in each of the assessment sessions. Separate analyses will be conducted for the forward and backward spans. Digit span scores can be analyzed using parametric methods. The trajectory of digit span scores during the course of the

hospitalization can be used to assess patients rates of recovery and whether this rate varies systematically as a function of treatment protocol.

We will apply longitudinal data analysis methods by assuming a linear mixed-effects model. Time zero will be randomization time. We will include a fixed effect for the intercept, for PECARN Clinical Center , for Clinical Center-time interaction, and for time-treatment interaction for each of the four treatment protocols. These last four parameters are the quantities of interest, as they represent the change over time due to each treatment. There will be no terms for treatment alone, since randomization guarantees the baseline scores are the same, on average, for all treatment groups.

Random effects will be included to help account for the correlation between repeated scores for each subject. These will include a random intercept and a random slope. To further account for dependence, a general correlation structure will be assumed.

Although it is likely that the true time-treatment and other time relationships will not be exactly linear, this pre-specified model should capture whether the scores increase or decrease over time as a function of treatment protocol. Nevertheless, we will additionally evaluate other possible models, including more interactions and non-linear relationships. The possibility also exists that individuals with a certain trend (e.g. increasing score) will have fewer measurements and thus receive less weight in the analysis and lead to biased estimates. If necessary, we will make adjustments to account for this. These additional analyses will be exploratory in nature and, should we report their results, will be clearly labeled as such.

Post-recovery memory function

The effects of treatment conditions on memory function will be examined in separate analyses of variance (ANOVA) in which each of the indices of the memory performance will be considered as outcomes. The proposed memory tasks yield two indices of performance, recollection of item-context associations and item recognition. Recollection of item-context associations will be measured as the rate at which participants remember the item in association with the correct contextual detail (color or spatial position, depending on the task) over the total of previously viewed items correctly recognized as seen before. This index is the primary measure of interest as it is thought to reflect the kind of memory process that is most likely to be affected by episodes of mild ischemia or hypoxia.

Item recognition will be measured with d' which is calculated from hit rates (correct identification of an item that was seen previously) and false-

alarm rates (incorrect identification of an item as being seen previously when it was not).[33] The d' measure reflects the ability to discriminate between old and new items. This measure varies from 0 (no ability to discriminate) to 4 (nearly perfect ability to discriminate). Measures of the extent to which participants have conservative or lax tendencies for endorsing an item as old, will be also obtained from the recognition data.

Given the randomized nature of the study, participants assigned to each treatment protocol are expected to be comparable on critical variables affecting memory and cognitive function in general (e.g. age, socio-economic status) or specific to children with type 1 diabetes (e.g. age at onset of diabetes, experiences of severe hypoglycemia). Nevertheless, we will investigate the effects of treatment after adjusting for such covariates in a linear model. The variables we will consider are age, gender, age at onset of diabetes, previous episodes of DKA or hypoglycemia, and HbA_{1C}level. Furthermore, additional multivariate analyses will be conducted to examine whether any of these variables interact with the treatment protocol.

Post-recovery intelligence quotient (IQ)

The same analytical approach proposed for memory will be used for the analyses of IQ measures. Each test will provide three scores: a verbal IQ, and performance IQ, and a total IQ score. Each of these three IQ measures will be analyzed using ANOVA as detailed above. We note that there are known age differences in measurement error and variance in IQ, which may diminish our ability to detect significant differences (e.g. protocol related differences) among younger compared to older children.[28, 34] General linear models, when appropriate, will be used to adjust for these differences, allowing for more precise comparisons of effect sizes across age groups.

2.8.3 Exploratory Subgroup Analyses

We would like to know whether the treatment effects are consistent across prospectively defined subgroups. Age, dichotomized as under 6 versus 6 and older, will be considered a variable for subgroup analysis with respect to all outcomes previously defined. For analyses that include subjects presenting with a GCS score < 14, we will also analyze this subgroup versus that of subjects presenting with a GCS score of 14 or 15. Another analysis will involve categorization of subjects according to whether or not the subject has experienced past episodes of DKA (possibly resulting in pre-existing neurocognitive alterations). The significance level for all subgroup-based

tests will be adjusted in order to keep the overall type I error rate less than 0.05. Results of subgroup analyses will be interpreted with caution and used primarily to confirm a consistent magnitude of treatment effect.

All analyses previously described will be based on the intention-to-treat principle. Additionally, we will perform per-protocol or fluid-received analyses for additional insight. These will not replace the intention-to-treat analysis, and the results will be examined with caution.

2.8.4 Child Behavior Checklist (CBCL)

The CBCL[1] provides an assessment of behavioral adjustment and psychological well being. The experience of chronic childhood disease, including type 1 diabetes and its complications, has been associated with increased CBCL scores. Higher CBCL scores have been shown to be negatively correlated with measures of cognitive functioning, including memory. While the randomization procedure will ensure that children with different CBCL levels will be equally distributed across the study arms, it will be of interest to account for changes in CBCL when we will analyze long-term neurocognitive outcomes.

2.8.5 Power Calculations

The primary analysis will be performed on a binary outcome: whether GCS scores decline below 14. The power of these analyses depends on the proportion of patients with GCS declining below 14 in each group considered. Data from our previous studies demonstrate that mental status abnormalities (GCS <14) occur in approximately 15% of children treated for DKA, and are associated with evidence of CE on neuroimaging.[7, 10, 35]

For this study, we are assuming that the factor level with the highest rate of developing abnormal GCS scores would have about a 20% overall frequency of GCS scores declining below 14 and we desire to detect an absolute beneficial treatment effect of 7.5% with 90% power. Using a two-sided Type I error rate of 0.025 and the hypothesized proportions yields a required total sample size of approximately 1200 patients.

Allowing for non-adherence to assigned treatment of up to 5% raises the required number to 1200/0.952, or about 1330. In order to adjust for O'Brien-Fleming interim monitoring, a 2% increase should be made, bringing the sample size up to approximately 1360. This represents the number of patients that present with a GCS score of at least 14. We estimate that approximately 10% of eligible patients with DKA present with a GCS score

less than 14. This means that in the time period required to enroll 1360 patients presenting with normal GCS scores, about 150 with abnormal scores will be enrolled. Thus, the total number that we plan to enroll in the study is 1510. The participating Clinical Center s see $\approx$ 700 children per year with DKA in their respective emergency departments. However, $\approx$ 10% have had treatment initiated at an outside facility, and another 10% will not meet the other enrollment criteria, and will be excluded. Assuming a capture rate of 60-80% of the remaining patients, we will require 3-4 years of patient enrollment.

2.8.6 Interim Analyses and Stopping Rules

This study will be monitored by the Data Safety Monitoring Board (DSMB) appointed by the funding institute (National Institutes of Health). The DSMB will have final jurisdiction regarding frequency of meetings, and appropriate formal monitoring boundaries for study stopping in terms of superiority. Here we present the anticipated interim analysis plan for the Fluid Therapy in DKA trial. A detailed version of this plan will be submitted to the DSMB for approval and possible modification prior to the beginning of study enrollment.

Interim monitoring for superiority of one treatment approach over the other will clearly be appropriate in this study. Symmetric monitoring boundaries are appropriate as one cannot rule out a detrimental relative effect of either strategy of fluid volume or sodium concentration.

Numerous clinical trials have found early treatment differences that diminished or even reversed as more subjects were enrolled. In a multicenter clinical trial, it is not unusual for early recruitment to be confined to a subset of centers that receive early IRB approval or have a smoother run-in phase; the experience at these centers may differ from others. Also, a "learning curve" in delivering the study therapies, at some or all centers, is not inconceivable. Because of these issues, we have selected monitoring boundaries that are conservative at the early looks at the data; we believe that O'Brien-Fleming-type boundaries,[36] implemented using the Lan-deMets flexible alpha spending function approach,[37] are appropriate for this study setting.

As this is an expensive study to conduct, early stopping of either or both of the factors in the Fluid Therapy in DKA for futility (low chance that a treatment effect is found if the trial for that factor continues) is a consideration. A conditional power approach, wherein the chance of the study finding a treatment effect (given the data accrued thus far in the study) under various assumed true scenarios is assessed, may be appropriate for the

DSMB to address futility issues if this becomes necessary.[38] This approach, which requires careful consideration of what treatment effect scenarios are realistic given the study data themselves, encourages dialogue and discussion among DSMB members. However, early termination of a clinical trial for futility may greatly reduce the value of the trial, and the investigators of this study do not anticipate that early termination for futility is likely.

The projected accrual period in this study is between three and four years. We assume that the DSMB will meet prior to study launch, and then after one, two and three years of subject accrual. The final analyses will be the fourth look. While flexible α spending will be used, we assume that there will be three meetings at which the DSMB will perform interim analysis, and that 25%, 50%, and 75% of study data (technically, of total statistical information for the primary outcome) are available at the respective meetings. Thus, there would be three interim analyses, with an additional final analysis of the study data if the study is not terminated early.

It is important to note that sample size adjustments are required to adjust for the interim analyses, although these are so slight as to be nearly negligible. This has been taken into account in the power calculations (Section 2.8.5 on page 34).

2.9 Human Subjects Protection

2.9.1 IRB Review and Communications

This protocol, the parental permission, and child assent forms must be reviewed and approved by each Clinical Center's IRB before the study begins at that Clinical Center. In addition, the Central Data Management Coordinating Center (CDMCC) must have documentation of current IRB approval at all times during the study. The CDMCC must also have a copy of the informed permission and child assent forms that were approved by the IRB for each Clinical Center before enrollment will be permitted at the Clinical Center.

2.9.2 Recruitment and Informed Consent

Parents or legal guardians of children with symptoms of DKA presenting to the pediatric emergency departments of the participating PECARN centers will be approached to provide permission for their child's participation in the study. The emergency medicine, pediatric critical care and pediatric endocrinology faculty and staff at each center will be informed about the

study and posters regarding the study, with contact information for the Clinical Center investigators and research personnel, may be placed in the emergency department and critical care unit (with approval of IRB). The Clinical Center investigator and/or research coordinator should be contacted when eligible patients arrive in the emergency department and they or other designated individuals will facilitate discussion of the protocol with the patients' parents or guardians. The parental permission document will be reviewed with the parents or guardians of eligible patients and the parents or guardians will be given time to read through the document before signing. An assent document may also be reviewed with and signed by eligible patients, as per local IRB institutional guidelines.

Parental Permission

This protocol requires that parents or other legally empowered guardians sign a parental permission form. The parent or legal guardian will be informed about the objectives of the study and the potential risks. HIPAA authorization should be incorporated into the permission process.

Child Assent

Subjects who are eligible for this study are in acute distress from the diabetic ketoacidosis. This will often impair the ability of children to be able to provide assent for participation in the study. For this reason, waiver of assent will be requested from the IRB for children during the hospital phase of the study.

At the three month follow up, an increased number of subjects will be capable of providing assent for participation in the follow up visit. Children who are capable of giving assent and who are alert and competent, will be asked, following an age-appropriate discussion of risks and benefits, to give assent to study participation. Assent will be waived if the child is too young, has a severely reduced mental age, decreased level of consciousness, psychological problems, or other legitimate reasons as judged by the Institutional Review Board at each Clinical Center.

Subject Consent

Subjects who are eligible for the Fluid Therapy in DKA study are under 18 years of age. If a subject attains the age of 18 years during the study follow-up period, it will be necessary to obtain informed consent from the subject. During the follow up after discharge from the hospital, 18 year old

subjects who are alert and competent and capable of giving consent will be asked, following an appropriate discussion of risks and benefits, to give consent to the study for collection of follow up information. Subject consent will be waived if the subject has a severely reduced mental age, decreased level of consciousness, psychological problems, or other legitimate reasons as judged by the Institutional Review Board at each Clinical Center.

2.9.3 Study Risks and Benefits

DKA treatment protocols similar to all four of the study arms are currently in use at PECARN centers involved in this proposal, as well as other hospitals throughout the United States. All of these protocols are within the standard of care for pediatric DKA. Depending on the treatment arm assignment and treating institution, it is possible that the treatment will not differ from that which the patient would have otherwise received if not enrolled in the study.

The risks to subjects in this proposal are reasonable in relation to the potential benefits to the participants. Fluid treatment protocols similar or identical to those used in the study are already in use currently throughout the United States, including some of the participating PECARN centers. Therefore, in some cases, the study treatment will involve no additional risk above that involved in standard DKA treatment in that center. In addition, the study risks will be minimized by very careful monitoring of neurological status of study participants, by allowing treating physicians to deviate from the study protocol if there is any concern about patient safety, and by review of study data by the Data and Safety Monitoring Board (see Section 2.10.1 on page 43).

Potential Risks

Inadequate fluid resuscitation. Two of the study arms specify that intravenous fluids be given at a relatively slow rate. Although this treatment is within the range specified in currently used guidelines at many institutions, there is nonetheless a risk of under-perfusion of vital organs caused by inadequate fluid resuscitation. The potential lack of adequate perfusion could result in an increased risk of renal tubular or gastrointestinal necrosis. In addition, a slower rate of fluid resuscitation could increase the risk of intravascular thrombosis during DKA treatment. To minimize the risk of these adverse events, physicians caring for the patients in the study will be allowed to administer additional IV fluid boluses, outside of those spec-

ified by the protocol if there is concern about hemodynamic instability or substantially diminished peripheral perfusion. On the other hand, other investigators believe that the more rapid rehydration protocol may increase the risk of cerebral edema and possibly pulmonary edema. Therefore, there is strong clinical equipoise entering this trial.

Hyperchloremic acidosis. Two of the study arms involve administration of 0.9% saline as the intravenous fluids. With a higher volume of chloride administration, there may be a higher frequency of hyperchloremic acidosis in these children, although rehydration with 0.9% saline is part of the institutional protocol at several PECARN Clinical Centers. Hyperchloremic acidosis is a known complication of DKA in children. There are no long-term consequences of this condition, and it generally resolves with a decrease in intravenous chloride administration. Because many DKA protocols require that the patient have a serum bicarbonate concentration above a specified level before transitioning to subcutaneous insulin, however, it is possible that transition to subcutaneous insulin could be slightly delayed in patients who develop hyperchloremic acidosis. Physicians caring for patients enrolled in the study will have the option of discontinuing the study treatment prior to 24 hours, if hyperchloremic acidosis is developing and the physicians feel that a change in intravenous fluid sodium chloride content is necessary. Hyperchloremic acidosis generally develops toward the end of DKA therapy, beyond the time frame when most episodes of cerebral edema or altered mental status occur. Treatment adjustments due to hyperchloremic acidosis therefore are unlikely to have substantial effects on the interpretation of study data.

Rapid sodium decrease. Two of the study arms involve administration of 0.45% saline, one at a more rapid rate. For children with hypernatremia in association with DKA (high corrected serum sodium concentration), it is possible that the serum sodium concentration could decline more rapidly than would be optimal using these protocols. To minimize this risk, the study guidelines will specify that children who are thought by the treating physician to require a specific fluid and electrolyte regimen should not be considered for study participation. Based on the literature in DKA and the primary investigators' experience, however, we anticipate that these patients will be encountered rarely.

Potential Benefits for Participants

Closer neurological monitoring. Mental status of children enrolled in the study will be monitored carefully, using GCS evaluations. Although some centers use GCS or other frequent mental status assessments during DKA as a routine, other Clinical Centers monitor mental status less frequently. It is possible that patients may benefit from this more intensive monitoring of mental status and possible earlier detection and treatment of cerebral edema or other cerebral injury were it to occur.

Improved mental status. Patients randomized to one or more of the study arms may experience a lesser frequency of mental status deterioration or other complications than if they were treated according to the standard fluid protocol of the particular study site.

Neurocognitive testing. Children enrolled in the study will undergo neurocognitive testing. This testing includes evaluation of IQ and memory capacity. Parents/guardians will be notified of IQ scores below 85 (more than 1 SD below mean). Although specific scores will not be disclosed, parents/guardians will be advised that the testing indicated "possible learning problems", and that follow up with the child's school and/or a psychologist for more formal testing should be considered. This information could be helpful for future educational interventions.

Potential Benefits for Future Patients

Future patients with diabetes and DKA will benefit from the study if the results determine that one treatment regimen is superior to others in decreasing the risk of DKA-related cerebral injury, cerebral edema, and/or other complications.

Minimizing Risk of Participation

Patients enrolled in the study will be monitored carefully for the development of mental status or other neurological abnormalities. Patients will be evaluated via GCS assessment on an hourly basis, and more frequently if abnormalities in mental status actually develop. If cerebral edema is suspected, prompt treatment will be administered per the routine of the treating facility. All study centers are tertiary care facilities with substantial pediatric expertise and are well prepared to evaluate and treat any complications that might arise.

The study guidelines specify that treating physicians can administer additional fluid boluses beyond those specified in the protocol, if necessary to restore hemodynamic stability. In these events, the use of additional fluid boluses will be documented on the study data collection form, however, the patient will continue to use the assigned protocol for the remainder of their DKA treatment and be analyzed according to intention-to-treat principles.

The study protocol can be discontinued if the attending physician feels that continuation of the protocol would result in risk of harm to the patient. All patients discontinued early from the study protocol will have a reason for the early discontinuation recorded on the appropriate case report form, and the circumstances leading to discontinuation will be described. All adverse events leading to discontinuation of study interventions will be fully documented and followed up as appropriate.

Subjects who are discontinued early from the study protocol are *not* considered to be withdrawn from the study, and will be included in the intention-to-treat analyses.

Withdrawal from Study

If a patient's parents/guardians withdraw permission for the patient to continue in the study, all study interventions will be discontinued, but the medical course of the patient will continue to be reviewed for adverse events until the patient is discharged from the hospital.

2.9.4 Data Security and Subject Confidentiality

All evaluation forms, and reports will be identified only by a coded number to maintain patient confidentiality. All records will be kept in a locked/ password protected computer. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring by the Federal funding institution (NICHD), the CDMCC, or other governmental regulatory bodies.

The Central Data Management Coordinating Center (CDMCC) at the University of Utah has a dedicated, locked server room within its offices, and the building has 24 hour on-site security guards. The CDMCC has a state-of-the-art computer infrastructure and coordinates its network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides the CDMCC with effective firewall hardware, automatic network intrusion detection, and the expertise

of dedicated security experts working at the University. Network equipment includes three high-speed switches and two hubs. User authentication is centralized with two Windows 2003 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using secure socket layer (SSL) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. The CDMCC will prepare an electronic data capture (EDC) system using commercial or open source products, and eRoom^{TM} is used for communications about the study. The EDC, eRoom^{TM} and other web applications use the SSL protocol to transmit data securely over the Internet.

Direct access to CDMCC machines is only available while physically located inside the CDMCC offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff are notified of intrusion alerts. Security is maintained with Windows 2003 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 10 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group level access to databases, tables, and views in Microsoft SQL Server.

The investigators and staff of the data coordinating center are fully committed to the security and confidentiality of data collected for the Fluid Therapy in DKA study. All personnel at the CDMCC have signed confidentiality agreements concerning all data encountered in the CDMCC. Violation of these agreements may result in termination from employment at the University of Utah. In addition, all personnel involved with CDMCC data systems have received Human Subjects Protection and HIPAA education.

2.9.5 Health Insurance Portability and Accountability Act

Data elements collected include the date of birth and date of admission. Prior to statistical analyses, dates will be used to calculate patient age at the time of the study events. The final data sets (used for study analyses and archived at the end of the study) will be de–identified, and will exclude these specific dates.

Data elements for race, ethnicity, and gender are also being collected. These demographic data are required for Federal reporting purposes to delineate subject accrual by race, ethnicity, and gender.

Each Clinical Center will be required to obtain informed consent from a legal guardian of eligible patients before the patient is enrolled in the study. For purposes of the CDMCC handling potential protected health

information (PHI) and producing the de–identified research data sets that will be used for analyses, all study sites have been offered a Business Associate Agreement with the University of Utah. Copies of executed Business Associate Agreements are maintained at the CDMCC.

2.10 Data and Safety Monitoring Plan

2.10.1 Data Safety Monitoring Board (DSMB)

The Fluid Therapy in DKA study will have a Data Safety Monitoring Board (DSMB) approved by the NICHD. The DSMB will have a charter, will approve the protocol prior to implementation, and will review interim analyses as described in Section 2.8.6 on page 35.

The purpose of the DSMB is to advise the Federal funding agency (NICHD) and the study investigators (Drs. Kuppermann and Glaser) regarding the continuing safety of study subjects and the continuing validity and scientific merit of the study. The DSMB is responsible for monitoring accrual of study subjects, adherence to the study protocol, assessments of data quality, performance of individual Clinical Center, review of serious adverse events and other subject safety issues, and review of formal interim statistical analyses of treatment efficacy (Section 2.8.6 on page 35). The CDMCC will send reports relating to these topics to DSMB members ten days prior to each DSMB meeting.

The proposed membership for the DSMB is five members, including a biostatistician, and the expected frequency of meetings is annual (an initial meeting and annually during the four years of patient enrollment.) However, the DSMB will have the discretion to alter meeting timing and frequency. Interim analyses are anticipated after the first, second, and third years of subject enrollment.

The CDMCC will staff DSMB meetings and produce minutes of open sessions. Minutes of closed or executive sessions of the DSMB will be produced and retained by the DSMB Chairperson. These closed minutes will not be available outside the DSMB or NICHD prior to the end of the study.

The DSMB Chairperson will prepare a summary of each DSMB meeting that conveys the public conclusions of the DSMB, with respect to protocol alterations and recommendations concerning continuation of the study. The summary will be provided to the CDMCC and the CDMCC will send this summary to all Clinical Center investigators for submission to their respective Institutional Review Boards.

2.10.2 Adverse Event Reporting

Definitions, Relatedness, Severity and Expectedness

Definition: An adverse event (AE) is any untoward medical occurrence experienced by a subject. An event constitutes a disease, a set of related signs or symptoms, or a single sign or symptom.

On each study day, the Clinical Center investigators will evaluate adverse events. Adverse events not previously documented in the study will be recorded on the adverse event record form. The nature of each experience, date and time (where appropriate) of onset, outcome, course, and relationship to treatment should be established.

Relatedness: The suspected relationship between study interventions and any adverse event will be determined by the Clinical Center investigator using the following criteria. *Relatedness may **not** be assessed by a research coordinator, and must be assessed by an investigator.*

Not Related: The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Possibly Related: The event follows compatible temporal sequence from the time of beginning the assigned study intervention, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Probably Related: The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention, and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Seriousness: The severity of clinical adverse events and laboratory abnormalities will be recorded by the Clinical Center investigator and categorized. A serious adverse event (SAE) is an adverse event that:

- results in death; or
- is life-threatening (the patient was, in the view of the Clinical Center investigator, in immediate danger of death from the event as it occurred); or

- requires inpatient hospitalization or prolongs an existing hospitalization; or
- results in persistent or significant disability or incapacity; or
- results in congenital anomaly/birth defect); or
- any other event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Expectedness of the Event: All adverse events, including serious adverse events, will be evaluated as to whether their occurrence was expected or unexpected. An adverse event is considered expected if it is known to be associated with diabetic ketoacidosis, the underlying medical condition of the subject, is directly related to study outcome (e.g. cerebral edema, somnolence), or is otherwise mentioned in the protocol, informed consent, or other study documents. For this protocol, expected events include death, thromboses, renal failure, cerebral edema or cerebral infarction, cerebral thrombosis, seizure, gastrointestinal necrosis, pancreatitis, hemolytic anemia, cardiac arrhythmias, rhabdomyolysis, pulmonary edema and hyperchloremic acidosis.

Treatment or Action Taken: For each adverse event, the Clinical Center will record whether an intervention was required:

- Intervention: Surgery or procedure
- Other Treatment: Medication initiation, change, or discontinuation
- None: No action taken

Finally, the Clinical Center will record the clinical outcome of each adverse event as follows:

- Death
- Recovered and the patient returned to baseline status
- Recovered with permanent sequelae
- Symptoms continue

Time Period for Adverse Events

For purposes of the Fluid Therapy in DKA study, adverse events occur following randomization through hospital discharge. Specifically, events that

occur following parental permission to participate in the study, but prior to actual randomization, will be not be reported as adverse events. These should be recorded as baseline conditions. Events that occur following discharge from the hospital will not be reported as adverse events. Adverse events will be followed until resolution or hospital discharge, whichever is earlier.

Data Collection Procedures for Adverse Events

After patient randomization, adverse events (including serious adverse events), whether anticipated or unanticipated, will be recorded according to the date and time of first occurrence, severity, and their duration, as well as any treatment prescribed. Any medical condition present at the time of randomization, recorded in the patient's baseline history at study entry, which remains unchanged or improves, will not be recorded as an adverse event at subsequent evaluations. However, worsening of a medical condition that was present at the time of randomization will be considered a new adverse event and reported.

Abnormal laboratory values that are clinically significant and are not included in Table 2.2 on page 24 should be recorded as adverse events and the Clinical Center investigator will assess the severity and relationship to the study. Laboratory values that are abnormal at the time of randomization and that do not worsen will not be recorded as adverse events. Since DKA is associated with a large number of laboratory abnormalities, for purposes of this study, abnormal laboratory values will be recorded as adverse events when the severity grade is grade 2 or higher on the Common Terminology Criteria for Adverse Events v3.0 (CTCAE).[39] Grade 1 laboratory abnormalities, if expected as described earlier, do not need to be recorded as adverse events.

It is not necessary to record abnormal laboratory results for those tests included in Table 2.2 on page 24 because all values for these parameters will be collected. If an abnormality of a laboratory parameter in Table 2.2 on page 24 is considered to be serious by the Clinical Center investigator (see Section 2.10.2 on page 44), however, it will be necessary for the site to record and report the event as a serious adverse event (SAE). This is described in Section 2.10.2 on the facing page.

Adverse events will be coded using the MedDRA coding vocabulary. Coding will be done centrally at the CDMCC because this requires specific training.

Monitoring Serious Adverse Events

The Principal Investigator of the CDMCC (Dr. Dean) will act as the medical monitor for the Fluid Therapy in DKA study. If Dr. Dean is unavailable, a qualified physician will be designated to fulfill this function. Clinical Center investigators and/or research coordinators will report serious adverse events to the CDMCC within 24 hours. A detailed completed report will be required to be sent to the CDMCC within 3 working days of the event, and the medical monitor will assess all serious adverse events reported from Clinical Centers. For each of these serious adverse events, the Clinical Center will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the trial. The medical monitor will sign each SAE report after review. All SAE reports will be retained at the CDMCC, and all SAE reports will be available for review by DSMB members and NICHD staff via the eRoom^{TM} facility.

In the unlikely event that the medical monitor believes an unexpected and study-related SAE warrants emergent cessation of enrollment in the trial, NICHD staff and the DSMB chairperson will be immediately consulted. If these individuals concur with the judgment of the medical monitor, or if the NICHD staff and the DSMB chairperson cannot be reached expeditiously, the CDMCC will notify the study investigators (Drs. Kuppermann and Glaser) and all Clinical Center investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NICHD staff after discussion with the DSMB.

Reporting Procedures

Assuring patient safety is an essential component of this protocol. Each participating Clinical Center investigator has primary responsibility for the safety of the individual subjects under his or her care. All adverse events will be evaluated by the Clinical Center investigator, and will be classified as noted in Section 2.10.2. All adverse events occurring after study randomization through hospital discharge will be recorded and entered into the electronic data entry system provided by the CDMCC.

The Clinical Center investigator will report all *serious, unexpected, and study-related* adverse events to the CDMCC within 24 hours. A detailed completed report will be required to be sent to the CDMCC within 3 working days of the event. After receipt of the complete report, the CDMCC will report such *serious, unexpected, and study-related* adverse events to the NICHD Program Official or Project Officer in an expedited manner (within

24 hours). In accordance with local IRB requirements, the Clinical Center investigator may be required to report such events to the IRB in addition to notifying the CDMCC. In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and NICHD staff cannot be reached expeditiously, the CDMCC will notify the study investigators (Drs. Kuppermann and Glaser) and all Clinical Center investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NICHD staff after discussion with the DSMB.

Unanticipated problems (UP) are defined as incidents, experiences, or outcomes that are unexpected, related to participation in the Fluid Therapy in DKA study, and suggest that the research places subjects at a greater risk of harm than was previously known or recognized. The Clinical Center investigator will report unanticipated problems to the CDMCC within 24 hours. A detailed completed report will be required to be sent to the CDMCC within 3 working days of the event. After receipt of the complete report, the CDMCC will report these unanticipated problems to the NICHD Program Official or Project Officer in an expedited manner (within 24 hours). In accordance with local IRB requirements, the Clinical Center investigator may be required to report such unanticipated problems to the IRB in addition to notifying the CDMCC. In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and NICHD staff cannot be reached expeditiously, the CDMCC will notify the study investigators (Drs. Kuppermann and Glaser) and all Clinical Center investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NICHD staff after discussion with the DSMB.

After notification of the NICHD Program Official or Project Officer, and the DSMB chairperson, of *serious, unexpected, and study-related* adverse events or unanticipated problems (UP), decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made to suspend enrollment in the trial, this will be reported to the study investigators (Drs. Kuppermann and Glaser) and all clinical investigators, who will be instructed to report this to their local IRB.

The DSMB will review all adverse events (not necessarily serious, unexpected, and study-related) during scheduled DSMB meetings. The CDMCC will prepare a Summary Report of Adverse Events for the DSMB meetings, classified with the MedDRA coding system.

Follow-up of Serious, Unexpected and Related Adverse Events

All serious, unexpected and related adverse events, that are unresolved at the time of the patient's termination from the study or discharge from the hospital, will be followed by the Clinical Center investigators until the events are:

- Resolved, subject is lost to follow-up, the adverse event is otherwise explained or has stabilized; OR
- 3 months has passed from the time of randomization.

Adverse experiences that begin after discharge from the hospital will not be reported as study adverse events.

2.11 Data Quality Assurance

2.11.1 Data Management

Data will be entered into an electronic data collection (EDC) system to be designed and implemented by the CDMCC. The Study Coordinator is required to use hard copies of worksheets for data collection. The paper worksheets should be retained at the Clinical Center in a secure location until the study is complete and all study publications have been published.

2.11.2 Study Training

A formal training program for investigators and research staff will be held prior to the start of enrollment. The training program will cover regulatory topics including applicable device regulations and good clinical practice. The training will also provide in depth explanations regarding study procedures, clinical care, adverse event reporting, data entry procedures, quality assurance, site monitoring and the informed consent process. A manual of operations will be provided to each Clinical Center investigator prior to the start of enrollment. The manual will detail specific information about the study procedures, regulatory information, safety reporting, and other necessary information. Updates and revisions to the manual will be made available electronically. The CDMCC, in collaboration with the study investigators (Drs. Kuppermann and Glaser), will be the main contact for study questions.

Clinical Center investigators and designated study staff will also receive small group instruction on the conduct of the neurocognitive testing. This

initial training will be accomplished by Dr. Ghetti and several graduate level assistants. Each trainee will do observed practice sessions including the neurocognitive testing procedures. Each session will be followed by feedback and additional practice.

The PECARN Steering Committee and all Clinical Center investigators will attend two PECARN meetings annually throughout the course of this study to discuss study issues and instruct Clinical Center investigators. Each Clinical Center investigator should instruct the group of ED physicians at their home institutions about the study, and serve as local advocates for the study and answer questions as they arise. Throughout the study, the Steering Committee will also have quarterly telephone conference calls, or more frequent conference calls as necessary.

2.11.3 Site Monitoring

The investigators recognize the importance of insuring data of excellent quality. Site monitoring is critical to this process. Site monitoring has been a very effective tool for maintaining data quality in previous PECARN studies, and we will utilize this process to ensure excellent quality data in the proposed study. Our site monitoring plan is designed to identify problems with sites and methods for handling problems that arise. Each site will have a monitoring visit during the initial study period (year one). Monitors will evaluate regulatory and protocol compliance and data quality. Subsequent site monitoring will be implemented with actual visits to each site, supplemented by remote site monitoring.

In addition to the site monitoring visits, neurocognitive testing procedures will be re-evaluated at intervals during the trial to insure that each site continues to conduct these procedures according to standardized methods. For quality purposes and when feasible, each Clinical Center investigator and/or research coordinator responsible for neurocognitive testing will be videotaped conducting the tests and the video tape will be reviewed by the collaborating neuropsychologist, Dr. Ghetti. Any deviations from the correct testing procedures will be reviewed with the individual conducting the tests and corrected. This same monitoring procedure will be followed later in the study, in the event of change in personnel requiring retraining.

Physical Site Monitor Visits

Site monitoring visits are conducted during the study to review patient entry, data quality, and patient safety and to assure regulatory compliance.

The ongoing site monitoring visits will include an on-site meeting of the monitor, the Clinical Center investigator and his/her staff. A site monitor will visit each study site during the study period and review compliance with the study methodology and adherence to Good Clinical Practice guidelines. The site monitor will provide each site with a written report and sites will be required to follow up on any deficiencies.

It is anticipated that the study monitoring visits for this protocol will consist of a site initiation visit (prior to patient enrollment), interim visits, and a close out visit. The site initiation may take place as a group training of site investigators and research assistants.

Interim visits will take place depending on financial constraints, site enrollment, and compliance issues identified. The first interim visit will take place within the first year of patient enrollment. Subsequent interim visit frequency will be determined by the results of the first visit and financial resources available for conducting site monitor visits. During interim visits, review of regulatory compliance and documentation, 100% review of consent documentation is anticipated, along with statistically controlled sampling for source verification.

Close out visits will take place after the last subject is enrolled at the site. The close out visit agenda would include resolution of outstanding queries and a review of adverse events, regulatory documentation, and archiving plan. The close out visit may need to be accomplished remotely, depending on available financial resources at the time of study completion.

Remote Site Monitoring

The data center will supplement on-site monitoring with remote monitoring activities. Remote monitoring involves detailed review of the data entered by the Clinical Center and telephone consultations with the Clinical Center investigator and/or research coordinator to review safety and data quality. This requires uploading de-identified copies of specific parts of the medical record to the CDMCC staff, who review those materials against the data recorded in the electronic data capture system.

Site Monitoring Plan

A supplemental study-specific monitoring plan, separate from the protocol, will be completed prior to the start of the study which outlines specific criteria for monitoring. This plan will include the number of planned site visits, criteria for focused visits, or additional visits, a plan for chart review,

and a follow up plan for non-compliant sites. The monitoring plan also describes the type of monitoring that will take place (e.g. sample of all subjects within a site; key data or all data), the schedule of when these activities are to take place, how they are reported, and a time frame to resolve any issues found. Remote site monitoring data elements and schedule will be determined by the CDMCC.

2.11.4 Record Access

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. The medical record must be made available to authorized representatives of the CDMCC, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, site local health authorities, the CDMCC and its authorized representative(s), the National Institutes of Health, and the IRB for each study site, if appropriate.

2.11.5 Record Retention

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

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Part II

Good Clinical Practice

Chapter 3

Good Clinical Practice (GCP)

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3.1 PECARN Data Coordinating Center Policy

The PECARN Data Coordinating Center (CDMCC) at the University of Utah School of Medicine has a policy that all PECARN studies will be conducted in compliance with Good Clinical Practices (GCP).[1] Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the

[1] Good Clinical Practice (GCP) was prepared by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH 1997) and published by the US Food and Drug Administration (FDA) on May 9, 1997 (see 62 FR 25691). GCP was published with the objective of providing a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. The intent of this policy is to safeguard human subjects' welfare, assure validity of research data, and help assure that the PECARN will remain, as a whole, in compliance with regulatory requirements.

The CDMCC will:

- present educational information about GCP to investigators and research coordinators at PECARN Steering Committee meetings and specific study training sessions;
- provide manuals and materials to assist each Clinical Center in organizing essential documents and records;
- advise and assist each Clinical Center in understanding and meeting GCP requirements throughout all PECARN studies;
- organize site monitoring visits to each Clinical Center, as appropriate to the specific study, in coordination and with approval from Maternal and Child Health, Emergency Medical Services for Children (EMSC) Program;
- and serve as a central point of review and distribution of site monitoring visit reports.

Personnel at a Clinical Center may contact the CDMCC Principal Investigator, Program Director or Project Manager with any questions concerning this material. Contact information is available in the *eRoom*^{TM} facility.

3.2 Project Site Monitoring

In most multi-institutional studies, the CDMCC assigns a site monitor to travel to each Clinical Center at times appropriate to the specific study. Site monitoring visits are often conducted at site initiation, during a study, and at close out of the study. Site monitoring for PECARN studies will be planned in accordance with the technical requirements and difficulty of the study, with approval by the EMSC.

It is anticipated that site monitoring will be required for the Fluid Therapy in DKA. For more information regarding site monitoring specific to this study, please refer to Chapter 4 on page 67. Certain documents should be

available at the Clinical Center so that at any time, these could be presented to an authorized visitor:

- Original study protocol
- Current study protocol
- Essential Documents Binder - maintained and current
- Institutional Review Board (IRB) submission packet and approval
- Protocol amendments and IRB amendment approvals
- Current IRB Approval

In order for a Clinical Center to participate in any study, the CDMCC must have a copy of the IRB approval from that site. The CDMCC at the University of Utah is prohibited (by the University of Utah IRB) from accepting data submission from a Clinical Center if this requirement is not met. More information concerning IRB approval is included later in this chapter (on the following page) and in Chapter 5 on page 75.

3.3 Essential Documents Binder

The Essential Documents Binder consists of regulatory records and materials at the participating Clinical Center pertaining to the study. This includes regulatory documents, IRB correspondence, and other documents listed in the previous section. In addition, subject files (both case report forms and supporting medical records) are referenced from this binder. This means that the binder should indicate where the subject records are maintained.

These documents comprise the investigator's portion of what GCP terms Essential Documents for the conduct of a clinical trial. When combined with the sponsor's documentation, these documents are used by Federal agencies to permit evaluation of the conduct of the trial and the quality of the data produced.

For the purposes of organizing the Essential Documents, the CDMCC adopts the approach most commonly used, and recommends maintaining Essential Documents in a physical binder called the "Essential Documents Binder". Each Clinical Center will be provided an empty Essential Documents Binder, by the CDMCC, for use in each PECARN study. Personnel at each Clinical Center are responsible to populate the binder with the relevant materials.

The Essential Documents Binder should be complete, well organized, and current. Materials can be filed elsewhere with a note of explanation placed in the binder, but it is intended that this binder serve as a directory to all study records and documents regardless of their physical location. Responsibility for maintaining the binder should be assigned to a specific individual. It is recommended that the binder be in a place where it is accessible to research staff for reference during their daily performance of duties.

3.4 Archiving Study Records

For PECARN studies funded by EMSC or other Federal agencies, there are specific requirements for archival of study data.

For this study, the investigator must retain subject records in an easily retrievable form until disposal has been agreed in writing with the study sponsor. The investigator must have a 'key' linking the subject's electronic data capture (EDC) number to the subject's clinical file. If investigators move or retire, they must nominate someone in writing to be responsible for record keeping. Archived data may be held on microfiche or electronic record, provided that a backup exists and a hard copy can be obtained from it if required.

3.5 IRB - Investigator Interactions

The Institutional Review Board (IRB) is responsible for review of clinical research and protection of patient rights and welfare at each Clinical Center where research is undertaken. During all PECARN studies, the IRB or its equivalent at the Clinical Center is responsible, on behalf of the Clinical Center, to perform an ongoing review of the study.

The Principal Investigator at each Clinical Center must assure that the study is appropriately reviewed by a qualified IRB. Prior to initiating the study, the investigator prepares an application for the IRB, in conformance with the requirements of the IRB. Depending on the type of study, this IRB application may include forms for informed consent, waiver of consent, compliance with the Health Insurance Portability and Accountability Act (HIPAA), protocol summaries, investigator biographies, and so forth. The format for IRB applications is different at each Clinical Center.

For PECARN studies, it is critical that the study protocol be identical at every Clinical Center. The local IRB application should refer to the

PECARN study protocol, which should be included or attached to the local application. The PECARN study protocol may not be modified by the Clinical Center for its IRB application. If the IRB is unable to approve the PECARN study protocol, forcing alterations of the protocol, then the protocol must be modified by the PECARN for every Clinical Center in the study.

The Principal Investigator is responsible to assure annual review and approval of the study throughout its implementation and the publication of study results. The Clinical Center IRB must review a study at least annually, or more often at IRB discretion. The annual renewal must be sent to the CDMCC when it is received.

The Principal Investigator must report to the IRB all protocol violations if associated with unexpected risks to subjects and serious adverse events.

Whenever possible, CDMCC will notify investigators of items requiring IRB review, but it is the responsibility of the investigator to be familiar with local IRB requirements and to determine what items need to be reported to or approved by the IRB or its equivalent. The CDMCC will also attempt to remind Clinical Center investigators to renew the IRB approval for the project, but it remains the responsibility of the investigator at each Clinical Center to assure maintenance of local IRB approval for each study.

3.6 Clinical Center Site Inspections

In addition to the visit by a site monitor, a Clinical Center may be visited for an *inspection* by a local IRB auditor, EMSC, FDA, or other auditor at various times during PECARN studies. The auditor is generally required to contact the investigator prior to the visit to arrange a mutually agreeable time. Following the visit, a site inspection report will be sent to the investigator summarizing findings and observations. All such reports should be filed separately from the Essential Documents Binder, but made available to the CDMCC or the EMSC as requested.

It is anticipated that site monitoring will be required for the PECARN Fluid Therapy in DKA. Regardless of whether a site monitoring visit actually occurs, site *inspections* may be carried out by EMSC, and Clinical Center investigators must be prepared to provide the materials described in this chapter.

3.7 Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for the CDMCC, EMSC, or other Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When investigators sign the protocol, he/she agrees to allow the CDMCC, Drug Regulatory Agency and EMSC auditors to inspect his/her study records. Furthermore, if an investigator refuses an inspection, his/her data will not be accepted.

The study sponsor is responsible for selecting qualified investigators, and has delegated responsibility to the CDMCC for ensuring proper monitoring of the investigation, and ensuring that the investigation is conducted in accordance with the general investigational plan and protocol. The PECARN network has a substantial investment in clinical studies. Having the highest quality data and studies are essential aspects of the PECARN network. The CDMCC and EMSC has Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that EMSC sponsored studies are in accordance with the relevant Good Clinical Practices regulations/guidelines.

To accomplish these functions, the CDMCC and/or Regulatory Compliance at EMSC selects investigational sites to audit. These audits usually take 1 to 2 days. The audits entail review of source documents supporting the adequacy and accuracy of data entered into the EDC system, review of documentation required to be maintained, and checks on drug accountability. The audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring the CDMCC and EMSC of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- IRB approval
- Test article accountability
- Approved study protocol and amendments
- Informed consent of the parents/patients (parental permission/assent)
- Medical records supportive of Source Document data

- Reports to the IRB and the sponsor
- Record retention

The CDMCC and/or EMSC will gladly help investigators prepare for an inspection.

Chapter 4

Site Monitoring Visits

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4.1 Monitoring by CDMCC

A site monitor may visit each study site during the study period to review compliance with the study methodology and adherence to Good Clinical Practice (GCP) guidelines. General descriptions of the monitoring visits and items reviewed during site visits are included in this section. Throughout the duration of the Fluid Therapy in DKA study remote monitoring will be conducted. Remote monitoring will be discussed in this section.

4.1.1 Site Monitoring Visits

If the study requires site monitoring visits, the site will be contacted to ascertain a mutually agreeable visit date. Once the visit date has been decided, an announcement letter (Page 72) is sent to the site. The site monitor will outline what they will be reviewing in the announcement letter. However, the site monitor will not be limited to the outline in the announcement letter. For instance, in addition to the items mentioned in the letter, the site monitor may ask to observe a mock consent process in order to better understand the consent process at the site.

Along with access to essential documents, the site monitor will expect provision for adequate workspace and access to the electronic data capture (EDC) system via the internet. The monitor will also expect to have access to key research personnel (e.g. the Clinical Center coordinator, and Clinical Center investigator) during the visit.

The Site Monitor will submit a visit report to the CDMCC, Clinical Center investigator and Clinical Center coordinator. If deficiencies are identified, the Clinical Center investigator is responsible for making corrections. Ultimately, in the unusual occurrence that the site does not respond to the recommendations to improve performance, the network leadership will discuss the appropriateness of the site's continued participation in the study protocol.

4.1.2 Document Review During Site Monitoring Visits

Essential Documents Please refer to Section 3.3 on page 61 for a detailed description of the essential documents required for this study. The Essential Documents Binder consists of all regulatory records and materials at the participating site pertaining to the study. These documents comprise the Clinical Center investigator's portion of what GCP terms "Essential Documents" for the conduct of a clinical study. These documents permit evaluation of regulatory compliance, conduct of the study, and the quality of the data produced.

The Essential Documents must be complete and well organized. The CDMCC may provide binders to each participating site to organize and file the regulatory documents, study correspondence and other essential documents using a format recommended for all CDMCC studies. Materials can be filed elsewhere with a note of explanation placed in this binder, but it is intended that this binder serve as a directory to all study records for documents contained in the binder and elsewhere.

All essential documents must be accessible at the time of the site monitoring visit. For instance, all original IRB correspondence, submissions, and attachments should be provided. Review of these items should provide clear documentation of consent revisions, protocol amendments and any correspondence with the IRB or any other regulatory body.

Source Document Verification A source document is the initial record of a data point. Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation

of the trial. Source data are contained in the source documents (original records or certified copies). A certified copy is a copy of original information that has been verified, as indicated by dated signature, as an exact copy having all of the attributes and information as the original. Types of source documents may include: protocol specific source documents, medical records, and notes to file.

If site monitoring is conducted during the study, access to the complete, original medical records and other applicable source documents at the site is required. This also pertains to remote monitoring; all source documents must be available to de-identify and submit to the CDMCC. Source documents will be compared to the data points entered in the EDC system.

If site monitoring is conducted at the site, it is imperative that sites confirm that there are no institutional restrictions to site monitor documentation access.

Data is transcribed from the source document to the EDC system. The EDC system contains each protocol specific data point. The site will maintain a patient study file referencing or containing each data point source that is entered in the EDC system.

The data point may be taken from protocol specific source documents. An example of this type of source document would be blood pressures taken at protocol specified time points which are not recorded in the medical record.

When a data point is taken from the medical record, a copy of the pertinent records may be placed in the patient study file. Although copies are not source documents, the copy will help direct you to the source data in the medical record for future queries or review. A certified copy from the electronic medical record is acceptable as a source document. To certify a copy of a medical record, ensure that the copy is an exact duplicate of the electronic medical record and has all of the attributes and information as the original. Sign and date the copy to indicate that the verification process was completed.

Another source document is the note-to-file. This note includes information that cannot be recorded elsewhere, it is not a data point per se, and usually requires a narrative. If the note-to-file documents a mistake or protocol violation made in the course of the study, a Corrective and Preventative Action (CAPA) form must be completed. This form provides an explanation of the event along with a plan of action to ensure that it doesn't happen again. As with any source document, the note-to-file needs to be signed and dated by appropriate personnel and reference the subject (if applicable) and protocol.

In summary, all source documents need to be signed and dated by appropriate personnel, and all data points entered in the EDC system require a source document (protocol specific source documents, medical record, or note-to-file).

4.1.3 Remote Monitoring

In addition to on-site monitoring, the CDMCC has developed protocol specific quality assurance plans which include remote monitoring from the CDMCC. The main purpose of remote monitoring is to review data quality, verify that data elements are being drawn from the correct source documentation, and verify adherence to Good Clinical Practice guidelines.

In addition, documentation of remote monitoring submissions and correspondence must be maintained by the site in the Essential Documents Binder. If site monitoring is conducted, the site monitor will review remote monitoring documentation at the site and perform source document verification for a portion of the primary data points submitted to the CDMCC.

The CDMCC will send a letter (Page 73) to the clinical site requesting data be sent for remote monitoring. The letter will include EDC numbers on the participants to be monitored and a list of data points and/or source documents to be sent on the identified participants.

1. The Clinical Center will respond by sending requested data to the CDMCC within 7 days of request. The Clinical Center should perform the following steps to send and identify documents appropriately:

    - Identify and gather source documents needed. Make a copy of source documents and de-identify this copy as is reasonably necessary by marking through provider and patient names with a black felt marker.
    - Write in the EDC number as close as possible to the top right corner, without obliterating underlying data.
    - Fax requested documents along with original request to the CDMCC fax server at 801-585-3243.
    - E-mail Marci Fjelstad (marci.fjelstad@hsc.utah.edu) and Hai Le (hai.le@hsc.utah.edu) when your documents have been faxed to obtain acknowledgment of receipt.
    - Print out and place original CDMCC remote monitoring request letter, documents that were faxed and acknowledgment of fax receipt from the CDMCC along with any other correspondence with

the CDMCC in the Essential Documents (Regulatory) Binder. This documentation may be reviewed during on-site monitoring visits.

2. The CDMCC will review the documents sent from the Clinical Center and respond to the Clinical Center with a written report of data validation discrepancies or other issues identified within one month of fax receipt.

3. The Clinical Center will have 21 days to respond to the written report by making corrections, submitting a CAPA, or refaxing documents, as appropriate.

4. The following will require re-faxing appropriate data to the CDMCC:

   - Source data is illegible.
   - Source data is not attributable to an individual subject and/or is not dated.

Central Data Management Coordinating Center

295 Chipeta Way • Salt Lake City • Utah • 84158-1220 • Phone • (801) 581-6410 • Fax • (801) 585-3243

PLEASE NOTE: THIS IS A SAMPLE ANNOUNCEMENT LETTER, THE REVIEW ELEMENTS REQUESTED OF THE SITE MAY BE DIFFERENT.

DATE

PI
Site PI
Address
Email

Regarding: Site Monitoring Visit for PECARN protocol 022 entitled "Application of Transcriptional Signatures for Diagnosis of Febrile Infants within the Pediatric Emergency Care Applied Research Network" (Short title: the Biosignatures study)

Dear Dr. _____:

This letter is to confirm plans for a site visit for the protocol referenced above on *DAY, DATE, 200X* at 11:00 am by *Site Monitor name, title etc.*

The main purpose of this site visit will be to review data quality, regulatory documentation, and adherence to Good Clinical Practice guidelines.

I anticipate my visit will take two full days. With this in mind, please reserve a space (e.g. empty office or conference room) for the duration of my visit. I will be comparing the source document to TrialDB. Therefore, please provide computer and internet access.

During my visit I would like to review the following documentation:
Essential Document Binder:
- **Curriculum Vitae Medical License (s)**
- **IRB Approval Letter (s)**
- **IRB Correspondence**
- **IRB Membership Roster &FWA # (Available through your IRB Office)**

Patient Study Files, Source document files, and TrialDB
Patient Medical Records
Manual of Operations
Any other applicable study documentation

If you have any questions or concerns, please feel free to contact me (Phone: email:).

Sincerely,

SITE MONITOR NAME
Site Monitor

cc via email:
Site Coordinator
Site PI
Study Principal Investigator

Central Data Management Coordinating Center

295 Chipeta Way • Salt Lake City • Utah • 84158-1220 • Phone • (801) 581-6410 • Fax • (801) 585-3243

PLEASE NOTE: THIS IS A SAMPLE LETTER, THE REVIEW ELEMENTS REQUESTED OF THE SITE MAY BE DIFFERENT.

January 9, 2008

[Site Study Coordinator]
[Study Coordinator e-mail address]
Sent via Email

Regarding: Remote Monitoring for PECARN Protocol 022 entitled "Application of Transcriptional Signatures for Diagnosis of Febrile Infants within the Pediatric Emergency Care Applied Research Network (PECARN)" (Short title: the Biosignatures study)

Dear [Study Coordinator]:

This letter is being sent to officially request documentation for remote monitoring. Please respond within 7 days of this request.

For the following Trial DB numbers:
ST03[XXXX00XX]
ST03[XXXX00XX]
ST03[XXXX00XX]

Please follow instructions below to fax appropriate and attributable source documents for the following data points:

1. Identify and gather source documents needed. Make a copy of source documents and de-identify this copy as is reasonably necessary by marking through provider and patient names with a black felt marker.
2. Write in the Trial DB number as close as possible to the top right corner, without obliterating underlying data.
3. Fax requested documents along with original request to the CDMCC fax server at 801-585-3243.
4. E-mail Heather Gramse (heather.gramse@hsc.utah.edu) and Kym Call (kym.call@hsc.utah.edu) when your documents have been faxed to obtain acknowledgment of receipt.
5. Print out and place original CDMCC remote monitoring request letter, documents that were faxed and acknowledgment of fax receipt from CDMCC along with any other correspondence with CDMCC in Essential Documents (Regulatory) Binder. This documentation will be reviewed during on-site monitoring visits.

If you have any questions or concerns, please feel free to contact me.

Chapter 5

Institutional Review Board and the CDMCC

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5.1 Documentation of IRB Review

Documentation of initial IRB review and approval must be received by the CDMCC before a Clinical Center can begin patient enrollment or data submission for any PECARN study. The Clinical Center IRB must approve the study protocol. If any advertisements or posters will be used in the study, these should also be IRB approved and stamped. The documentation required by the CDMCC consists of the following:

- An approval letter signed by the IRB Chairperson (on Chairperson's official stationery) stating:
  - That participation in the study is approved
  - The date or version number of the final protocol
  - Date of the IRB review/approval

  - Date of expiration
  - Any action or problems that the IRB noted

- If the IRB did not note the version number or date of the protocol in the approval letter, the CDMCC will request the site to contact their IRB for a revised approval letter that includes the information listed above.

- If the PECARN study involves informed consent, assent, advertisements, or other materials that require IRB approval, the CDMCC also requires documentation of approval of the specific items, either by having the IRB stamp the materials, or by explicit documentation in the letter from the IRB.

Documentation of annual IRB reviews must be sent to the CDMCC. If documentation is not received, sites will be unable to continue participation in the study (patient enrollment or data submission) until the documentation is received by the CDMCC . The documentation required for IRB annual renewal is the same as described above for the initial IRB review and approval. When PECARN studies involve informed consent, the CDMCC requests a copy of the approved informed consent form from each Clinical Center. If the consent form is translated into other languages, a copy of the translation and a letter from the certified translator should also be provided to the CDMCC .

5.2 What If IRB Approval Is Denied?

If a PECARN protocol is submitted to the Clinical Center IRB and not approved, do not alter the protocol in order to achieve approval. Identify whether the lack of approval is related to a component of the PECARN approved protocol, or whether the lack of approval is related to something in the other parts of the IRB application. In nearly all instances, lack of approval is related to something *outside* the underlying network study protocol.

For example, a PECARN approved study protocol might state that waiver of informed consent is requested because of reasons one, two and three. The Clinical Center IRB may determine that informed consent should not be waived at the specific Clinical Center. The local application merely needs to indicate that informed consent will not be waived at that site. It is not necessary to alter the original PECARN study protocol. On the other

hand, if the PECARN approved study protocol requires informed consent, the Clinical Center IRB may not reduce this requirement to waiver of consent. That is, a Clinical Center IRB may not reduce the human subjects protection required by the PECARN.

For another example, the Clinical Center IRB might require more details from local investigators concerning certain aspects of the study. These details may be provided in the application without necessarily being added to the underlying study protocol. The study protocol might indicate that data are submitted via secure electronic methods, but the Clinical Center IRB may require several pages of details. Such details can be provided in the IRB revised application, but are not added to the study protocol itself.

If the IRB refuses to approve a protocol and it is intrinsically related to material in the PECARN study protocol, then the PECARN will need to reevaluate the original protocol, for every Clinical Center, and the IRB approval process most often will have to be restarted at all sites. In this situation, it will be helpful if the Clinical Center IRB allows the PECARN to see the minutes of the discussion, to facilitate appropriate alteration of the study protocol.

5.3 Review Date Clarification

Renewal of Clinical Center IRB approval must take place on at least an annual basis, based on the date of the last approval.

Example 1. If the Clinical Center IRB approves the study on 1/15/00, then the renewal must take place on or before1/14/01.

Example 2. If a study's initial IRB approval date is 1/15/00 and the annual renewal occurs on 1/8/01, then the next annual renewal would need to take place on or before 1/7/02.

If it is the policy of the Clinical Center IRB for the approval to take effect at the end of the month, then the next renewal can be accomplished anytime that month. In this case, the CDMCC must have a copy of that IRB's policy on file.

Example 3. If the IRB approved a study on 1/15/00, and it is the policy of that committee that the effective date will be the end of the month, then the approval date would be 1/31/00. Therefore, the next annual renewal can take place on or before 1/30/01.

Date of approval is the date the board or committee met, not the date of the Chairperson's signature.

5.4 Consequences of Tardy Annual Review

The CDMCC is prohibited by the University of Utah IRB from accepting study data from any Clinical Center that does not have IRB approval.

5.5 Local IRB Amendments

Amendments may occur at a Clinical Center for administrative reasons, such as a change in participating investigators. The Clinical Center Principal Investigator is responsible for adhering to the local Clinical Center IRB requirements. It is not required that the CDMCC receive IRB documentation concerning approval of revised investigators or insignificant administrative changes, as long as the PECARN study protocol itself is not amended.

In the event that the study protocol is amended by the PECARN in a non-administrative manner, the amendment will almost always require Clinical Center IRB approval, and the CDMCC will need to receive documentation of the IRB amendment approval.

Chapter 6

Investigator Responsibility

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6.1 Investigator Qualifications and Agreements

Principal Investigators, alternate PIs, and other participating investigators at Clinical Centers are personally responsible for all aspects of the clinical study, though it is evident that many activities are specifically delegated to other staff. This delegation of tasks is not a delegation of responsibility. It is important for each investigator to recognize the importance of careful supervision and oversight of all activities relating to a PECARN study. Some specific requirements for investigators engaged in human subjects research include:

- The Principal Investigator and all sub-investigators at the Clinical Center must be qualified by education, training and experience to assume responsibility for the proper conduct of the study.

- All participating investigators at the Clinical Center must be aware of, and comply with, Good Clinical Practice (see Chapter 3 on page 59) and all applicable regulatory requirements. For PECARN studies involving the Food and Drug Administration (drug or device studies), each investigator must provide necessary regulatory documents to the CDMCC, including signed agreements acknowledging investigator responsibilities.

- The Principal Investigator and the Clinical Center *must permit* site monitoring and auditing by the PECARN CDMCC and the Maternal and Child Health, Emergency Medical Services for Children (EMSC) Program. For certain studies, inspections may be required and conducted by other Federal funding or regulatory agencies. Site monitoring is anticipated for the Fluid Therapy in DKA. This is described in more detail in Chapter 4 on page 67.

- The Principal Investigator or an alternate investigator at the Clinical Center must ensure that they have sufficient time to conduct and complete the study within the agreed upon study schedule.

- The Principal Investigator must have adequate staff and appropriate facilities that are available for the duration of the study and must ensure that other studies do not divert essential patients or facilities away from the study at hand.

- The Principal Investigator is responsible for reporting serious adverse events (SAE) that occur during a clinical study.

- The Principal Investigator and all collaborating investigators at the Clinical Center must ensure that all persons assisting with the study are adequately informed about the protocol, the investigational product (when applicable), and their study-related duties and functions.

6.2 Communication with IRB

Before initiating a study, the Principal Investigator must have written and dated approval from the IRB at the Clinical Center, for the study protocol, written informed consent forms, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects, as applicable.

The Principal Investigator at the Clinical Center is responsible to assure renewal of IRB approval for all PECARN studies conducted at the Clinical Center, from onset of study through completion of final publication of study results.

6.3 Compliance with Study Protocol

The Principal Investigator and Clinical Center must conduct the study in compliance with the protocol agreed to by the PECARN protocol subcommittee, approved by the PECARN Steering Committee, and approved by the IRB at the Clinical Center.

When a PECARN study protocol is modified, the Principal Investigator must assure that the local IRB is aware of the modification. Local IRB requirements will differ concerning requirements to file immediate amendments for such modifications, or to allow certain administrative changes to be submitted at the time of annual IRB review and renewal of approval.

The investigator must not implement any deviation from the approved protocol, nor make changes in the study protocol, without agreement by the PECARN protocol subcommittee, the CDMCC Principal Investigator, and the Clinical Center's local IRB.

Unintentional or intentional protocol deviations *do* occur during the course of nearly all studies. The investigator, or a person designated by the investigator, must document and explain any deviation from the approved protocol. Such documentation should be stored in the Essential Documents Binder, and may, according to local IRB policy, require IRB notification. In addition, the documentation should be transmitted to the PECARN CDMCC in order to assure proper analysis and interpretation of study data.

6.4 Protocol Amendments

No changes to the study protocol will be allowed unless agreed to by the PECARN protocol subcommittee, approved by the PECARN Steering Committee, and filed as an amendment/modification to this protocol.

Any amendment/modification to the protocol will be adhered to by the participating center (and all participating centers) and will apply to all patients following approval as appropriate by each Institutional Review Board.

6.5 Premature Study Termination

6.5.1 By Principal Investigator

If the Principal Investigator terminates or suspends a study without prior agreement from the PECARN protocol subcommittee, and the Steering Committee, the investigator must promptly inform the PECARN CDMCC and the Clinical Center IRB. If this occurs, the investigator should provide a detailed written explanation of the termination or suspension to the PECARN CDMCC and the Clinical Center IRB. This written documentation, and all derivative correspondence, should also be stored in the Essential Documents Binder.

6.5.2 By Clinical Center's IRB

If the Clinical Center IRB terminates or suspends its approval of a study, the investigator must immediately (within 48 hours) notify the PECARN CDMCC. If this occurs, the investigator should provide a detailed written explanation of the termination or suspension to the PECARN CDMCC. The written documentation, and all derivative correspondence, should also be stored in the Essential Documents Binder.

Chapter 7

Staff Responsibilities

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7.1 Staff Training

While the Principal Investigator and all collaborating investigators are ultimately responsible for all aspects of a PECARN study at a Clinical Center, many other staff will play significant roles in most studies. The Clinical Center Principal Investigator is responsible to assure that all staff have received adequate training to accomplish the tasks that have been delegated from the investigator to the staff member. Such training must be documented, and in certain studies, may require periodic repetition. For the current study, the Principal Investigator is responsible to assure that all Clinical Center staff involved have a clear understanding of the procedures in the study protocol and in this Manual.

7.2 Screen Locations for Eligible Patients

Staff may be assigned the task of screening patients as they present to the emergency department. For more detailed screening information relating to this study please refer to 9.2.

7.3 Enrollment of Patients

Staff may be assigned the task of approaching families for permission to participate in the study. These staff must be qualified for this task. They may be assigned the task of entering data into the electronic data system implemented at the CDMCC. See B for more information about the electronic data capture system. For more information regarding patient enrollment specific to this study, please refer to 10.4.

7.4 IRB Approval

Staff may be assigned the task of assisting the Principal Investigator in preparation and submission of IRB documents, but the investigator remains primarily responsible to assure IRB approval prior to initiation of the study, and annual renewal of the IRB approval throughout the life of the study (until all publications have been completed)or as specified by the local IRB.

7.5 Maintain Essential Documents Binder

Staff may be assigned the task of maintaining the Essential Documents Binder with up to date information.

7.6 Document Responsibilities

Delegation of responsibilities from the Principal Investigator to other personnel should be documented in writing in the Essential Documents Binder, as appropriate to the study.

For this study, document the specific individual who is responsible for each of the tasks.

- obtain and monitor local IRB approval and send copy of approval to CDMCC

- make eligibility decisions during patient screening
- entering data in OpenClinica as described by the MOO
- enrolling patients
- maintain Essential Documents Binder
- tracking participants
- training study personnel on study procedures
- administering 3-months neurocognitive follow up

The Principal Investigator should sign and date this documentation of responsibilities. In many studies, especially interventional studies, it is desirable to have each staff member provide signatures and initials for designated activities. This provides express acknowledgment of the delegation of responsibility and enables a site monitor to identify signatures and initials on study documents. On the next page, please find the suggested assignment of tasks as well as a template Documentation of Responsibilities form.

7.7 Study Specific Staff Responsibilities

The responsibilities listed are study specific. Please complete Signatures and Delegated Responsibilities form to include all individuals who are participating in the study at each site, then place in Essential Documents Binder in the section titled "Roles and Responsibilities / Signatures - Research Staff / ED Staff."

1. Read and understand protocol and study procedures (Site PI/RC)
2. Verify that all those required by the site IRB to complete Human Subjects training have certification on file (Site PI and/or RC)
3. Submit study for site IRB approval (Site PI and/or RC)
4. Maintain file of signature and delegated responsibilities forms (RC)
5. Train study personnel and maintain documentation of staff training (Site PI and RC)
6. Maintain Essential Documents Binder (EDB) and Manual of Operations (MOO) (RC)

7. Screen patients for eligibility (Site PI or Enrolling Physician)
8. Determine and verify patient eligibility (Site PI/Enrolling Physician/RC)
9. Parental permission/HIPAA process for eligible participants(Site PI/RC/Enrolling Physician)
10. Distributes parental permission/HIPAA copies to enrolled participants(Site PI/RC/Enrolling Physician)
11. Patient Enrollment (Site PI or Enrolling Physician)
12. Maintain tracking list of enrolled patients and parental permission refusals as directed by the CDMCC(RC)
13. Documents eligibility on the inclusion/exclusion worksheet(Site PI or Enrolling Physician)
14. Enters study data into OpenClinica (RC/PI)
15. Submits ongoing IRB materials: Amendments, Continuations, Adverse Reactions/Unexpected Events (RC/PI)

Table 7.1: Signatures and Delegated Responsibilities

Name of Individual	Title or Position	Delegated Task	Signature	Initials	Effective Dates
					From: To:
					From: To:
					From: To:
					From: To:
					From: To:
					From: To:
					From: To:
					From: To:
					From: To:
					From: To:

Principal Investigator Signature: Date of Signature:

Part III

Study Management

Chapter 8

Preparation

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8.1 General

In the Diabetic Ketoacidosis Study (FLUID), sites will be enrolling patients for a period of 3-4 years. The following tips may help you prepare for this study:

1. Familiarize yourself with the ED charts, paper and electronic medical records, and patient logs. For data points, especially those that can be collected retrospectively (those that can be abstracted from the medical record later), you will want to review the study data collection worksheets and identify where the study data points can be obtained in the patient's hospital records. For timelines and details about what data can be retrospectively abstracted, see Step 8 (15.3 on page 175). General medical record review and worksheet completion.

2. A note about source documents: When the data are recorded directly onto a worksheet for the purpose of the study this is called the source document. When a worksheet is referred to as the source document, it means that these data are not routinely collected in the medical record and the first place the data are recorded is the study worksheet.

3. Unique to the FLUID study, you will also need to be familiar with the operations of the Pediatric Intensive Care Unit (PICU) and/or general floor unit, their medical records, patient logs, and processes, as well. This includes knowing who will collect data using study source data (ED RN staff, Floor RNs, RC or PI) and how you will ensure the study tasks are completed. Communication to all these parties will be critical to the success of the study at your site.

4. Identify ED staff, PICU staff, and/or floor staff that are participating in the study or helping with patient identification and enrollment. Make sure that all personnel participating in the study have been trained on the applicable study procedures and that the training has been appropriately documented on your training log. A sign-in sheet will be necessary for documentation of training sessions for ED, PICU and floor staff. These individuals should also be listed on the Signature & Delegated Responsibilities Log with their initials. (Note: If personnel are only completing the hourly GCS scores and log, they do not need to be included on the Signature & Delegated Responsibilities Log, unless your IRB requires it.)

5. If you cannot decipher someone's handwriting in the medical record, check with the physician, nurse, or other personnel involved in the study as soon as possible. If you have questions, check with the site PI. If you are unsure of either the definition or the value of any data worksheet item, refer to the Manual of Operations, site PI, or CDMCC staff, in that specific order.

6. Site Principal Investigators (PIs) are responsible for all aspects of this randomized controlled clinical trial at their respective sites. RCs may assist and be assigned specific duties, but thorough PI oversight is required for this study. Make sure that at least weekly meetings between RC(s) and PI are set, and any questions are promptly addressed by the PI.

7. Timing is a very crucial part of the FLUID study since study-required tasks must be completed at specific times (e.g. short enrollment window, Digit Span every 4 hours, GCS every hour). RCs and PIs should come up with a system of reminders and indicate how these tasks will be accomplished in their Site Specific Workflow. Additionally, several study tools have been developed to help study staff stay on schedule.

Please see eRoom for an Overview Grid (A.29) and an Hour Conversion chart (A.31).

8. Familiarize yourself with OpenClinica and the FLUID OpenClinica data entry. Some Open Clinica tips are:

   - If you use Internet Explorer when accessing OpenClinica and ensure that your "compatibility view" is checked. Firefox may work better with OpenClinica.
   - Recall that all OpenClinica dates are entered in the DD-MMM-YYYY format; use the calendar icon to the right of dates for ease of entry. Month must be written with the first letter in caps and remainder in lower case e.g 02-Apr-2010
   - All times should be entered as HHMM (without the colon in between hours and minutes). No colon should be entered. All times use military time (see A.32 for a reference table). Always enter the leading zero, if needed (e.g. enter "0130" instead of "130" for 1:30 AM).
   - OpenClinica does allow you to use tabs to skip fields.
   - Do not enter spaces after data.
   - After you upload a file to OpenClinica, you must click "save" in order for it to save to the database.
   - Read the questions; OpenClinica will allow you skip some questions you need to answer and to answer questions you shouldn't. Make sure you understand which questions should be answered. (referred to as "skip logic")
   - Double check your data entry to prevent possible queries.
   - Patient study file worksheets have extra data on them that do not need to be entered into OpenClinica, but all OpenClinica data appears on a worksheet. For a list of all OpenClinica events, CRFs and corresponding Patient Study File worksheets see A.1.
   - For more details and screenshots of OpenClinica, see Appendix B on page 349
   - If you need to delete a patient, unschedule an event, or delete a eCRF, please email the CDMCC with the request including the patient ID and the specific data to be removed. You will not be able to do these tasks on your own.

9. Certified copies: electronic copies will be considered to be certified by the RC if RCs sign and date the document. RCs should print out any data that is obtained via the electronic system and sign and date it then place it in the patient study file. Their signature and date indicates they have certified that this is an exact copy of the original data. Certified Copy is a copy of original information that has been verified, as indicated by dated signature, as an exact copy having all of the same attributes and information as the original.

8.2 Study General Workflow

Here A.2 you will find an overview of the general workflow for the study. This is a general workflow to help with understanding the overall study processes and data that are required at each point in the study.

This general workflow does not account for the site specific clinical/operational variations that may be applicable at each individual site. It is the responsibility of the PI (with RC input) to come up with a Site Specific Workflow for each individual institution. Your site should have one of these developed for the study, called a "Site Specific Workflow". Make sure you know where that document is and that you understand it. These workflows should be used frequently throughout the study and updated as needed. It should be a resource for study team members to know what step is next as patients move through the study. It should document the specific study processes and particulars of how study tasks will be conducted at your site. In addition, site monitors will review this document and assess whether you are following both the study protocol and your own site specific workflow. Keep in mind, the site specific workflow **may not** conflict or deviate from the protocol and should be a more detailed version of the general study workflow above. If you have questions, check with the site PI or the CDMCC.

This MOO will follow the general workflow outline and should serve as a guide to help you through each step of the process, from initial patient screening in the ED to the 3-month neurocognitive follow up.

Chapter 9

Step 1: Patient Screening

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9.1 Worksheets & Sources:

Time point: Patient Screening in the ED *Screening and Enrollment worksheet:* the enrolling physician should complete; this is a study source document.

9.2 General

If it's suspected that a patient is in DKA, appropriate study personnel should be contacted (i.e. PI and/or RC). The process of communicating the presence of a DKA patient in the ED should be clearly defined and communicated with all study staff prior to the first patient enrollment and documented in your Site Specific Workflow.

There are three circumstances in which patients are likely to present to the ED: 1) A patient will present to the ED with a suspected diagnosis of DKA, 2) A patient with DKA but without a known history of diabetes will present with symptoms, but the diagnosis of DKA will be somewhat delayed given the lack of previous history of diabetes, or 3) A patient will be transferred to your ED, likely already diagnosed with DKA. There are some specific exclusion criteria applicable to *transferred patients only.*

The Screening and Enrollment worksheet, along with the Physician Treatment Initiation worksheet, are short study source documents that can be completed quickly by the enrolling physician, including the Site PI if they are in the ED for patient enrollment.

Sites may find it helpful to keep screening logs for all patients screened for eligibility (this should be a part of the Site Specific Workflow). If so, a sample template can be found here: A.33. This may be particularly helpful in determining which patients have been previously enrolled in the study to help eliminate enrolling patients more than twice. However, patients may be screened multiple times for the study. Enrollment is defined as randomized to a treatment arm; enrollment more than twice is an exclusion criterion.

9.3 Screening

The enrolling physician or study PI (not the RC) should complete the Screening & Enrollment worksheet A.3 to determine if the patient is eligible for the study, as clinical judgment is needed to evaluate some of the inclusion and exclusion criteria. Patient screening is to be completed in the ED. The Screening and Enrollment Worksheet is a study source document that can be completed quickly. The Screening & Enrollment worksheet will walk the enrolling physician through the study specific inclusion and exclusion criteria to determine patient eligibility. Inclusion and exclusion criteria should be evaluated based on the patient's condition at the time of ED presentation.

Inclusion Criteria: Patients must meet ALL inclusion criteria to be eligible for the study.

1. Patient is younger than 18 years of age
2. Patient has a diagnosis of DKA, defined as:
   (a) Serum glucose or finger stick glucose concentration >300 mg/dL, AND
   (b) Venous pH <7.25 or serum bicarbonate concentration <15 mmol/L.

Inclusion criteria #1 refers to the patient's age at the time of the ED evaluation or the inpatient hospitalization of the study. If the patient will turn 18 before the 3-month follow-up visit, they are still eligible for the study; see the follow-up section (Section 16 on page 194) for details on this instance.

Inclusion criteria #2 refers to a diagnosis of DKA. If a formal diagnosis of DKA has not yet been made, but the patient meets Inclusion criteria #2a and #2b, and DKA is likely, they should be considered eligible for the study (see the Screening & Enrollment worksheet, Inclusion criteria #2). For study purposes, DKA is defined as a serum glucose or fingerstick glucose >300 mg/dL and either a ph <7.25 or serum bicarbonate <15 mmol/L. To be eligible, both #2a AND #2b must be met.

If the patient had a serum glucose >300 mg/dL at an outside hospital or office and was transferred to a PECARN ED where the glucose is now lower than 300, the outside hospital's glucose should be used (so the patient would still be eligible). Additionally, pH or bicarb results from outside hospitals are acceptable. If a result from an outside hospital or office is used verbal identification of the results is acceptable for screening; however, an attempt should be made to obtain the documented result from the outside provider for the patient study file. At the a minimum, the verbal result should be documented in the patient study file.

Point-of-care or iSTAT glucose results should also be considered for inclusion criteria, even if they were done within 15 minutes of a lab result and have different findings. Home glucose kits or patient's own personal glucose meter readings are not enough for inclusion and a hospital test should be used. Any glucose test (lab, point-of-care, iStat, etc.) that is >300 mg/dL should be used for inclusion criteria, with the exception of a home or personal glucose meter result. Initial serum bicarbonate may come from a BMP or an electrolyte panel. Point-of-care or iSTAT serum bicarbonate results should also be considered for inclusion criteria.

The glucose and pH or bicarb do not need to be done at the same point in time. Inclusion labs do not necessarily have to be the initial labs done for the patient, either. For example, labs could be drawn and the glucose meets the inclusion criteria but the ph or bicarb do not. An hour later, additional labs are drawn and the ph now meets inclusion criteria. This patient should be considered eligible (the earlier glucose and the second ph meet the inclusion criteria).

Any blood bicarbonate testing may be used for the inclusion criteria. This can be a result from an outside hospital or physician's office. Inclusion criteria blood bicarbonate testing results can come from a iSTAT, lab, elec-

trolyte panel, BMP, or blood gas. Whatever bicarbonate is used to meet the inclusion criteria should be included on the lab log in OpenClinica on the Electrolyte data entry tab; for on-going labs, after the patient is enrolled, only bicarbonate and serum electrolytes that appear in the electrolyte panel should be included in the data entry.

(Please note: a positive ketone test is not required for study enrollment, but presence of ketones should be documented as soon as possible.)

All patients who meet inclusion criteria should be data entered into OpenClinica. See 9.5 on page 102 for more information.

Exclusion Criteria: If any ONE of these EXCLUSION criteria is met, patient is ineligible.

1. Patients with pre-existing neurological disease that substantially impacts mental status or neurocognitive exam (e.g. cerebral palsy with developmental delay or autism)

2. Patient presented with concomitant alcohol or drug use, head trauma, meningitis or other conditions which might affect neurological function.

3. Patient has been transferred after initiation of DKA treatment and has already received more than one 10 cc/kg intravenous bolus.

4. Patient is known to be pregnant.

5. Patient has been enrolled in the study twice previously.

6. Patient has been receiving IV fluids at a maintenance rate or greater for more than two hours. (Maintenance is defined as 4-2-1 rule)

7. Patients for whom it has been more than <u>four</u> hours since DKA therapy (IV fluids, IV bolus, or IV insulin) began.

8. Patients who have been given hyperosmolar therapy (i.e.mannitol or 3% normal saline) prior to or since arriving at the participating study site.

9. Patients for whom the treating physician intends to immediately administer hyperosmolar therapy (i.e.mannitol or 3% normal saline).

10. Patients whose baseline GCS is 11 or less.

Exclusion criteria #1 allows for some clinical judgment and should be made on a case-by-case basis by the enrolling physician or site PI. Typically, this exclusion should exclude only patients with severe neurological diseases that may affect their ability to participate in the neurological testing (e.g. Digit Span Recall Test) or GCS assessment. For example, a patient might be excluded for cerebral palsy with developmental delay but NOT for typical ADHD.

Exclusion criteria #2 requires clinical judgement. Please note that patients who were in a car accident, have an illness, or some other stressor that may have pushed them into DKA should be considered eligible.

Exclusion criteria #3 refers to IV bolus ONLY and does not refer to maintenance fluid (see exclusion #6) or other DKA treatment like insulin (see exclusion #7). If transferred patients received less than 10 cc/kg IV bolus, they should be considered eligible for the study (see protocol violation). If transferred patient received MORE than 10 cc/kg IV bolus, they should be excluded. If transferred patients received some a bolus of than 0.9% saline (NS) (so 1/2 NS or 0.45% saline, for example), they should be considered eligible. Transferred patients who received insulin at the other hospital should be considered eligible (as long as they meet all other criteria).

Exclusion criteria #4 does not require that female patients of childbearing age be tested for pregnancy, unless your site's IRB requires this. Only patients known to be pregnant should be excluded.

Exclusion criteria #5 requires that patients only be enrolled twice maximum in the study. This may be hard to identify up front during screening. Patients may be enrolled for a second enrollment if they have not yet completed the 3 month follow-up visit. In this case, patients should only complete a follow-up visit for the second enrollment. If a patient is discovered to have been enrolled in the study for a third time after randomization, the patient should be included in the study. Continue study treatment and data collection, complete a protocol deviation (Section 18.2 on page 234), report the issue to your IRB as required by your site, and notify the CDMCC immediately upon discovery. For information on data entry and worksheets for a patient's second enrollment, see Section 12.5.

Exclusion criteria #6 refers to "maintenance or greater" IV fluids given regardless of an initial fluid bolus. Evaluate just the rate of fluids given after the initial bolus, if an initial bolus has been given. The FLUID study definition of a bolus is: greater than or equal to 10 cc/kg over one hour or less. The FLUID study definition of maintenance rate is defined by using the 4-2-1 rule. (The 4-2-1 rule is 4 cc/kg/hr of IV fluid for the first 10 kg of weight, 2 cc/kg/hr of fluid for the next 10 kg of weight, and 1 cc/kg/hr of

fluid for each subsequent kg of weight.)

Exclusion criteria #6 and #7 should be evaluated at the time of screening and then again after parental permission is obtained. If a patient is randomized after either time limit, continue study treatment and data collection, complete a protocol deviation (Section 18.2 on page 234), report the issue to your IRB as required by your site, and notify the CDMCC immediately upon discovery.

Exclusion criteria #8 and #9 refer to patients who will receive or have received hyperosmolar therapy (i.e. mannitol or 3% normal saline). Any patient who has been given hyperosmolar therapy prior to or since arriving at the participating study site should not be randomized to the study. If a patient has not received hyperosmolar therapy prior to arrival at the participating study site, but the treating physician intends to give hyperosmolar therapy as part of the patient's care, the patient should not be randomized to the study.

Exclusion criteria #11 refers to the patient's baseline Glasgow Coma Scale (GCS). If the total score of the patient's baseline GCS is equal to or less than 11, the patient should not be randomized to the study. Should the patient's total score equal 12 or greater on the baseline GCS, the patient can be included so long as they do not meet any other exclusion criteria.

Please note that if the treating physician believes a specified fluid and electrolyte regimen was warranted for the patient, this does not appear in the Exclusion criteria section of the Screening & Enrollment worksheet. This would include patients for whom the treating physician plans to treat or who are already being treated with subcutaneous insulin rather than IV insulin. It appears on the next page in the Parental Permission, approached section. Please enter all data including the Inclusion and Exclusion criteria up to the approached question on the Screening & Enrollment eCRF in OpenClinica. Also complete the Not Enrolled worksheet for these patients. For more information, see the Not Enrolled chapter, 17.

9.3.1 Patients who return frequently to your ED for DKA

Remember, patients can be enrolled twice in the FLUID study. After patients have been enrolled twice, they no longer need to be approached for the study (but are still screened and entered into OpenClinica as meeting the "more than twice" exclusion criteria).

If you have patients who come into your ED frequently, please screen and approach them for the study for each visit. Only if the patient or parent says "no! I don't want to be in your research! Don't ask me again!", add these

patients to a Do Not Screen list at your site (add this list to your EDB). Patients on the Do Not Screen list should not be screened or approached or entered into OpenClinica at all, if they return again. Check in with the families once a year or so to offer the opportunity to change their mind, as appropriate.

Please note: patients should only be added to this list if they specifically request to not be approached again. All other frequent patients should be screened and approached with each visit, just like every other patient in DKA.

9.3.2 What if a patient is seen outside of our ED, discharged, and then comes to our ED?

A patient was seen in an outside ED and discharged home from the ED. It was unclear whether the patient had DKA when presenting to the outside ED or just hyperglycemia or ketonuria. Several hours later, the patient was feeling worse and came to the PECARN ED in DKA. The patient otherwise met eligibility criteria for the study, but the site team was uncertain if the patient should be enrolled or not. Based on this very specific and uncommon instance:

- If a patient is admitted for DKA and discharged within 48 hours of screening for FLUID, the patient is excluded from enrollment.
- If a patient is seen in an outpatient setting for DKA (ED or doctors office) within 48 hours of screening for FLUID, the patient is excluded from enrollment.
- If a patient is admitted or seen in outpatient for any reason other than DKA (as defined by the study inclusion criteria), the patient is eligible and include the patient. This includes hyperglycemia or ketonuria, but without DKA.
- If a patient is admitted or seen in outpatient for an unknown reason, the patient is excluded from enrollment.

9.4 GCS at ED Evaluation

Once a patient is determined eligible for the study (all inclusion criteria have been answered as "yes" and all exclusion criteria as "no"), the enrolling physician should record the Glasgow Coma Scale (GCS) score on the Screening & Enrollment worksheet.

The **patient's total GCS score at the time of ED evaluation must be written** on the Screening and Enrollment worksheet.

This GCS is critical to the study as it will be used during randomization to assign the treatment the patient receives. Total GCS at ED evaluation needs to be recorded on the Screening and Enrollment worksheet as part of the study source document. This will be referred to throughout the study process for the patient and is a required and critical part of the study.

If more than one GCS is done prior to randomization, use the GCS done closest to (but prior to) randomization for the randomization GCS. On the Screening & Enrollment worksheet, the GCS done at ED evaluation goes on page 1 (and is entered into OpenClinica on the Screening & Enrollement eCRF). But, when you make the randomization phone call, use the latest GCS available, marking the appropriate range box on page 2 of the Screening & Enrollment worksheet.

9.5 OpenClinica Data Entry: Screening

Study staff should review the Screening and Enrollment worksheets *as soon as possible* to ensure all data have been completed!

The Screening portion of the Screening and Enrollment worksheets should be entered on the Screening and Enrollment Event, Screening & Enrollment eCRF. Enter the screening date & time on the Screening Date & time tab. This should be the date & time that the screening was done in the ED by the enrolling physician. If the enrolling physician did not complete the date and time, study staff should try to complete the worksheet with their best estimate, based off ED evaluation time and with help from the enrolling physician. If the patient is an eligible patient who was not approached for the study (not screened until later), enter the date and time the patient was screened.

Enter the inclusion criteria on the Screening and Enrollment Event, Screening & Enrollment eCRF, Eligibility tab. If these are not completed, study staff must get the enrolling physician or site PI to complete the missing data as soon as possible. These cannot be left blank!!

Eligible patients should be entered into OpenClinica as soon as possible to obtain an OpenClinica Study Subject ID by Adding the Subject (for details on adding a subject see: **??**). To add the subject and create the Study Subject ID, all that is needed is the date of enrollment into FLUID (which should be the date of data entry). "Sex" on the Add Subject screen should be left blank instead entering "sex" on the Demographics eCRF

(in the Screening Event). As soon as this Study Subject ID is obtained (generated for you by OpenClinica after Adding a Subject), it should be added to all study worksheets. Refer to your Site Specific Workflow for determining when, where and how this should be done at your site and what unique identifier your site uses until the OpenClinica Study Subject ID is determined. Some suggested unique identifiers could be the randomization number give to you by Perry Point (see 10.4 on page 113), or a MRN (though if this is used, be sure to de-identify all documents once the Study Subject ID is added).

All patients who meet inclusion criteria should be entered into OpenClinica on the Screening and Enrollment Event, Screening & Enrollment eCRF, Eligibility tab. If a patient is excluded because of an exclusion criterion, enter the Screening and Enrollment worksheet including all exclusion criteria, enter "yes" in OpenClinica for the appropriate exclusion criteria(on) that made the patient not eligible. Enter "no" for "Is patient eligible to be approached for participation in this study?" No other Screening & Enrollment event data is needed for these patients. Demographics for these patients should be entered, if possible. No additional data are needed for these patients. For more information see the Not Enrolled chapter 17 on page 229.

Total GCS at the time of ED evaluation should be entered as a whole number between 3 and 15 on the Screening and Enrollment Event, Screening & Enrollment eCRF, Screening tab in OpenClinica. Even if more than one GCS is done prior to randomization, the GCS at ED evaluation should be entered here, on the Enrollment Event, Screening & Enrollment eCRF, Screening tab. If more than one GCS is done prior to randomization, use the GCS done closest to (but prior to) randomization for the randomization GCS. All GCS assessments done from ED evaluation through randomization through DKA resolution must be included on the GCS Log (and entered into OpenClinica on the GCS eCRF). (See 13.4 for more details on the GCS Log.)

For enrolled patients, be sure to enter all labs used for inclusion criteria on the Lab Log (see 15.8 for more information on Lab Log data entry).

Chapter 10

Step 2: Consent, Enroll & Randomize

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10.1 Worksheets & Sources

Time point: At ED evaluation, enrollment into the study.

Screening & Enrollment (continued): Enrolling physician should complete; this is a study source document

IRB-approved Parental Permission & Assent (if needed) documents: RC, enrolling physician or site PI with parent signature; this is a study source document

Not Enrolled: RC with the review of medical records should complete this worksheet

10.2 General

After screening is completed and the patient is determined eligible for the study, the enrolling physician (who could be the PI) should sign the Screening and Enrollment worksheet. The next step is to enroll the patient by:

1. Obtaining parental permission
2. Randomizing the patient to study arm (You will need patient's GCS at time of ED presentation documented on the Screening and Enrollment worksheet)
3. Completing Enrollment Packet of patient information (remaining page of the Screening and Enrollment worksheet and the Physician Treatment Initiation worksheet)

10.3 Informed Consent Process

Recall that informed consent is a process that should be on-going throughout the study. The FLUID study has asked for waivers regarding consenting issues (waiver of consent for not enrolled patients and a waiver of assent for enrolled patients). Your IRB-approved specifications should be well understood by all enrolling physicians and study staff at your site. These specifications should also be clearly documented in your Site Specific Workflow.

GCP reminder: Informed Consent advice from OHRP :

> Informed Consent is a process, not just a form. Information must be presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is a fundamental mechanism that ensures respect for persons through

> provision of thoughtful consent for a voluntary act. The procedures used in obtaining informed consent should be designed to educate the subject population in terms that they can understand. Think of the document primarily as a teaching tool not as a legal instrument. http://www.hhs.gov/ohrp/policy/index.html#informed

The Informed Consent process for FLUID should be a collaborative effort between the RC and the Enrolling Physician or Site PI. DKA and diabetes is a complex disease in which clinical expertise is needed as part of the consent process; especially in cases where individuals are being diagnosed with diabetes for first time. Parents and patient may have questions that RCs cannot answer; physicians need to be available to ensure that questions get answered. PIs are responsible for ensuring that RCs understand what they can and cannot answer and for ensuring the informed consent process is completed appropriately.

10.3.1 Parental Permission, Assent or Informed Consent?

For the FLUID study, there is a possibility that parental permission, assent and informed consent will be utilized. The CDMCC will provide you with a template for all three types of documents, found in eRoom.

ALL Informed Consent documents must be approved by site IRBs before you can use them for the study. Sites will need to adapt the CDMCC provided templates, incorporating site specific requirements and formats to meet the individual needs of your IRB. Prior to submitting your Informed Consent templates to your IRB, the CDMCC will do a thorough review to ensure all regulatory elements are included. Once the CDMCC determines that your documents include all regulatory elements applicable, sites will submit them to their IRBs for approval.

Below is an explanation of the three kinds of Informed Consent documents in use for FLUID:

- *Parental Permission*: The Parental Permission form (sometimes referred to as "consent form") is the documentation that parents give permission for their child (who is a minor) to participate in research. **ALL patients** participating in the FLUID study must have a signed, dated and timed consent form as a part of the patient study file record. Parental Permission forms must also be signed and dated by the person obtaining the consent. The Parental Permission form should also be available in Spanish for Spanish-only speaking parents.

- *Assent*: Assent requires that minor patients of an age set by local IRBs who are able must also provide their permission to be enrolled and participate in the study. The FLUID protocol requests a waiver of assent and most sites have received this waiver. Patients eligible for this study may be in distress from DKA, and are often impaired in their ability to provide assent. If you have approval of the waiver, assent is not required at your site until follow-up. Some IRBs may have waived assent all together. Refer to your IRB and Site Specific Workflow to be certain what is required at your site.

  For sites that are required by their local IRB to obtain assent, an assent form must be completed. The assent process, if required by your IRB, is an important part of the overall consent process and must be followed as specified by your IRB. If your IRB has determined that assent is required, an age appropriate explanation of risks and benefits must be explained to the subject, and a signed assent form must be obtained. This documentation of assent template must be approved by the CDMCC and your IRB. If your IRB requires assent, Spanish assent forms must be made available for Spanish-only speaking children.

  Even if your IRB does not require assent, the rights of the patient should always be respected and the patient treated in an ethical manner. The idea behind assent is that the patient (especially older patients who are still minors) has a say in what happens to them and should understand the study in an age-appropriate way.

- *Adult Patient Informed Consent*: In some cases, informed consent documentation will also need to be collected. Informed Consent is when adults give permission to be a participant in a research study. For FLUID participants who turn 18 years of age between their ED enrollment and the time of their neurocognitive testing, Informed Consent will need to take place. Patients who turn 18 after hospital discharge but before neurocognitive follow up will only need to consent to the neurocognitive (follow-up) portion of the study. Each site should have received IRB-approval for an Informed Consent template at the start of the study for this instance. Ensure that Informed Consent takes place and is signed & dated by the participant and the person obtaining the consent. In this instance, the RC may consent the patient, though PIs should be available to answer any questions.

10.3.2 Approaching parents for permission

RCs should not approach parents for permission to enroll the patient into FLUID study by themselves. The treating physician or site PI must be available to explain the medical issues of the study and answer questions. The Screening and Enrollment worksheet will help document the process and outcome of parental permission.

What if the parent is not approached for permission and the patient is not enrolled?

Every attempt should be made to approach parents for parental permission. However:

- If the treating physician thinks the patient needs a specific type of fluid treatment and therefore does not want to enroll the patient, document this on the Screening and Enrollment worksheet Parental Permission section by checking "Treating physician believes a specific fluid & electrolyte regimen is warranted".

- If the patient was eligible, but study staff were not available (e.g. too many patients already on the FLUID study) to gain parental permission, document this on the Screening and Enrollment worksheet Parental Permission section by checking "Site investigator or coordinator resources inadequate".

- If the patient was eligible for the study, but no one realized it at the time the patient was in the ED or in time to obtain consent within 2 hours of maintenance IV fluids or 4 hours of DKA therapy start, document this on the Screening and Enrollment worksheet Parental Permission section by checking "Impossible to consent/randomize patient within study timeframe".

- If the parent/guardian was not approached for any other reason, check "Other" and describe the reason, using additional pages, if needed.

In all four of these instances, Demographics are needed. In OpenClinica, enter the data from the Screening & Enrollment event, Screening, Eligibility, and Permission tabs. Not Enrolled data collection is needed for these patients as they are patients not enrolled in the study. For more details on these situations, see chapter 17 on page 229.

What if parents refuse permission? What if a patient refuses assent?

If the parent denies permission for the patient to be enrolled in the study, thank the parent for their time. In OpenClinica, enter the data from the Screening & Enrollment event, Screening, Eligibility, and Permission tabs. On the Permission tab, select "yes" the parent was approached and "no" permission was not given. Skip the rest of the form. Enter Demographics, if available.

If your IRB has approved the waiver of consent for patients not enrolled (see your Site Specific Workflow for details), continue to the Not Enrolled worksheet. Enter the four required data points from the medical record into OpenClinica on the Unscheduled event, Not Enrolled tab. For more details on these situations, see chapter 17 on page 229.

10.3.3 Note about Spanish-Speakers

Parental Permission documentation must be available in Spanish for Spanish-only speaking parents. If a parent only speaks Spanish, they should be consented in Spanish. The CBCL is available in Spanish and should be given to Spanish-speaking patients.

If the child is Spanish-only speaking, then they will not do the neurocognitive follow-up; these patients should be enrolled in the study and only complete the inpatient phase of the study. Patients who speak both Spanish and English are eligible for the hospitalization phase of the study and the neurocognitive follow up of the study. The digit span memory test will be made available in Spanish but the neurocognitive follow up materials are available only in English.

10.3.4 Informed Consent Checklist

An Informed Consent Checklist to help you ensure the consenting process is properly documented can be found in eRoom and here A.30. This checklist is intended to help document the informed consent process by checking off topics covered. As you go through the consent process, check off the items that you've completed so as not to miss any crucial steps. Sign and date the checklist accordingly.

Documentation of the informed consent process for FLUID is mandatory. Use of the checklist to do so is optional (sites may use another format to the document the process, if desired). Documentation of the informed consent

process is different from the IRB-approved Informed Consent Documents (which are also required).

10.3.5 Time Limits

Two of the FLUID exclusion criteria (#6 & #7) are directly about timing of enrollment from DKA therapy initiation. Ideally, the patient should be randomized within 2 hours of receiving an IV bolus and within 4 hours of starting any DKA treatment. This means that there is an end time to when parental permission can be obtained. Consenters should keep this in mind when discussing the study with parents. Inform the parents that there is a time at which the patient is no longer eligible for the study, but parents should not be pressured to consent.

10.3.6 Tips

Tips for completing the Informed Consent process:

- Introducing the study: It's really important for someone to summarize the gist of the study for the family and let them know that the consent contains a lot of details about things that can occur but are rare.
- Make it clear that the child's well-being is of primary concern to the treating physician.
- Make a distinction between clinical care and research. The clinical care of the patient will NOT be compromised for this study. All 4 treatment arms are in use in PECARN and pediatric centers across the country - we just don't know which is best.
- Help the parent get to a decision.
- Speak at a pace and with words that the parent can understand.
- Acknowledge parents' concern but do not advise the parent on whether to participate.
- Allow adequate time to review consent information, but acknowledge timeline.
- Ask yourself: Does parent have capacity to understand the study and do they understand the essential elements?

- Document all pertinent information that is relevant to the consent process.

Some helpful talking points for FLUID when talking with parents and patients are:

- This study is going on at many hospitals throughout the United States.
- IV fluids are always used to treat DKA, but we don't know which type of fluid regimen is best.
- In the study, we will use 4 different fluid treatments that are already used at some hospitals in PECARN and throughout the US - none of the treatments are new or "experimental"
- During the study, your child will be assigned at random to one of the fluid treatments used typically at some hospitals in the US. We will be monitoring your child's mental state very carefully during DKA treatment - this monitoring is likely more intensive than would usually happen and this might be a benefit to your child because we might pick up problems sooner.
- When talking about the study, we try to tell parents that we are evaluating 4 regimens that are all commonly used. But in spite of what we say, parents tend to hear things very differently - i.e. "if you enroll in this study, your child might get cerebral edema or brain injury." To try to make this more clear, some possible language might be: "Treatment for DKA in children basically involves treating them with insulin and with IV fluids. For the insulin part, almost all doctors use the same dosage and regimen, but for the fluid part, no one knows which fluids are best. There are different types of fluid treatments that are all used at different hospitals in the US. In this study, we want to compare these. None of the fluid treatments are "new" or "experimental" - they are all currently in use in various parts of the US - but we just want to know which is best. In particular, some children with DKA can develop brain injury. For almost all of these children, the brain injury is very mild - mainly some mild problems with memory - but for very rare children, it can be quite severe. We are especially interested in knowing whether one or another of the fluid regimens might be safer for preventing any type of brain injury. So for that reason, if your child is in the study, he/she will be monitored very closely to follow his state of alertness and thinking during treatment."

- After your child recovers from DKA, we will also do testing of his/her memory and learning ability.
- We have asked your doctors here in the Emergency Department whether it would be safe for your child to participate in the study. If he/she did not feel it was safe because your child needed some specific type of treatment for DKA, he/she would not have allowed us to ask you about participation.
- Your child will receive $60 ($10 for hospitalization part and $50 for follow-up)for helping with the study, sometimes this makes kids feel a little better about having to be in the hospital.

GCP points to remember for documenting consent:

- Make sure parent has signed the parental permission form.
- Make sure that the person consenting signs the parental permission form.
- Make sure that any areas that are to be initialed are complete.
- Make sure the parent signing the form is the parent or legal guardian.
- Make sure that you give a copy of the Parental Permission form to the parent and file the original in the patient study file.

10.3.7 OpenClinica Data Entry: Informed Consent Process

Because informed consent documentation must be identified with the patient's name, date of birth, parents name and signature, these documents should be treated as PHI by the site. Informed consent documents will not be uploaded into OpenClinica.

To record the parental permission process in OpenClinica, on the Screening and Enrollment Event, Screening & Enrollment eCRF, Permission tab enter, enter "yes" the parent was approached and "yes" permission was given. Enter the date and time that parental permission was obtained (that the form was signed).

10.4 Enroll and Randomize

Once eligibility has been determined and Parental Permission obtained, the patient must be randomized to one of the four treatment arms through the telephone randomization system (Perry Point).

Patients should be randomized as soon as possible following parental permission. Before randomizing please make sure the patient is eligible and that the consent process has been completed correctly. The Screening and Enrollment worksheet has a Final Eligibility Re-check section to make sure the patient is still within the exclusion criteria time window (see 10.3.5 on page 111). The enrolling physician should complete this Final Eligibility re-check. Data entry of the Eligibility re-check should be entered on the Screening & Enrollment event, Final Check tab. Both "Was informed consent (parental permission) obtained within 2 hours of IV fluid maintenance initiation?" and "Was informed consent (parental permission) obtained within 4 hours of DKA treatment initiation?" must be answered as "yes" in order for the patient to still be eligible.

Attention: Patients should only be randomized if treating physicians are comfortable randomizing the patient to any of the four possible study treatment arms. If not, the patient should not be randomized. Treating physicians must be prepared and willing to treat the patient according to the treatment arm to which the patient is randomized. This is treatment arm compliance! (If the patient is not randomized for this reason, enter the patient into OpenClinica as directed in Section 10.4.6. For the reason the patient was not randomized, indicate that the treating physician was unwilling to the give the patient all four possible study treatment arms.) If a patient comes into the ED with cerebral edema, for example, the treating physician may not want the patient on the study as the physician may not be ok with the patient receiving any of the four of the study arms. In this case, the patient would be excluded (due to treating physician preference for a specific regimen). Remember, if you enroll a patient, all four arms should be acceptable treatment to the treating physician. If the treating physician is comfortable with all four arms, enroll the patient.

10.4.1 Randomization

Randomization is the procedure by which subjects are assigned to the study arms. It assures that treatment assignment is independent of any baseline characteristics, thus eliminating many sources of possible bias. It also forms the statistical basis for conclusions to be drawn at the end of the study about the primary and secondary outcomes. It's how sites will find out which study treatment to give which patients.

Randomization is the official point where the patient is considered "in the study". This is the point of study enrollment.

How to randomize: Below is a hierarchical listing how a site may ran-

domize. **Randomization options must be done in this exact order!** Options lower down the hierarchy can only be utilized if the previous option is not working. First, sites should always use the telephone randomization service. Second, if the telephone service is not working, sites may use an internet-based service (https). Third, only if the telephone service is not working and the internet service is not working, and with permission of the CDMCC, sites MAY open their emergency back-up randomization envelope.

10.4.2 First method of randomization: Telephone service

This should be your primary method of randomization! Telephone randomization is done via Interactive Touch-Tone Randomization System (ITTRS) provided by Perry Point Cooperative Studies. This interactive phone service will provide you with various prompts and verifications before providing you the appropriate randomized treatment arm for the participant. Follow along with a paper script found here A.5 when randomizing.

The following number will connect you to the telephone randomization service: (888) 814-6525

The automated system asks for the Study Number, followed by the pound (#) sign.

The study number is: 026

The automated system asks for the study password, followed by the pound (#) sign.

The study password is: 393

Once the study number and study password are entered, the automated system asks for your site number, followed by the pound sign (#). Below are the site numbers specific to your site:

- Boston Children's Hospital (BOST): Site Number =28
- Chicago Memorial Northwestern (CHIC): Site Number =27
- Children's Hospital of New York Presbyterian (CHON): Site Number =06
- Children's Hospital of Philadelphia (CHOP): Site Number =07
- Children's National Medical Center (CNMC) : Site Number =08

- Nationwide Children's Hospital (NWCH): Site Number =31
- Primary Children's Medical Center (PCMC): Site Number =23
- The Children's Hospital of Denver (DECH): Site Number =32
- University of California, Davis (UCDA) : Site Number =20
- Washington University (WASH): Site Number =25

Once you enter your two-digit site number the automated system asks for the following data:

1. Your site's three digit password, followed by the pound (#) sign. Your individual site password can be accessed here: https://www.nedarcssl.org/eRoom/NDDP/StudyDiabeticKetoacidosis/0_61881
2. Randomization personnel's two-character initials (to enter alpha letter, use the guide on the randomization script, A.5). You will be asked to confirm the initials you entered. Press 1 if they are correct, 2 if they are incorrect.
3. Press 1 to indicate you are ready to randomize (enroll) the patient.
4. Verification that the patient has met all eligibility criteria (inclusion and exclusion; as documented on the Screening and Enrollment worksheet), then press 1.
5. Patient's 2-digit GCS (Glascow Coma Score; this is the GCS from ED evaluation, documented on the Screening and Enrollment worksheet. If more than one GCS is done prior to randomization, use the GCS done closest to (but prior to) randomization for the randomization GCS.). Enter the actual total GCS number (should be from 3 to 15); if the GCS is below 10 enter using two-digits with a leading 0 (e.g. "03"). You will be asked to confirm the GCS you entered. Press 1 if they are correct, 2 if they are incorrect.
6. Verification that the patient's parent/guardian has signed parental permission by entering 1.
7. You will then be asked to start randomization with the GCS you have entered. Press 1 if the information entered is correct.

Once you have entered all this data, the system will randomize the patient. It will tell you the randomization date and time (mm/dd/yyyy; hh:mm) and the randomization protocol number that randomization was assigned to in the format of ##-####. Make sure that you write down the exact protocol randomization the patient was given on the Screening and Enrollment worksheet, Randomization number. The patient has now been randomized and enrolled into the study. Also note the date and time on the Screening & Enrollment worksheet.

You will be asked to verify the randomization protocol number (##-####) by reentering it into the phone system.

Once you've verified the randomization protocol number assigned, the system will provide you with the appropriate treatment arm that the participant must be started on:

- A1: Additional bolus of 10 cc/kg Normal Saline; 0.45% Normal Saline rehydration fluid for assumed 10% body weight deficit
- A2: Additional bolus of 10 cc/kg Normal Saline; 0.90% Normal Saline rehydration fluid for assumed 10% body weight deficit
- B1: No additional bolus; 0.45% Normal Saline rehydration fluid for assumed 5% body weight deficit
- B2: No additional bolus; 0.90% Normal Saline rehydration fluid for assumed 5% body weight deficit

Note: All treatment arms assume the patient has already received 10 cc/kg bolus prior to randomization.

RECORD THE EXACT TREATMENT ARM THE PATIENT IS RANDOMIZED TO!!!

Make sure that you write down the treatment arm the patient was given on the Screening and Enrollment worksheet, by checking the appropriate treatment arm box. For easier reference, you can refer to the arms as A1, A2, B1, or B2. You will be asked to verify the treatment arm by reentering it into the phone system:

- A1 = press 1
- A2 = press 2
- B1 = press 3

- B2 = press 4

The randomization call is now ended, though you can request to repeat the randomization information (arm and protocol randomization number) by pressing 1.

Alpha conversions on Perry Point

On page 4 of the randomization script (found here: A.5) you will find a Letter Conversion for Reference Code key used for the randomization system. You will need this when entering your initials into the system.

10.4.3 Second method of randomization (first back-up): Website Randomization

Only use this option if the phone randomization service is unavailable (i.e. phone systems are down). You must locate a phone to try to use the telephone service first; the website should only be used as a back-up. Not having a phone nearby is not a good enough reason to use the website.

The website address is as follows:
https://www.pecarn.org/fluid/randomization

*This is a secure webpage so when entering the web address, DO NOT forget the **"S"** in https!* Once you successfully access the webpage, you will be directed to a "Log In" screen where you will need to enter your site's four-letter initials (see list above, 10.4.2 on page 115) and your site's three numeric password ID # https://www.nedarcssl.org/eRoom/NDDP/StudyDiabeticKetoacidosis/0_61881. Once you've logged in, you will be required to fill out the following information before you can randomize:

- Site personnel's initials
- Subject's date of birth
- Subject's GCS score (3-15)
- Verification that the patient met all enrollment criteria
- Verification that the patient's parent or guardian signed the informed consent

There will be an icon labeled "Cancel Randomization" if for any reason you need to cancel the randomization process.

Once all requested data have been completed, click the "Proceed to Randomize" icon to obtain randomization instructions, the randomization number, and the treatment arm. Once you click on "Proceed to Randomize" the web system will randomize the patient. Make sure EVERYTHING is completed correctly before you select the "Proceed to Randomize" icon.

If the back-up website randomization is used, the site will receive a confirmation of randomization. However, please note that the time on the confirmation will be in MST. Sites should adjust the time to their timezone and use their time as the correct time of randomization.

10.4.4 Third method of randomization (second back-up): Envelope Randomization

This option is only available if the telephone system is down AND the website is unavailable, AND you have contacted the CDMCC team and received approval to use the envelope!

If telephone randomization service AND website randomization service are unavailable, contact the CDMCC for further instructions on how to use the envelope for randomization. Contact one of these CDMCC personnel at their daytime (8AM-5PM MST) contact number listed below:

- Sally Jo Zuspan: (801) 585-9284
- Charles Casper: (801) 587-7649
- Mike Dean: (801) 581-5271

If envelope randomization is needed after hours (anytime after 5PM MST), please use the numbers listed below to contact the appropriate CDMCC personnel:

- Sally Jo Zuspan: (801) 699-6327
- Charles Casper: (801) 867-2682
- Mike Dean: (801) 739-4510

If the CDMCC cannot be contacted despite your best efforts, proceed with envelope randomization process as described below:

1. Verify that the phone service is still unavailable by attempting the numbers listed above, again, 10.4.2 on page 115

2. Verify that the web service is still unavailable (address is entered correctly, paying close attention to the **"S"** in https.)

3. After the two previous methods have been verified as still unavailable, proceed to open the envelope for manual randomization.

4. Once the envelope is opened, complete the following data:

   (a) Subject's GCS score

   (b) Date of when the randomization envelope was opened in the following format: DD/MM/YYYY

   (c) Time of when the randomization envelope was opened in exact 24-hour time format.

   (d) Reason why the randomization envelope was opened.

   (e) Name of the person randomizing the subject (i.e. the person opening the envelope).

   (f) Signature of the person randomizing the subject (i.e. again, the person opening the envelope).

5. Once the above data are completed, you will get the randomization number. Record this number, exactly as it appears, onto the Screening & Enrollment worksheet (under the "Randomization" heading).

6. Once the Randomization Number has been recorded, proceed to the "Assigned Treatment Group". This will tell you which of the four treatment arms the patient should be randomized to. *DO NOT forget to record this number on the Screening & Enrollment worksheet!*

7. Once the patient is randomized into the appropriate treatment arm, **contact the CDMCC immediately!** Fax the completed form immediately to the CDMCC at 801-585-3243. You will also need to **contact Sally Jo Zuspan at 801-585-9284 within 24 hours of opening the envelope for further instructions.**

Each site received one randomization envelope at the FLUID study training in September 2010 in Davis, California for the purpose of emergency use only. If you have to use your envelope, the CDMCC will provide a replacement.

10.4.5 Randomization Tips

- Once a patient is randomized their data will be part of the study analysis, regardless of what might happen to the patient. **If they are randomized, they are in the study.** Once a patient is randomized, you must continue to follow the patient and collect their data; even if they decide to withdraw. It is a regulatory requirement that we continue to the follow the patient to monitor and be aware of any adverse events that might occur after patient withdraws from the study. This is for the safety of the patient.

- Since study enrollment starts with randomization, this is also the time that AE tracking begins. For more information on AE tracking, see chapter 19 on page 240.

- Do not wait to randomize the patient once parental permission is obtained. Randomize immediately to ensure the patient is within the time window and still eligible.

- Check the eligibility criteria once more before calling Perry Point for randomization. The patient might have been eligible at the time of consent, but something could have happened between the time of consent and the time of randomization to make the patient ineligible. Make sure you double check eligibility criteria before attempting to randomize.

- If for some reason you randomized a patient that was actually ineligible, DO NOT panic. **If this happens NEVER, NEVER, NEVER re-randomize the patient.** Never remove the patient from the study. Proceed to complete treatment according to the treatment arm unless it is clinically unsafe to do so. Notify the CDMCC immediately and provide the subject ID information. Once the CDMCC have been notified, you will need to complete the OOPS form 18.2. This should also be noted on the Screening & Enrollment worksheet to reflect the situation that occurred at the time of randomization. A note-to-file will also likely be needed.

- The automated system is setup to minimize the likelihood of mistakes, but you must be vigilant when you are about to randomize a subject! Once you've received the randomization number the patient MUST be randomized to that study arm. Hanging up the phone will NOT resolve the issue, or stop, or reset the randomization process! You will

proceed as if that subject was indeed randomized in that arm, contact CDMCC as soon as possible, and complete the OOPS form.

- If more than one GCS is done prior to randomization, use the GCS done closest to (but prior to) randomization for the randomization GCS. On the Screening & Enrollment worksheet, the GCS done at ED evaluation still goes on page 1 (and is entered into OpenClinica on the Screening & Enrollement eCRF). But, when you make the randomization phone call, use the latest GCS available, marking the appropriate range box on page 2 of the Screening & Enrollment worksheet. All GCS assessments done from ED evaluation through randomization through DKA resolution must be included on the GCS Log (and entered into OpenClinica on the GCS eCRF).

What if you accidentally entered the wrong Glasgow Coma Score (i.e. entered 14 but the GCS was actually a 13)?

The automated system asks you to reconfirm that the GCS is correct, but if for any reason you had a brain lapse and confirmed that the GCS was correct, when it wasn't, DO NOT panic. **If this happens NEVER, NEVER, Never re-randomize the subject. You have already randomized the subject, and that subject original random assignment MUST be used!**

Again, if more than one GCS is done prior to randomization, use the GCS done closest to (but prior to) randomization for the randomization GCS. Contact the CDMCC immediately with subject ID number, and carry out the assigned treatment unless it's clinically unsafe to do so. Once the CDMCC has been notified, you will need to complete the OOPS form and explain what happened.

10.4.6 OpenClinica Data Entry: Randomization

IMPORTANT: Once a patient is randomized, enter into OpenClinica as soon as possible in order to generate a unique Study Subject ID for the subject. Once obtained, the OpenClinica study subject ID (a 5 or 6 digit number) should be added to all study worksheets as the identifier.

Randomization data will be entered on the Screening and Enrollment Event, Screening & Enrollment eCRF, on the Randomization tab. Enter if the patient was randomized, the randomization number provided by Perry Point, the treatment arm assigned, and the date and time of randomization. This data can be found on the randomization confirmation letter from Perry

Point. On the confirmation letter, the date and time that should be entered is listed under "Randomization Date" field.

If the patient was not randomized, indicate the reason why. Provide clear details explaining why the patient was not randomized. This should rarely occur! No further completion of data entry is needed.

If more than one GCS is done prior to randomization, use the GCS done closest to (but prior to) randomization for the randomization GCS. On the Screening & Enrollment worksheet, the GCS done at ED evaluation still goes on page 1 (and is entered into OpenClinica on the Screening & Enrollement eCRF). But, when you make the randomization phone call, use the latest GCS available, marking the appropriate range box on page 2 of the Screening & Enrollment worksheet. All GCS assessments done from ED evaluation through randomization through DKA resolution must be included on the GCS Log (and entered into OpenClinica on the GCS eCRF).

Chapter 11

Step 3: Start Treatment Arm

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11.1 Worksheets & Sources

Time point: Just after randomization, start the study treatment.

*Physician Treatment Initiation:*Enrolling physician should complete this worksheet; this is a study source document.

Once consent has been obtained and the patient has been randomized to a treatment arm, the enrolling physician will need to calculate the fluid rates for the patient's treatment arm. The Physician Treatment Initiation worksheet will assist the enrolling physician with these calculations and must be used to document the fluid given. Additionally, some initial ED evaluation

clinical data will be collected on the Physician Treatment Initiation study source worksheet.

Please make sure that the time gap between randomization and fluid start is as short as possible! There should be no delays in the patient receiving fluid treatment because of the study. Please work with your site to help ensure this is a very quick process. Please do your best to help ensure there is NO delay; the study treatment arm should begin as soon after randomization as possible.

11.2 ED evaluation clinical data

The ED evaluation data should reflect the patient's condition prior to fluid initiation. The enrolling physician should complete the initial ED evaluation data after the consent process and after randomization. These data may come from the patient's initial evaluation in the ED, but should not be documented on the worksheet until after consent is obtained. This section may be completed after the treatment arm is started, but the clinical data should be assessed based on the patient's condition before the study bolus or fluid initiation. While the Physician Treatment Initiation data must be completed by the enrolling physician, the RC can work with the enrolling physician to ensure complete documentation.

Study staff should review completed Physician Treatment Initiation worksheets to ensure these data are documented; if not, study staff should follow up with the enrolling physician to collect the data of the patient's condition before the study fluid was given. It is the responsibility of the PI to ensure that as a study source document, the Physician Treatment Initiation worksheet is completed.

Data in this section include:

- presence of headache and if so, severity of headache
- peripheral pulses
- capillary refill at ED presentation, and
- previous diagnosis of diabetes

ED evaluation date and time should be the date and time that the patient was first assessed for these conditions, even if that was prior to consent or randomization. These should be the date and time of the exam for these conditions, not the presentation to the ED or the triage in the ED. This date

and time should be the time of the ED evaluation done in your PECARN HEDA, not at an outside transferring hospital.

Note: if the patient has been previously diagnosed with diabetes, please complete a Diabetes History worksheet before the patient is discharge. See 13.8.1 for more information.

11.3 Fluid Calculations

The Physician Treatment Initiation worksheet will also serve as a tool for the enrolling physician to calculate the fluid rate for the assigned study arm. There is also an Excel fluid calculator available to assist with fluid calculations found here: https://www.nedarcssl.org/eRoom/NDDP/StudyDiabeticKetoacidosis/0_60d3e. The Excel fluid calculator will likely be very helpful and should be made easily accessible for enrolling physicians.

There are four steps to study treatment arm calculation:

1. IV Bolus prior to randomization
2. Patient's weight
3. Additional IV boluses received after randomization
4. Replacement Deficit & Maintenance fluid rate calculation

11.3.1 IV Bolus - Fluid Prior to Randomization

All previously received IV boluses must be subtracted from the calculations for the maintenance/deficit replacement rate of the study treatment arm. The Physician Treatment Initiation worksheet asks the enrolling physician if the patient received any IV fluid boluses before randomization occurred. The FLUID study definition of a bolus is: greater than or equal to 10 cc/kg over one hour or less.If the patient received an IV fluid bolus prior to randomization (including any IV fluid boluses received at an outside hospital), record the total amount of IV boluses the patient received on the Physician Treatment Initiation worksheet, along with the date and time of the initial IV bolus that was given.

Reminder: If a patient was transferred from an outside hospital and received more than a 10 cc/kg fluid bolus, then they would be ineligible for the study. However, if a patient was seen directly in your ED first (without being transferred) and received greater than 10 cc/kg bolus, that patient is still eligible. (See exclusion #3 on the Eligibility and Screening worksheet, A.3.)

11.3.2 Weight

An accurate, actual weight must be used for study calculations to help ensure that the same weight is used throughout the study for treatment arm fluid calculations. Therefore, enrolling physicians should obtain the patient's exact weight, if it has not already been done. Please no estimates!

For the FLUID study, weight must be a measured, actual weight, NOT an estimated weight. Weight must be measured with no shoes and the patient in pajamas or a gown. Weight should always be in kilograms. For fluid calculation purposes, the maximum weight used should be 100 kg. If a patient weighs more than 100 kg, please record the correct weight on the worksheet but use "100 kg" for study fluid calculations for both the IV bolus and the IV fluid.

Enrolling physicians should record the weight used for calculations on the Physician Treatment Initiation worksheet, along with the date and time of the weight.

11.3.3 Additional IV Bolus received after randomization

The next set of questions on the Physician Treatment Initiation worksheet deal with IV boluses given after randomization. This includes the additional 10 cc/kg IV bolus in assigned treatment arms A1 or A2 (assuming the patient already receive an initial 10 cc/kg pre-randomization IV fluid bolus). The patient should only receive the additional bolus if they have not already received the fluid bolus indicated on the specific treatment arm. (A summary of the treatment arms can be found here 2.1.)

If the patient already received previous IV boluses totaling more than 10 cc/kg, SUBTRACT the previous bolus amount over 10 cc/kg from the treatment arm additional bolus. For example:

- If the patient received a previous IV bolus of LESS THAN 10 cc/kg (e.g. 5 cc/kg) and is assigned to either arm B1 or B2, an additional fluid bolus should be given to meet the total of 10 cc/kg, so give an additional 5 cc/kg. If assigned to A1 or A2, the additional bolus amount (20 cc/kg minus the fluid bolus already given) should now be given, so give 15 cc/kg.

- If the patient received a previous IV bolus of 10 cc/kg and is assigned to either arm B1 or B2, no additional fluid bolus should be given. If assigned to A1 or A2, the additional bolus amount (20 cc/kg minus the fluid bolus already given), so 10 cc/kg should now be given.

- If the patient has been given 15 cc/kg and is assigned to either arm B1 or B2, no additional bolus should be given; but if assigned to either arm A1 or A2, 5 cc/kg additional bolus should be given, to total 20 cc/kg.
- If the patient has been given 20 cc/kg (or more) IV bolus no additional bolus should be given, regardless of treatment arm.

If any additional IV boluses were given after randomization, enrolling physicians should enter and the date and time on the Physician Treatment Initiation worksheet.

11.3.4 Replacement Deficit & Maintenance rate calculation

All IV boluses, both prior to and after randomization, must be subtracted from the calculations for the maintenance rate of the study treatment arm. Maintenance rate fluid calculations can be found on the Physician Treatment Initiation worksheet (A.4) and by using the Excel fluid calculator (https://www.nedarcssl.org/eRoom/NDDP/StudyDiabeticKetoacidosis/0_60d3e). Rates in the A1 & A2 arms use an assumed 10% body weight deficit and are calculated to replace 1/2 the deficit over the first 12 hours and the remaining half of the deficit over the following 24 hours; rates in the B1 & B2 arms use an assumed 5% body weight deficit and are calculated to replace the deficit evenly over 48 hours. Rates in the A1 & B1 arms use 0.45% saline (1/2 NS) for rehydration; rates in the A2 & B2 use 0.9% (NS) saline for rehydration. To be clear, all arms use 0.9% for the IV fluid bolus.

Please note that all boluses should be subtracted during the rate calculations. This includes all boluses given and all boluses planned to be given. So, if a patient is assigned to the A arm and hasn't yet received the additional 10 cc/kg bolus, plan ahead, knowing that its going to be given and calculate the study maintenance rate as if it has already been administered. So, subtract out the full 20 cc/kg bolus(es). In cell B9 on the calculator, put all the boluses (likely 20 cc/kg if on arm A) to get the rate, even if the additional bolus is still going in or has not yet been started. To determine the maintenance rate, the total amount of boluses (20cc/Kg) should be subtracted (whether the boluses were already completed or not).

11.4 Tips and tools

- All fluid rates and calculations must be done by the enrolling physician or PI. These cannot be done by the RC.

- Study treatment arms must be based on these calculations and should be used until DKA resolution, even if this is outside the study period of 24 hours.
- Using the calculation tables on the Physician Treatment Initiation worksheet or the Excel fluid calculator should help sites verify the correct fluid amounts have been given. The total rates calculated must be documented on the Physician Treatment Initiation worksheet as a study source document.
- Adapting your site's order sheets may be useful to help with fluid calculations. UC Davis order sheets may be used as examples and can be found here: https://www.nedarcssl.org/eRoom/NDDP/StudyDiabeticKetoacidosis/0_60b76
- A fluid rate calculator has been developed in Excel and can be found here: https://www.nedarcssl.org/eRoom/NDDP/StudyDiabeticKetoacidosis/0_60d3e

Once a patient has been randomized, they are in the study. This means that the patient must be given the IV fluid in the treatment arm to which they were assigned, regardless of what happens between randomization and fluid start. It is the site PI's responsibility to ensure that this happens and that the fluid regimen in the treatment arm to which they were assigned remains in place throughout the patient's hospitalization.

If, for example, after randomization the treating physician decides that the patient will get subcutaneous insulin instead of IV insulin, the patient should still get the treatment arm fluids until DKA is resolved. In this case, the PI or treating physician would need to use clinical judgment in determining when the DKA resolves (and document in the patient study file with a NTF and add an OOPs entry for the DKA resolution determination). But, since the patient has been randomized to a treatment arm already, the patient must get that treatment arm fluid and rate.

11.4.1 What if there's a delay between randomization and when the Study Treatment Arm starts?

Sites should do all possible to minimize any delay between the time the patient is randomized into the study the assigned treatment arm starts. If there is an unavoidable delay between bolus administration and when the IV maintenance fluid can begin, sites should at least change the rate of whatever

type of the fluid the patient is already received by adjusting the rate to the study calculated rate. Once the correct type of fluid is available, it should be started without further delay. Adjust whatever fluid the patient is receiving to the study calculated rate. Change to the correct type of fluid, once you are able. The time that the study IV fluid rate begins for maintenance fluid begins must be recorded and entered on the Fluid Administration Log.

11.5 OpenClinica Data Entry: Treatment Start

On the Study Initiation Event, Physician Treatment Initiation eCRF there are 5 tabs under: MD Eval, Weight, Pre Bolus, Post Bolus, and Fluid Calculation.

ED evaluation data should be entered on the MD Eval tab. Enter the date and time of the ED evaluation (the date and time the patient was first assessed for the conditions listed). For headache at ED presentation, Peripheral Pulses & Capillary refill, select from drop down from "Yes", "No", or "Not Documented". Use "Not Documented" if the answer to that question is not on the Physician Treatment Initiation worksheet.

Weight should be entered on the weight tab. Enter the patient's actual weight in kg and the date and time that weight was obtained.

Fluid calculations should be entered on the Pre Bolus, Post Bolus, and Fluid Calc tabs. Use the Pre Bolus tab to enter any IV boluses the patient received before randomization, the Post Bolus tab to enter any IV boluses the patient received after randomization, and the Fluid Calc to enter the total IV rate calculations. On the total IV rate calculations, only the total IV final rates calculated need to be entered (so for arms A1 or A2 the 12 and the following 24 hour rates; for B1 or B2, the 48 hour rate).

Chapter 12

Step 4:Complete Enrollment Data Collection

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12.1 Worksheets & Sources

Time point: After the patient has been randomized and the study treatment arm has started, additional data must be completed.

- *Review of Medical Conditions:* RC with PI oversight should complete this worksheet
- *Physical Examination:* RC with PI oversight should complete this worksheet
- *Digit Span Recall Test:* RC, PI or Bedside care provider should complete these worksheets; these are study source documents
- *Demographics:*RC, Enrolling physician, or Site PI can complete this worksheet with parent/patient interview

These remaining worksheets must be completed as soon as possible after the patient is randomized. The first digit span recall test must be completed as close to randomization as possible. Additional data worksheets may be completed by study staff, with enrolling physician input and ideally, should be completed before the patient leaves the ED.

12.2 Review of Medical Conditions and Physical Examination

If at all possible, the enrolling physician should complete these forms when enrolling the patient. These are brief and are important for documenting subsequent AEs. However, the RC may abstract this data from the medical record, with VERY CLOSE PI oversight. PIs are responsible to ensure that this data is accurate. RCs may complete the documentation to save time, but the PI is responsible. Since these data can be abstracted from the medical record, any clinician (e.g. NP or fellow) who is authorized to complete and document these data in your site's medical record by your site's standard operating procedures may complete the study worksheets. If the data are abstracted later by the PI and RC, the RC should write the physician's name on the worksheet and initial next to it indicating abstraction.

The Review of Medical Conditions and Physical Examination worksheets are the baseline data from which AEs and SAEs will be determined. For this reason, these are critical worksheets that must be completed accurately.

Both the Review of Medical Conditions and Physical Examination worksheets reflect the patient's condition at or PRIOR to randomization. Since an AE is, by definition, a sign or symptom that starts or worsens AFTER randomization, the data in these worksheets must represent the patient's status before randomization. See AE chapter for more details chapter 19 on page 240.

Data on either of these worksheets can be updated to capture any conditions that may have been missed during the initial assessment, but were later captured through chart abstraction or parent report. Any condition found at a later time must still represent the patient's status prior to randomization. For example, if the mother recalls that the child has had abnormal liver function test in the past, this information can be added to the Review of Medical Conditions worksheet since it existed prior to randomization.

Both worksheets should be completed as close to randomization as possible. If, on either worksheet, any organ system is listed as "Abnormal", a description of the abnormality must be provided. Enter the date and time the examination to assess was done. If no time is documented on the study worksheet or in the medical record, use the best available time to determine when the examination was done.

12.2.1 What's the difference between Review of Medical Conditions and Physical Examination?

The Review of Medical Conditions captures any medical conditions that the patient had and knew about (in existence) prior to randomization. This worksheet should be medical history, such as conditions the patient/parent knew they had before coming to the ED (e.g. asthma for 3 years). The Physical Examination captures the physical condition that the patient was in at the time of the ED visit or at the time of randomization.

12.2.2 OpenClinica Data Entry: Review of Medical Conditions and Physical Examination

On the Study Initiation Event, Review of Medical Conditions eCRF and Physical Examination eCRF enter both worksheets. Use the Review of Medical Conditions eCRF and worksheet and Physical Examination eCRF and worksheet; please be sure you are entering the correct data on the correct forms. These two are very similar; check to ensure your data entry is correct. If you cannot find documentation in the medical record for a certain organ system, enter "not assessed." Only enter "not assessed" after the RC and PI

have thoroughly reviewed the medical record. Remember that the PI must provide the oversight and data for these questions. The PI should decide if something should be "normal" or "unknown" or "not assessed." If any "abnormal" is selected, include a detailed description in the text field.

12.3 Critical Study Task: Digit Span Recall Test

The Digit Span Recall Test ("digit span") is a short, quick memory assessment tool that is critical to the study outcome. Digit Span Recall Test packets are here in eRoom^{TM}: https://www.nedarcssl.org/eRoom/NDDP/StudyDiabeticKetoacidosis/0_61545 and should be compiled into packets to stay with the patient throughout the study. The digit span will be documented and scored directly within the packet itself, and thus the Digit Span packet are study source documents. Each Digit Span packet is composed of several separate sheets; each sheet is used for one complete Digit Span test.

A RC, PI or nurse can administer the Digit Span Recall Test, as long as they have been trained (and that training is documented in the site's EDB). Who will do the digit span at your site should be documented in your Site Specific Workflow and on the Staff Responsibilities delegation form in your EDB.

The digit span is only for patients who are 3 years of age and older at the time of testing. Conduct Digit Span only on patients who are 3 years of age at the ED visit time of enrollment. The digit span takes 5-10 minutes to complete.

The first digit span should be completed as soon as possible following randomization (enrollment), as long as its within normal waking hours of 7 AM to 10 PM. The digit span must be done every 4 hours between the hours of 7 AM and 10 PM for the first 24 hours of the study. If the patient is napping during this time frame, the digit span still must be done (e.g. the patient must be awakened). Digit span testing should be done as many times as needed (every 4 hours) during the 24-hour study period. If a digit span test is needed in the morning, the first one should be completed, as soon as possible (e.g. patient enrolled at 7:00 PM, first digit span done at 7:30 PM, the next digit span should be done at 7:00 AM). Stop collecting digit spans at study hour 24 or DKA resolution, whichever comes first. (If a Digit Span is done after DKA resolution, complete an OOPS entry.)

12.3.1 How do I administer the Digit Span Recall Test?

For each testing session, you will conduct two parts in each Digit Span, one forward and one backward, in this order. Clearly read the instructions on the packet worksheets to the participant. Each testing session should have one completed set (i.e. 1 forward and 1 backward). Use a new worksheet in the same packet for each new testing session (every 4 hours).

Before performing a Digit Span Recall Test, consider the environment so that the patient is able to concentrate. Turn off or volume down the TV, remind the parent/guests that the test is for the patient to complete. Try to make it fun!

Each "Item" is a permutation of a set of numbers beginning with a sequence of two numbers, and two "Trials" (i.e. Trial 1 and Trial 2) for each Item. You will administer Trial 1 and Trial 2 of each item, regardless of what the participant does on Trial 1. Read one digit per second, and drop your voice on the last digit. Do NOT repeat any trial of an item. If the participant asks you to repeat a trial simply asked them to just take their best guess.

- **Starting Point:** The starting point designates at which point you should start the test.
  - *Digit-Span Forward* - You will need to begin with item 1.
  - *Digit-Span Backward* - You will begin with Practice Trial A & B before proceeding to Trial 1.
- **Discontinuation Criteria:** Participant may make mistakes. You will need to stop administering the task upon meeting the appropriate discontinuation criteria.
  - *Digit-Span Forward* - Stop after participant makes an error on both trials of an item.
  - *Digit-Span Backward* - Stop after participant makes an error on both trials of an item.

  An *error* is defined as reporting the digits in the wrong order, forgetting one of the digits, or adding digits that were not actually included in the current sequence. If the patient adds extra digits to the end of of a Trial, it is an error.
- **Scoring Digit Span:** Each "Trial" is worth 1 point, thus each "Item" total would be 2 points for a total of 16 points possible (i.e. 8 items)

on each test. As you go down each item, keeping in mind the Discontinuation Criteria listed above; you will check the box for each Trial that the participant answers correctly. Each checkmark is equal to 1 point. Once the Discontinuation Criteria is met, you will sum up the total of each item(s) that the participant answered correctly. This total will be the number you will data enter into OpenClinica. This method of scoring is used for both Forward & Backward Digit Span test.

- If a patient changes their mind on during the Digit Span assessment, it is ok to give them count the response as correct. For example, if the examiner says "2 5 7" and the patient says "2 6 7 no, I mean 2 5 7", this is an acceptable answer.

Tip: to help smooth data collection and help you keep track of participants' responses, as the participant recites the sequence back to you, mark each number that is not reported in the correct sequence. For example, if the digit forward sequence is 6 2 9 3, and the participant recites 6 2 3 9, you will mark 9 and 3 in your data sheet. In the backward sequence case, you will do the same, but because participants are requested to recite the sequence in reversed order, you will have do your markings by starting from the right side of the sentence. This procedure will make it obvious if participants make mistakes and won't tax the experimenter memory (i.e., as the trials test longer and longer digits spans, this may become an issue).

At each testing session (every 4 hours), new digit permutations will be presented to prevent children's performance from reflecting, in part, memorization from earlier testing sessions.

12.3.2 What if parents are bothered or patients are unable or unwilling to complete the Digit Span?

Some children, particularly very young children (3-4 year olds), may be unable/unwilling to cooperate with digit span testing because they feel unwell and/or are frightened by the hospitalization. Parents may also become bothered by attempts to get the child to cooperate with digit span testing during this time if the child is unwilling. It is not the intention of the study to pressure children/parents to complete this and study personnel may need to omit this testing if parents are very resistant or bothered. This will help to avoid patients dropping out of the study prior to completion. If parents are unwilling or patient unable, skip that particular digit span test and it will be "missing." Attempt the next digit span in four hours.

If an attempt is made, the Digit Span Recall Test started but the patient makes it through one item, gets it wrong and then wont keep going, they would get a score of 0 for that particular Digit Span Recall Test. This should be documented on the Digit Span Recall Test packet. If a patient has a low GCS or the Digit Span Recall Test is never started, even if the RC goes to room to attempt it, or if the RC goes to do it, but never starts the digit span script, count it as not done. If the patient refuses to participate or theres a nurse in the room doing something, RCs should come back in 15 minutes and try again. If the patient still refuses, count it as not done. If you introduce the test, make it through the practice round, the patient would get a score of 0. If you introduce the test and the patient says I dont want to, you should try again in 15 minutes. If the answers still the same, count it as not done. If a Digit Span Recall Test is not done, the packet documented the not done test should still be uploaded to OpenClinica and an OOPs entry should be made explaining why the test was not done. However, only Digit Span Recall Tests that are scored should be data entered in the rows of data in OpenClinica.

In these cases of missing digit spans, the reason digit span testing was not done should be documented on the digit span packet on that particular testing score sheet in the "notes". Missing a digit span test is a protocol deviation, so study staff should complete an OOPS Log entry for the patient study file and enter it into OpenClinica on the Unscheduled event, OOPS log. For more details on OOPS, see 18.2.

12.3.3 Digit Span Tips

- Digit Span assessment occurs every 4 hours and could possibly coincide with the collection of GCS. For more information on GCS, see section 13.4 on page 152.

- If needed, it is ok to discontinue a digit span test and try again in 10 minutes or so. There are extras provided in each packet. (A new page should be used.)

- Be sure to record the time the digit span was actually given on the Digit Span scoring sheet.

- NEVER EVER repeat any numbers. Patients should do their best after one recitation. If no answer can be given, it should be scored as incorrect.

- If a digit span testing time is missed, do a digit span test as soon as you realize it was missed and then the next one 4 hours later. There is no "time window" for digit span testing. The digit span testing should be completed as close to every 4 hours as possible.

- If a patient has a GCS of 13 or below, they likely cannot complete the digit span. No digit span test is needed. But, study staff should check back and if the patient's GCS rises above 13, a digit span test should be conducted.

12.3.4 OpenClinica Data Entry: Digit Span

On the DKA Treatment Event, GCS & Digit Span Log eCRF, on the Digit Span tab enter the date, the time each digit span was given, forward and backward score of each digit span conducted. (Use "Add" to get additional rows for data entry.) Upload full completed Digit Span Recall Test packets (de-identified, labeled with study subject IDs).

If the Digit Span Recall Test is administered incorrectly for any reason (not terminated correctly, wrong test given at the wrong time),please make a note on the uploaded digit span packet, complete the OOPs entry, but do not enter the score into OpenClinica. If the error affected both the forward and backward Digit Span Recall Test, don't enter either score into OpenClinica. If the error affected just one of the tests (either the forward or the backward), please enter the date and time and the score for the one not affected. If a Digit Span Recall Test is done after DKA resolution or Study Hour 24, still include it on the upload and add it to the OpenClinica data entry. Also complete an OOPs since the Digit Span Recall Test would only be done for study purposes (rather than clinical reasons).

12.4 Demographics

The patient's demographics should be collected at any point following randomization, but prior to discharge. For enrolled patients, demographics may be easiest collected along with the Caregiver Demographics (see 13.8.2).

The Demographics worksheet should be completed with parent/guardian input. For patients for whom demographics are required but the patient or parent are not available (e.g. patients eligible but not approached) the medical record should be abstracted for demographic data.

The Demographics worksheet contains several fields for the use of the patient study file, including some PHI. Only data below should be entered

in OpenClinica:

- Patient's Date of Birth (MM/DD/YYYY)
- Patient's sex
- Patient's race
- Patient's ethnicity
- If the patient has been previously enrolled in the study, the patient's previous study subject ID

The rest of the data elements on the worksheet will be for site internal use and will not be entered in the database. This information included is important to obtain for your site study records, especially accurate contact information to be used for follow-up reminders. Please ensure your study file is complete and parents give you current, preferred contact information. For patients who will still be under the age of 3 at the time of follow-up, contact information may not be necessary. Parents should be directly asked for demographic information, rather than collecting it from the medical record to ensure accuracy.

12.4.1 Race and Ethnicity

Race and ethnicity for the FLUID study are self reported. This is defined as the parent/guardian's (or child's if age 18) report of the child's race and ethnicity. It is not ok to abstract this data from the medical record for enrolled patients.

Race/ethnicity must be collected using the NIH guidelines. Using the categories on the Demographics worksheet is important! The categories listed are the categories to be used. If patient or parent/guardian has questions regarding race and ethnicity below is the NIH guide you can provide them. For your convenience, the Demographics Instructions are also located with the Demographics worksheet. (For easy access to these instructions, RCs should print the Demographics sheet double-sided with the Demographics Instructions on the back.)

Race: Patients who ask should be told to mark all races that apply to them (multiple choices are ok). Choices are defined by the NIH Policy on Reporting Race Data as follows:

- **American Indian or Alaska Native:** A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

- **Asian:** A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

- **Black or African American:** A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American".

- **Native Hawaiian or Other Pacific Islander:** A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

- **White:** A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Ethnicity: Only one choice should be made for the ethnicity. Patients who ask should be told to mark the ethnicity that they most identify as. Choices are defined by the NIH Policy on Reporting Ethnicity Data as follows:

- **Hispanic or Latino:** A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino".

12.4.2 OpenClinica Data Entry: Demographics

On the Screening and Enrollment Event, Demographics eCRF, Demographics tab, enter the patient's date of birth and select the appropriate sex of the patient. Enter all the Race boxes indicated by the parent (a multi-select option), and the one Ethnicity indicated (a single select from the drop down menu). If the patient's parent/guardian does not answer race or ethnicity, it should be entered into OpenClinica as "unknown."

Please note that repeat enrollment data, found on the Demographics worksheet, are entered into OpenClinica on the Screening and Enrollment Event, Screening & Enrollment eCRF, Randomization tab (at the bottom). For more information on repeat enrollment, see 12.5 on the next page.

12.5 Repeat Enrollment

If this is the patient's second enrollment in the study, they are eligible. (Patients may be enrolled twice.) Please give the patient a new, second OpenClinica number. For patient enrolled in FLUID for the second time, check "yes" on the Demographics worksheet and document the patient's original OpenClinica study subject ID.

The OpenClinica number really represents one patient screening, so each time there is patient screened, think of it as a separate visit, even if its the same patient. If a patient who has already been enrolled once and is screened but not eligible for the second enrollment, still enter that patient's screening information under a new, second OpenClinica ID number. (In this case, complete Not Enrolled data collection for the second visit, as indicated in Chapter 17. If the patient had been enrolled the second time, you would enter the first OpenClinica ID on second OpenClinica IDs Screening event, Screening & Enrollment eCRF, Randomization tab. For Not Enrolled patients, there is nowhere to document the original patient ID in OpenClinica. However, it probably would be a good idea to note it on your screening log somehow, though, for reference.

If the second enrollment is after the first enrollment neurocognitive follow up visit or if it has been more than 4 months since the first enrollment, study procedures should be exactly the same for the second enrollment. If the second enrollment is before the first enrollment's scheduled follow up visit or if it has been less than 4 months, the follow up visit from the FIRST enrollment is not needed. In this case, conduct follow up for the second enrollment only.

If it's a patient's second enrollment, the follow up visit and history obtained should apply to the correct DKA episode. So, if the patient completes two separate follow up visits (e.g. the two enrollments are more than 4 months apart), the first follow up visit and history data under the original OpenClinica ID represent the patient's history and data at the time of that first follow up visit (3 months $\pm$ weeks from the original DKA episode ED visit). The second follow up visit history and data will be recorded under the second OpenClinica ID, following the second DKA episode ED visit and study enrollment. If the patient completes only one follow up visit (e.g. the second enrollment occurs before the first follow up visit could take place; the follow up visit is done 3 months $\pm$ 4 weeks from the second DKA episode ED visit), then the follow up history and visit data should reflect the patient's status following that second enrollment only. This is confusing, so contact the DCC if you are unsure what to do.

Completion of the Diabetes worksheet and eCRF (Section /refdiabeteshistory) follows the same strategy. Complete the Diabetes History based on the specific enrollment; so the first Diabetes History under the first OpenClinica ID references the patients history at the time of the initial enrollment. The second Diabetes History, under the second OpenClinica ID references the patient's history at the time of the repeat enrollment. The parent's completion of the CBCL and Caregiver Demographics follows this strategy, too.

Compensation for a repeat enrollment is exactly the same as an original enrollment. The study budget allows for compensation of $60 per patient. $10 should be given for the inpatient portion of the study, $50 for showing up to the follow-up. Note: the follow-up visit does not need to be fully completed for the patient to receive the $50. Distribution of the compensation money should follow site policy and procedures. IRBs should be aware of this and the compensation amount should appear in all consent documents, as required by your institution. . However, for repeat enrollments that occur before the first follow up visit is conducted, so the patient only completes one follow up visit, the patient should receive compensation for two study inpatient portions but only one follow up visit.

12.5.1 OpenClinica Data Entry: Repeat Enrollment

Enter the patient as a whole new patient. Create a new OpenClinica Study subject ID for the patient's second enrollment and enter all study data from the second enrollment under this new study subject ID. On the Screening and Enrollment Event, Screening & Enrollment eCRF, Randomization tab, answer "yes" to previous enrollment and enter the patient's study subject ID from the first enrollment. **This is important to get correct! If you have questions, please ask the CDMCC!**

If patient is re-enrolled prior to 3-month follow-up appointment they will no longer qualify for that appointment time. The 3-month follow-up history form will need to be completed for the first enrollment. The time period for this history will incorporate the time from original enrollment to re-enrollment. Their new follow-up window will be 3 months (+/- 4 weeks) from re-enrollment date, and new appointment should be scheduled.

Chapter 13

Step 5: Patient Admitted and Step 6: Inpatient Treatment

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13.1 Worksheets & Sources

Time point: End of ED care, transition to inpatient hospitalization, and then inpatient hospitalization

- *GCS Log:* this is a study source form and must be completed by bedside care providers.
- *Digit Span Recall Test Packets:* this is a study source form and must be completed by trained study staff.
- *Study Treatment Arm:* ensure patient continues to get the correct fluid type and fluid rate based on assigned treatment arm (either A1, A2, B1, or B2).

13.1.1 Additional Treatment Packet Worksheets

- *Diabetes History (if applicable):* RC/PI completes, with parent interview
- *Caregiver Demographics:* RC/PI completes, with parent interview

- *CBCL:* Parent completes
- *AE Log/SAE reporting:* PI/RC completes
- *Concomitant medication log:* PI/RC completes

13.2 General

One of the most challenging parts of this study will be to make sure that study treatment arms and study processes (GCS and Digit Span) started in the ED continue with the patient into their admission to the hospital. It is the responsibility of the PI to ensure that all study tasks are completed both in the ED and on the inpatient unit. RCs should assist with this process. Each site should come up with a Site-Specific Workflow plan to document how this will happen and record this plan in their Site-Specific Workflow document.

Study processes that must be completed through inpatient phase are:

- Continuation of assigned study IV fluid treatment arm through DKA resolution
- Hourly GCS through DKA resolution (or study hour 24, whichever comes first)
- Digit Span Recall Test (every four hours during the hours of 7 AM and 10 PM) through DKA resolution (or study hour 24, whichever comes first)
- AE/SAE monitoring through hospital discharge
- Additional data collection

13.3 Ensuring study treatment arm follows patient and continues

It is the site PI's responsibility to ensure that the assigned treatment arm is the fluid the patient receives while on the study (unless a deviation is needed for safety of the patient). It is critical that the patient receives the fluid treatment to which they were assigned at randomization (A1, A2, B1, or B2) throughout the study period and until DKA resolves (DKA resolution is defined for study purposes as the date and time when the IV insulin drip

is stopped.). Since the AE/SAE review period is through hospital discharge, the patient should continue with study fluids until the DKA is resolved, even if this is after study hour 24. If the patient receives anything other than the randomized study treatment arm (A1, A2, B1 or B2), this should be documented as a protocol deviation and included on the OOPS form (see 18.2).

Each site PI is required to communicate with floor staff and other clinicians caring for study patients to ensure that assigned fluid type and fluid rate remains the same throughout the study period (until DKA resolution). Details of how each site will ensure compliance with the protocol should be documented in the site-specific workflow plan. Sites are encouraged to share ideas with each other and to be creative about the best ways to do this. Sites should also re-evaluate this process at points during the study and update their process if needed.

Please do everything you can to insure that patients receive the correct bolus, rate, and type of saline as indicated by the treatment arm, as close to as real time as possible. This means that the Site PIs need to closely review each enrollment, and be in close contact with the ED and admitting team with each enrollment. Reasons for protocol deviations are variable, but several common issues are the following:

1. Errors Some deviations are simply errors, rather than deviations for a clinical reason. To try to reduce errors:

   (a) Increase communication with all members of the PICU team residents, nurses, fellow, etc, to advise them of the protocol remind them of the details of the protocol and try to communicate directly with as many team members as possible.

   (b) Call to remind the PICU team of the 12 hour rate change (for fast arms)

   (c) Consider having two people check rate calculations at the time of patient enrollment

2. Dehydration - protocol deviations due to severe dehydration may be necessary for patient safety (i.e. patient with signs suggesting hemodynamic instability or close to it). However, this is not the case for patients who simply look dry or appear dehydrated in which case deviation from the protocol is likely not necessary for safety. Try your best to educate the clinical teams to reserve extra fluids for patients where it is truly necessary for safety reasons.

3. Treatment delays - Wherever possible, please look into the reason for these and determine whether there are any systematic problems that could be corrected. Again, these should be investigated by the PI/RC team as soon as possible after patient enrollment.

4. Please investigate all deviations at your site and make sure you are clear about why they occurred. Again, we strongly encourage the Site PI and Site RC to review these regularly.

BOTTOM LINE: Please be sure to investigate all protocol deviations at your site as soon as possible after patient enrollment to make sure you know why they occurred and whether there are any issues that could be addressed for future patients. Communication with the admitting team as soon as patient enrolled is critical. Educate your ED team about the necessity to keep to the correct protocol arm fluid bolus, except for extenuating circumstances of patient safety.

If a patient is removed from the treatment arm for clinical reasons or for any error, the PI should talk to the clinical team to ensure that the patient is returned to the study treatment arm as soon as is clinically possible. If a patient meets the study definition of cerebral edema, the patient should be treated per the judgment of the clinical team. For the study, if the patient meets the study definition of cerebral edema, then the patient has met the primary outcome of the study. In this case, there is no need to put the patient back on the protocol treatment arm (unless the treating physician decides to do so). Treatment after the patient has met study criteria for cerebral edema is up to the treating team. See Section 15.6 for more information on data collection for patients who meet the study definition of cerebral edema.

13.3.1 AEs and treatment arms:

If a patients treatment arm is changed from the study specific treatment (rate, type or bolus amount), it should be done for a clear, clinical reason. Please be sure to document these reasons both in the OOPs entry 18.2 and on the AE Log A.13. The two entries should match. For example, if an OOPs entry references hyperchloremia, we will expect to see hyperchloremia on the AE Log. If the OOPs entry indicates that a drop in sodium was enough to cause the treating physician to alter the treatment arm, we will except to see an entry on the AE Log and hyponatremia.

Remember that AEs are reportable if they occur after randomization and before hospital discharge. Some additional boluses may have been given

prior to randomization. If this is the case for your patient, a complete OOPs entry (including the clinical reason why the additional bolus was needed) is all that is needed no AE entry is required unless the issue occurred after randomization. For more information about defining an AE, please see the 19.

If the patient had an electrolyte change that was enough of a concern to cause a change in the patients treatment, then we DO want it included on the AE Log as an AE, even though it is a lab result. Rule of thumb: if it was bad enough to cause someone to change the patients treatment, off the study protocol arm, then it should be appear on the AE Log and the change should be documented as an OOPs.

Remember that the protocol allows for more fluid to be given for clinical need, which should be uncommon. This would mean that we expect most protocol deviations to show extra fluid that's given, not less. *However, deviations in which LESS fluid than expected is given should almost NEVER happen! It suggests some clinician bias in thinking that fluid administration is associated with cerebral edema.* On occasion, a patient has a significant drop in serum sodium, which is addressed by increasing the sodium content of fluid, not adjusting the rate. So if you find that for your site, there are frequent deviations BELOW the expected fluid line, the Site PI and RC should investigate, and re-educate all clinicians involved with the study that fluid rates should almost never be lowered. *Important!* The DSMB will really care about this, and sites that remain out of compliance will likely have extra monitoring and intervention.

13.3.2 Clarifications about arms and calculations:

- A arm patients get 20 cc/kg bolus and this bolus amount is subtracted from the total to be replaced. A arm patients have a rate change 12 hours after beginning fluid rate. Please remind the admitting team.
- B arm patients get 10 cc/kg bolus and this bolus amount is subtracted from the total to be replaced.
- 1 arm patients get NS; 2 arm patients get NS.
- If theres a delay in getting the fluid, start the study calculated rate ASAP, while waiting for the correct type of IV bag.
- Everybody needs a weight (while in hospital gown) at baseline, 12 hours and discharge. Please remind the admitting team!

- If the patient gets an additional bolus later in treatment, at any time after the patient is started on the calculated rate, the rehydration rate does not need to be re-calculated for the remaining rehydration time (but please just include the additional bolus as an OOPS entry).

Additionally, clarifying the study timelines:

1. Study Hour 12: weight should be obtained for all patients 12 hours after randomization, and fluid tabulated at the same time.

2. 12 hours of fluid for A arm patients: For A arm patients, the 12 hour rate change should occur 12 hours after the study calculated rate started! This typically starts slightly later than above.

Although these two times may be different, we hope the difference is minimal. To briefly summarize the process again, please start the study calculated rate as soon as possible, following randomization. If you have to wait for study fluids from the pharmacy, start the calculated rate with whatever fluid the patient is currently getting. The time that the patient's rate is changed to the study calculated rate is the study start time, regardless of the fluid type, for the purposes of calculating the changeover. If a patient is randomized to one of the A arms, as soon as the full 20 cc/kg bolus has been administered, be ready to start fluid at the study rate. Please work with your pharmacy to get the study type of fluid as soon as possible and please make every attempt to limit treatment start delay to as little time as possible. **Hint: If treatment delay is minimal the Study Hour 12 weight and the A-arm 12 hour changeover rate will be close together!**

OOPS entries should be clear, concise and complete explaining what happened, the specific clinical reason for the change, how long and what the change was.

13.3.3 What if a patient doesn't receive the correct study treatment arm?

Any change to the IV fluid that differs from what the patient was randomized to (A1, A2, B1, or B2) should be documented as a protocol deviation on the OOPS form. This includes a change to the IV rate, or the saline content (.45% or .9%) or to both.

IV fluid can change from the assigned treatment arm with the addition of dextrose. No matter what sugar is added (D5 or D10), the rate and

saline content (.45% or .9%) of the solution must stay at what the patient was randomized to. Adding dextrose or other electrolytes (except saline) to the IV fluid is not a protocol deviation as long as the fluid rate remains in line with the assigned study arm.

If the treating physician makes a decision to remove the patient from the study, please document the protocol deviation on the OOPS form (see 18.2). OOPS entries should be clear, concise and complete explaining what happened, the specific clinical reason for the change, how long and what the change was.

13.3.4 Error in Fluid Type or in the Rate of Fluid given to the Patient

If the patient is given the wrong IV fluid by mistake, this is a protocol deviation and should be documented on the OOPS form. The PI should work with the patient's medical care team to assess the reasons why and attempt to correct the problem (i.e. Get the patient on the assigned treatment arm), if possible.

If the error is discovered during the study treatment time period, the fluid or rate should be changed to the assigned study treatment arm (A1, A2, B1 or B2) that the patient was randomized to for the study. Document the protocol deviation on the OOPS form (see 18.2).

If the error is discovered after the patient has completed the inpatient part of the study, the research team should review the study processes and procedures and discuss the case with the appropriate parties to determine what happened. Determine how this issue happened and correct the process to avoid future issues. A plan should be made to keep this from happening with any future patients. Document the protocol deviation on the OOPS form (see 18.2). Document a corrective action plan with a CAPA form (see 18.3).

13.4 Critical Study Tasks: Hourly GCS

The Glasgow Coma Scale (GCS) score is a measure of neurological status and is made up of three assessments: eye opening, verbal response and motor response. The numerical score of these three assessments are added together to make a total score that ranges from 3 to 15. For patients who are preverbal (less than two years of age), the modified preverbal GCS scoring should be used, and preverbal cues can be found in parenthesis on the GCS Log.

This study requires hourly GCS for the first 24 hours or until DKA resolves. Specific changes in GCS are critical to the study outcome.

Thus, hourly GCS is critical to the study!!!

13.4.1 When is GCS done?

For the FLUID study, GCS must be done every hour. The first GCS, typically done during initial ED evaluation, is required for randomization purposes (see 9.4). Following randomization, GCS should be done hourly for 24 hours or until DKA is resolved, whichever comes first. DKA resolution is defined for study purposes as the date and time when the IV insulin drip is stopped.

13.4.2 Resetting the GCS clock

GCS scoring can be done more frequently than every hour, if needed. Therefore, the GCS needs to be done at least hourly, but if the clock needs to be reset to match your site's practices, it can be done more frequently. For example, the patient is randomized at 10:30, but your site does GCS every hour on the hour and so the patient received a GCS score at 11:00. No GCS needs to be done at 11:30 for the study because the 11:00 GCS effectively reset the clock, meaning the next study GCS should be done at 12:00. All three (10:30, 11:00, and 12:00) GCS scores should be recorded on the study-source GCS log and entered into OpenClinica.

13.4.3 What if the patient is sleeping?

GCS should be done every hour, regardless of the patient's sleeping. This means that patients need to be awakened every hour for the GCS for the first 24 hours or until DKA has resolved. Most sites do this as standard of care in the ED or in the PICU. PIs are responsible for ensuring this happens and may need to work with floor staff especially to ensure it happens.

Tip: Because fingerstick glucose will be measured every hour while on the insulin drip, we suggest the following procedure. If the child is sleeping, first wake up the child and let them know that you are going to obtain a fingerstick glucose. Make sure that the lights are on in the patient room. After obtaining the fingstick glucose, assess the GCS according to standard procedures. It is important to record the best response (using the preverbal cues for patients under two years of age): Best eye response (E)

1. No eye opening

2. Eye opening in response to pain. (Patient responds to pressure on the patient's fingernail bed; if this does not elicit a response, supraorbital and sternal pressure or rub may be used.)

3. Eye opening to speech. (Not to be confused with an awaking of a sleeping person; such patients receive a score of 4, not 3.)

4. Eyes opening spontaneously

Best verbal response (V)

1. No verbal response

2. Incomprehensible sounds. (Moaning but no words)

3. Inappropriate words. (Random or exclamatory articulated speech, but no conversational exchange)

4. Confused. (The patient responds to questions coherently but there is some disorientation and confusion.)

5. Oriented. (Patient responds coherently and appropriately to questions such as the patient's name and age, where they are and why, the year, month, etc.)

Best motor response (M)

1. No motor response

2. Extension to pain (abduction of arm, internal rotation of shoulder, pronation of forearm, extension of wrist, decerebrate response)

3. Abnormal flexion to pain (adduction of arm, internal rotation of shoulder, pronation of forearm, flexion of wrist, decorticate response)

4. Flexion/Withdrawal to pain (flexion of elbow, supination of forearm, flexion of wrist when supra-orbital pressure applied ; pulls part of body away when nailbed pinched)

5. Localizes to pain. (Purposeful movements towards painful stimuli; e.g., hand crosses mid-line and gets above clavicle when supra-orbital pressure applied.)

6. Obeys commands. (The patient does simple things as asked. Note that this could be "give me your finger" for a fingerstick glucose.)

What if the patient awakes but does not respond normally?

For an accurate GCS exam, the patient should be awakened enough to open their eyes and respond appropriately to the person doing the evaluation. A sleepy child should be gently prodded to open their eyes and answer a simple question, or the person evaluating the patient can evaluate whether the child's verbal response is "appropriate" For example: a child opens their eyes and says "leave me alone I want to sleep". This may be judged by the evaluator to be an appropriate response based on the child's age and that it is the middle of the night. This is a judgment that should be made by the nurse or clinician doing the exam, not the RC.

What if the patient is so sleepy they cannot open their eyes?

Most children should be able to be briefly awakened and should be able to respond to vocal commands and move their body in a normal way. If a child is sleeping so deeply that they cannot open their eyes when aroused, nor respond to simple instructions, the nursing staff and the treating physician should be notified.

13.4.4 What is the GCS "time window"?

There is no GCS "time window" since it's the hourly interval that matters; GCS should be done every hour. The GCS clock should be reset so that the next one occurs one hour after the previous. Extra GCS scores are ok, so the clock can be reset to match site protocols (an extra one done to line up with hospital hours). See "Resetting the GCS clock" 13.4.2.

13.4.5 Verification of a GCS score of 13 or below

If a GCS score is 13 or below, it must be repeated 15 minutes later for verification of the score (and attending physician notified). ***Since this is the primary outcome of the entire study, this verification is critical!!*** This repeat GCS for verification is for study purposes and may be outside the scope of standard practice at your hospital. It is the PIs responsibility to ensure that repeat GCS verification occurs within 15 minutes. GCS verification should be recorded on the GCS log as an additional GCS score and entered into OpenClinica as an additional row of data.

A low GCS assessment (13 or less) only needs to be verified **once per patient**. ***It is critical that a low GCS be verified at least once (as this is a study outcome!)***, but once a patient has a verified low GCS,

they will be analyzed as meeting the outcome. Therefore, if a patient has an initial hourly GCS assessment that drops to 12, it should be verified fifteen minutes later. If the repeat GCS is again 12, no further repeat GCS assessments for this patient are needed; on-going hourly GCS assessments, however, are still required. If a patient's hourly GCS assessment drops to 13 (and they have never dropped to 13 before) and the repeat (verification) GCS done fifteen minutes later is 14, this does not count as a verified "low" GCS. If, in this case, the next hour GCS assessment drops to 13, the 13 must be verified fifteen minutes later. If this verification repeat GCS is 13, the patient has now met the outcome and no further GCS repeat assessments are needed (just the on-going hourly GCS assessments). Remember, from the study perspective, extra GCS assessments are ok and all GCS assessments done should entered as study data. The minimum GCS assessments needed are hourly and repeat if the GCS is 13 or less fifteen minutes later, until at least one drop to 13 has been verified. Please let the CDMCC know if you have questions.

If the score is 13 or below, this should be reported to the attending physician per your usual hospital protocol. Both the original score and the verification score should be entered on the GCS log and in OpenClinica. Hourly GCS scores for the patient should continue.

If the score is not verified and the second score is a 14 or 15, the hourly GCS score evaluation should resume, beginning an hour later from the repeated GCS.

A GCS of 13 or below should also be recorded as an AE by describing the symptoms observed (e.g. "excessive sleepiness", "altered mental status", "decreased responsiveness", or "confusion").

13.4.6 Who can do GCS scoring?

GCS scoring requires clinical training and so must be completed by a physician or nurse or other licensed individual as per the local hospital protocol. Therefore, in almost all instances, GCS scoring for the study must be performed by a bedside care provider (e.g. the patient's nurse) rather than an RC. If an RC is a physician or a nurse, they could potentially complete the GCS scoring for the study. This is only possible, however, if they are tied into the patient's medical care such that they could follow-up with the appropriate medical staff, if the GCS is low. If a site plans to have anyone other than a bedside care provider assess GCS, please alert the CDMCC for more guidance.

13.4.7 Where is the study GCS score documented?

Because the hourly GCS score is a study outcome, its documented source must be a study source document. The initial GCS score (used for randomization, very first GCS done at ED evaluation) may not be documented in the medical record, so it is essential that it is documented on the Enrollment worksheet (see A.3). All GCS scores done on the patient, including the initial GCS, should be recorded on the GCS log as the study source document (see A.9). Using this study log will also help ensure that verification of a GCS 13 or below is done.

Using the GCS Log Source Document

Study staff should be extremely familiar with the study source documents and ensure that all bedside care providers are as well. Study staff should ensure that the GCS Log accompanies patients through admission and remains at their bedside to be completed by all care providers. See A.9 for the GCS Log.

The GCS Log is made to be printed back-to-back and to walk bedside care providers through obtaining the hourly GCS scores and verifying any scores that are 13 or below. The Log should be used by going down the columns. The initial GCS score goes in the first column with the date and time noted. All date and times should be the actual time the GCS was assessed. A score for each of the three parts of the GCS should be circled, and the score totaled in the box at the bottom of the score. The next GCS score goes in the next column and so forth.

If a GCS score was 14 or 15, circle "no" to the "Is this GCS 13 or below?" question. The next GCS score done in an hour should be recorded in the second column, and so forth. If a GCS is 13 or below, answer the question "Is this GCS 13 or below?" as "yes" and repeat the GCS in 15 minutes. This repeat GCS should go in the next column, with the time listed as the exact time the GCS was repeated.

The top of the GCS log has a blank for study staff to complete at the time at which the study period ends, indicating when the GCS log use can be discontinued. This should be completed by the RC to make it easy for the bedside clinical staff or physician to determine when it is Study Hour 24. If DKA is resolved before Study Hour 24, then the GCS Log should no longer be utilized.

The GCS Log also indicates that an actual weight is to be obtained at Study Hour 12. Study staff should enter the time for Study Hour 12 so

bedside staff can obtain that weight at the appropriate time, even if the child is sleeping. For the FLUID study, weight must be a measured, actual weight, NOT an estimated weight. Weight must be measured with no shoes and the patient in pajamas or a gown. Weight should always be in kilograms. See 13.6 for more details on the Study Hour 12 weight.

13.4.8 What if a GCS score is missed?

Study staff should frequently review the GCS Log and check in with the beside care providers to ensure that the GCS scoring is being done every hour and being documented on the GCS Log correctly. PIs are responsible to ensure that GCS as a study outcome task gets done at least every hour. Study staff should develop relationships with floor staff and partners, use champions and retraining activities to ensure this gets done. PIs can also do the hourly GCS to be certain it is done. Missing GCS scores should almost never happen. However, if a GCS is missed, once noticed, a GCS should be done immediately and the next GCS should be done at the next hour. (Remember, you can "reset the clock" to get back on track by doing additional GCS scores, see 13.4.2 As a very last resort, if the missed GCS is available in the medical record, it may be abstracted. However, as a GCS 13 or below cannot be retrospectively verified, abstraction should be not be relied upon. Instead, every effort should be made to never miss a GCS score. If an hourly GCS is missed, the RC must complete a OOPS form in the study database and should notify the study PI at their site.

13.4.9 Is retrospective medical record abstraction of a GCS score ok?

Hourly GCS is the main study outcome and should be completed on the GCS Log as study source document. Verification of a GCS of 13 or below score 15 minutes later is likely done only for study purposes and so would not likely be done or be documented in medical records. If a GCS is missed and no other option is available (see 13.4.8 for more details on missed GCS scores), it is acceptable to retrospectively abstract a GCS score. Also, if the only option available to a site is retrospective medical record abstraction of hourly GCS and the PI can ensure that any time a GCS is 13 or below, it will be verified 15 minutes later, it is acceptable to abstract GCS from the medical record. If a site anticipates the need to abstract GCS from the medical record in most instances, please alert the CDMCC. This will only be acceptable if the verification GCS process is included in study process

order sheets or hospital protocols. ABSTRACTION IS NOT THE STUDY PREFERRED METHOD OF COLLECTING GCS SCORES.

13.4.10 What if the patient's GCS is 13 or below, should the Digit Span still be attempted?

If a GCS is 13 or below and is verified, no Digit Span Recall Test needs to be performed at that time. This Digit Span should be entered into OpenClinica as "unable to assess." However, if the patient's GCS rises above 13 again, the Digit Span test should be completed. When in doubt, complete the Digit Span Recall test, if possible. Refer to 12.3 for more details Digit Span details.

13.4.11 OpenClinica Data Entry: GCS

On the DKA Treatment Event, GCS & Digit Span Log on the GCS tab, OpenClinica requires the date, time the GCS was assessed, and the total GCS score for every GCS performed to be entered. Complete GCS logs must be uploaded to OpenClinica.

Every GCS score obtained during the study period must be entered including the GCS from ED Evaluation and the GCS used for randomization. All GCS assessments from the very first GCS done at ED Evaluation through DKA resolution MUST be included. If a GCS is done after DKA resolution or Study Hour 24, still include it on the upload and add it to the OpenClinica data entry. No OOPs is needed for additional GCS assessments since the GCS was likely done for clinical reasons.

The weight obtained at Study Hour 12 must also be entered along with the date and time that weight was obtained (see 13.6).

13.5 Critical Study Tasks: Every four hour Digit Span Recall Test

Ensure that Digit Span Recall Tests are correctly completed every 4 hours during the hours of 7 AM and 10 PM and documented on the Digit Span Recall Test packet. Refer to 12.3 for more details.

13.6 Critical Study Tasks: Study Hour 12 Weight

The study requires that a weight be obtained at Study Hour 12. This will mostly likely occur during the patient's hospitalization period. It is the PIs responsibility to ensure that this weight is obtained. This weight is necessary even if Study Hour 12 falls during the night and the patient is sleeping.

For the FLUID study, weight must be a measured, actual weight, NOT an estimated weight. Weight must be measured with no shoes and the patient in pajamas or a gown. Weight should always be in kilograms.

Study documentation of the Study Hour 12 Weight appears on the GCS Log (see 13.4.7). Data entry of the Study Hour 12 Weight into OpenClinica should be done on the DKA Treatment Event, GCS & Digit Span eCRF on the GCS tab. Enter the weight and the date and time the weight was actually obtained.

If the Study Hour 12 Weight is missed, complete an OOPs entry and leave the data blank in OpenClinica (date, time, and weight). When queried, indicate that the weight was not done and verify that the OOPs entry has been made. Review the missed weight with the study team, as appropriate, to ensure that future weights are obtained.

If the patient is discharged before Study Hour 12, then no weight is required, no entry should be made in OpenClinica (date, time or weight), and no OOPs entry is required. However, a Discharge weight should still be obtained. If the patient is discharged any time after Study Hour 12, both a Study Hour 12 and a Discharge weight should be obtained, regardless of DKA resolution status.

13.7 Critical Study Tasks: Continue AE/SAE monitoring

Monitoring of AEs and SAEs begins with randomization and continues until hospital discharge. PIs should monitor for AEs and SAEs at least daily during hospitalization. See AE/SAE section for more details, chapter 19 on page 240.

13.8 Additional data to collect during inpatient hospitalization

During the patient's hospitalization, study staff should ensure the following pieces of data are collected. These can be obtained at any point during

the study before hospital discharge and will need parent involvement. RCs can complete these worksheets with parents, but PIs should be available to address any questions (from parent or RC). Study staff should work with hospital staff and parents to be sensitive to appropriate times to obtain this data. This data may be collected while the patient is in the ED, if appropriate.

13.8.1 Diabetes History

If a patient has previously been diagnosed with diabetes, (is known to have diabetes) you will need to complete a Diabetes History worksheet and obtain some past medical history for the patient. If the patient has been previously diagnosed, the question "Has the patient been previously diagnosed with type 1 diabetes?" on the Physician Treatment Initiation Worksheet should be answered "yes." (If previous diagnosis of diabetes is discovered later in the patient's hospitalization, this answer may be corrected on the Physician Treatment Initiation worksheet using appropriate GCP methods for crossing out, initialing and dating the error).

For patients with a previous diabetes diagnosis, their year of diagnosis, previous hypoglycemic episodes, and previous DKA episodes should be assessed. The past 12 months of HbA_{1C}lab results should also be obtained. For patients with known diabetes, this includes HbA_{1C}done up to and including the same day as randomization for the study. The $HbA_{1C}$is typically measured about every 3 months for children with diabetes. The Diabetes History should be obtained by study staff with parent interview. To help study staff obtain this data, prompting questions can be found on the Diabetes History worksheet (see A.10 for the worksheet). Study staff should discuss the patient's diabetes history to obtain the most accurate information possible. PIs should ensure that RCs understand these questions; it is the PIs responsibility to ensure accurate data are collected.

If patient/parents are unsure, even with the prompting questions, the PI should follow up with the patient's primary endocrinologist or diabetes healthcare provider. This means that study staff should obtain a medical release from the patient for the PI to call and discuss with the endocrinologist. The PI can document the results of this call on the Diabetes History worksheet and note that answers were obtained via endocrinologist call. This method of obtaining data is not preferred; study staff should make every effort to obtain the required data from the patient and parents first. This information should not simply be abstracted from the medical record as some episodes may not be included (if they were treated at a different

hospital, for example).

Additionally, the study requires all HbA_{1C}lab results from the past 12 months. HbA_{1C}measures the amount of glycated hemoglobin in blood and is typically a measure of the patient's glucose control in the short-term past. If the patient is typically seen within your hospital system for their primary endocrinology care, the labs can be abstracted from the medical records. Study consent applies. However, if the patient is typically seen by an outside endocrinologist, those lab results will need to be obtained with a medical release process. Collect the outside endocrinologist's or diabetes healthcare provider's contact information and obtain the parent's signature on your hospital's medical release form. Follow up to ensure that lab results are obtained and entered into OpenClinica in a timely manner. For these patients, if patients/parents were unable to recall the other diabetes history (year of diagnosis, previous hypoglycemia, previous DKA episodes), this data may be requested from the primary endocrinologist via the medical release as well. However, this information should first be requested by parent recall.

A note about time lines: $HbA_{1C}$is requested for the past 12 months. Previous episodes of severe hypoglycemia and previous DKA episodes are ever, meaning we are looking for the total number of episodes the patient has ever had.

OpenClinica Data Entry: Diabetes History

On the Study Initiation Event, use the Diabetes History eCRF, Diabetes History tab to enter the year of the patient's first diabetes diagnosis (use YYYY format), hypoglycemic and DKA history. Indicate where the patient receives their primary care. On the Study Initiation Event, Diabetes History eCRF HbA_{1C}tab, enter all the HbA_{1C}results and date from the past 12 months. $HbA_{1C}$are reported as a percentage with one decimal (e.g. 7.1%); enter only the numeric value as the "%" is already there for you. If a HbA_{1C}has been reported as greater than a number, enter one higher than that number (ex. A result of "¿14" should be entered into OpenClinica as "15"). All patients with a Diabetes History form must have at least one HbA_{1C}result entered. Add one row for each HbA_{1C}result in the 12 months prior to the patient's ED visit.

13.8.2 Caregiver Demographics

At some point, before the patient is discharged, parents must complete the Caregiver Demographics worksheet. This worksheet can be handed to parents with the baseline CBCL (see 13.8.3 on the next page) and can be completed directly by them or with RC/PI interview. This worksheet attempts to collect data to be used to calculate socio-economic status for outcomes of the study, so it is critical to the study. Please note, some of the questions on this worksheet may be sensitive to parents and should be approached with care. Study staff should do their best to obtain the data without being too aggressive.

Once a parent completes the form, study staff should review it while parents are still present to ensure completion.

Who is Caregiver A and Caregiver B?

If at all possible, Caregiver A should be the patient's mother and should also complete the CBCL (both at baseline and at follow-up). Caregiver B should be whichever other person cares for the patient most often (typically, a father). Both columns should be completed on all patients (unless the patient only has one caregiver). Caregiver A can complete the worksheet for both caregivers (or vice versa). The Caregiver's initials are there to help you identify which caregiver completed which column. Initials will not need to be entered into OpenClinica.

Household Income

Household income should encompass the entire household's income where the patient lives most of the time. It should include all resources available to the patient, so the income of both parents should be represented, if applicable.

OpenClinica Data Entry: Caregiver Demographics

Enter Caregiver Demographics on the Family Data event, Caregiver Information eCRF. Always use "CBCL Respondent" tab for the Caregiver who completed the CBCL - this should be Caregiver A, however, if caregivers switched on the paper worksheet, data enter the CBCL respondent on the CBCL respondent tab. The other caregiver (typically Caregiver B) should be data entered on the "Additional Caregiver" tab. Enter Household Income on the Household Income tab. If the parents refuse part or all of the

worksheet, enter these answers as "not provided". In all questions, only one choice can be selected.

13.8.3 CBCL

At some point, before the patient is discharged, parents must complete a baseline CBCL. The CBCL provides a general assessment of behavioral adjustment. It may take parents a bit of time to complete the CBCL, so try to provide it to the parent(s) sometime before discharge.

We would like to obtain a baseline assessment at intake reflecting behavioral adjustment prior to study participation, and one assessment at the follow up to capture change since DKA. The CBCL allows us to control for potential sources of individual variation within the sample which might affect neurocognitive outcomes directly or in interaction with the treatment received. For example, one of the treatment arms may result in slower or more difficult recovery, which might induce higher stress or anxiety in the family and the child. Anxiety is associated with lower memory performance and we may find lower memory in the group associated with the treatment; not because of the treatment per se, but because of higher anxiety resulting from the experience.

The CBCL survey can be handed to parents with the Caregiver Demographics worksheet (see 13.8.2 on the preceding page) and should be completed by the parent. Once a parent completes the survey, study staff should review it while parents are still present to ensure completion. Again, some questions on this survey may be sensitive for patients. Please approach appropriately. Parents may leave questions blank, if they prefer, though should be encouraged to complete all questions. Ask for clarity on any questions where handwriting is illegible, no answer was provided, or two answers have been selected. Use GCP to indicate the correct answer or a Note-to-File, as needed.

A Note about age: Please ensure the correct age CBCL is provided. For this baseline CBCL, parents of patients ages 3 through 5 years old at the time of inpatient hospitalization should complete the preschool CBCL. Parents of patients 6 years through 17 at the time of inpatient hospitalization should complete the older age CBCL.

OpenClinica Data Entry: CBCL

Upload the de-identified, completed CBCL completed during hospitalization on the Family Data Event, Caregiver Information eCRF CBCL Respondent

tab. The parent who completed the CBCL, the CBCL Respondent, should be entered as Caregiver A on the Caregiver Demographics. Ensure the study subject ID is on the CBCL and all pages have been uploaded correctly. If a CBCL was not completed, indicate why it was not completed. Please remember to completely de-identify the CBCL (the patient's name, date of birth, parent name, age, race, grade and date or service should all be blacked out). Also clearly label the CBCL with the study subject ID and "Treatment". Name the upload "Treatment CBCL xxxxxx" (xxxxxx = study subject ID).

If a CBCL is completed for a patient that it should not have been completed for (under 3 years of age) or the wrong age CBCL is completed, please answer "yes" to "Was CBCL completed by this parent?" on the Family Data Event, Caregiver Information eCRF CBCL Respondent tab. However, do not upload the CBCL, complete a NTF for the patient study file explaining why it was not uploaded, and complete an OOPs entry indicating the error.

13.8.4 Concomitant Medications Log

All pharmacological agents (medications) given to the patient from randomization through discharge should be recorded on the Concomitant Medications Log and entered into OpenClinica, see A.16. Medications should be entered with the generic name, if possible. Record the date and time the medication was started and stopped and indicate if the medication was related to an adverse event. If a medication is ongoing at the time of discharge, leave the stop date blank. If a medication ends at the time of discharge, enter the discharge date as the stop date. It is the PIs responsibility to ensure that the Concomitant Medications Log is correctly completed; RCs can assist.

Insulin or IV fluid should not be considered a concomitant medication for the FLUID study. There is no need to record dextrose (e.g. D5) or other IV fluid additives, unless the site PI determines they are related to a SAE and should be recorded. All other medications, even just one oral dose, should be included. Dosing or route information should not be included on the concomitant log; only the drug name in the medication field is needed.

A "continuing" concomitant medication is one that is given past discharge; only answer 'yes' to "continuing medication" if the patient is discharged with the medication. If it is a "continuing" medication, no stop date should be entered. If a patient receives a medication over a period of time while in the hospital or if they receive a medication multiple times, the medication should only be entered once on the Concomitant Medication

Log with a start date and time of the first administration and a stop date and time of the last administration, as 'no' to "continuing".

All medications given in relation to an AE should have a corresponding AE on the AE Log. A medication given in response to an abnormal lab already collected for the study should be entered on the Concomitant Medication Log as given in relation to an AE. In this case, add the medication to the Log, say 'yes' for "relation to an AE", and enter the AE on the AE Log. For more information on abnormal labs already collected for the study, see 2.7.2 on page 24. For more information see AE and SAE sections, chapter 19 on page 240.

OpenClinica Data Entry: Concomitant Medications Log

Enter all concomitant medications into OpenClinica on the Safety Data Event, Concomitant Medications Log eCRF Con Meds tab. Each medication and each instance of the medication should have its own row. If the medication was given in relation to an AE, please provide a brief reason.

Chapter 14

Step 7: Patient is discharged

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14.1 Worksheets & Sources

Time point: End of inpatient hospitalization

- *Discharge Data:* study staff ensures data collection, RC and PI abstract from the medical record CBCL: parent completes.

14.2 General

The study ends when DKA is resolved or it has been 24 hours since the patient's randomization, whichever comes first. DKA resolution is defined for study purposes as the date and time when the IV insulin drip is stopped.

Discharge Data must be collected whenever discharge occurs. AEs/SAEs must be followed through hospital discharge and some additional data must be collected at hospital discharge (not at study ending). So, regardless of the patient's study status, the study team must ensure these tasks take place at hospital discharge. Each site will need to figure out how to ensure these get done (e.g. Study staff will be paged when a patient is preparing for discharge, tasks are routinely done and documented in the medical record, floor staff will be trained on discharge tasks).

14.3 Discharge checklists

A checklist to ensure all tasks are done prior to the patient's discharge appears on the Discharge Data worksheet. See A.17, labeled "for patients/parents".

For patients/parents:

- Discharge weight done
- Three month follow-up appointment made (patients age 3 years and older)
  - Contact information confirmed for reminder
  - Reminder to bring: parent, glucose meter, & ketone strips
- Study contact info given to parents
- CBCL completed by parent
- Future Studies Form completed

14.4 Data to be collected at discharge

14.4.1 Weight

One last weight needs to be collected right at patient discharge. For the FLUID study, weight must be a measured, actual weight, NOT an estimated weight. Weight must be measured with no shoes and the patient in pajamas or a gown. Weight should always be in kilograms. This final weight may

be recorded on the Discharge Data worksheet. Discharge weight may be abstracted from the medical record if your hospital's standard procedure for obtaining weight matches the study procedure. The PI is responsible for ensuring an accurate, actual weight is obtained at discharge. Discharge weight may be documented on the GCS Log if it is not documented in the medical record. If it is added to the GCS Log, it should be clearly labeled as the discharge weight and include the date and time done. Once added to the GCS Log, it becomes the source for discharge weight. This should only be used in cases where the discharge weight cannot be documented in the medical record. The typical source of the discharge weight should be included in the Site-Specific Workflow for each site. Enter the final discharge weight into OpenClinica on the DKA Treatment event, Discharge Data tab.

14.4.2 Hospital Discharge date and time

The date and time of the patient's discharge from the hospital should be recorded on the Discharge Data worksheet and entered into OpenClinica. If the patient died during hospitalization, the discharge date and time should be the date and time of death.

14.4.3 Planned three-month follow up visit

Enter the date of the planned three-month follow-up visit on the Discharge Data worksheet and in OpenClinica. If this visit isn't scheduled before discharge, leave blank until the follow-up is scheduled. Schedule the visit as soon as possible.

14.4.4 Future Studies consent

Indicate if the parent/patient consented to being contacted for possible future studies. In most cases, this was added as a sentence to the informed consent process on the parental permission form. Some sites may have a separate form for this. Refer to your Site-Specific Workflow for more explanation of your site's practice. In OpenClinica on the DKA Treatment event, Discharge Data eCRF indicate if the parent consented. If it's not documented or the form is not completed, enter "no".

14.5 Scheduling the Follow-up Visit

The follow-up visit should be scheduled 3 months $\pm$ 4 weeks after the ED visit. This means it should occur sometime between two months and four months after the ED visit. Scheduling the visit earlier will allow for more time for rescheduling and reminding, but it should not be scheduled too soon. We recommend scheduling the follow-up visit for roughly 10 weeks from the ED visit (2 months) in order to account for scheduling difficulties.

Ideally, the follow up visit should be scheduled prior to the patient leaving the hospital (prior to discharge). Ensure that you have appropriate contact information to follow-up and remind the patient and family of the visit. Remember that the patient will need to bring:

- parent to complete the CBCL
- ketone testing kit
- glucose testing kit

14.6 Study contact info

Ensure that patients/parents have received study contact info so they can ask any future questions or contact you regarding the follow-up visit.

14.7 Study Source Forms

Once the patient is discharged, the study staff should immediately collect the two study source forms from the patient's bedside. These are the GCS log (see 13.4) and the Digit Span Recall Test (see 12.3) packets. Additionally, study staff should ensure they have the parent-completed CBCL. These forms are study source documents and cannot be re-created later. It is crucial that these forms be complete and legible as possible.

Upon retrieval, study staff (PI or RC, whoever collects the forms) should immediately review the forms to ensure completeness and address any questions with appropriate floor staff immediately. Study staff should also review to determine if additional training may be needed with floor staff to ensure proper completion of these study outcome data points for future study patients.

14.7.1 GCS Log

Once a completed log is retrieved, enter the total GCS scores for each time point into OpenClinica. Upload all pages of GCS log to OpenClinica. See 13.4.11 on page 159 for more details.

14.7.2 Digit Span Recall Test Packets

All tests should be reviewed for accurate scoring calculations and complete administration. Each Digit Span test should be entered into OpenClinica and all pages uploaded. See 12.3.4 on page 140 for more details.

14.7.3 CBCL

As soon as the parent completes the CBCL, study staff should review for completion, asking parents to complete missing answers (if appropriate). The completion of the CBCL should be entered into OpenClinica (on the Family Data Event) and the complete survey uploaded. See 13.8.3 on page 164 for more details.

Chapter 15

Step 8: PI/RC review of medical record, data entry

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15.1 Worksheets & Sources

Time point: At patient's discharge

- *Discharge Data:* RC and PI abstract from the medical record
- *Vitals & Lab Log:* RC abstracts from the medical record
- *Fluid Administration Log:* RC abstracts with PI oversight from the medical record
- *Specific Treatment Log:* PI abstracts from the medical record
- *Finalization of AE Log & SAE reports:* RC abstracts with PI oversight from the medical record

15.2 General

Once the patient has been discharged, the PI and RC should meet to review all final study data and to discuss the patient's study enrollment. PI and RC should determine if any study processes should be updated or changed to ensure a better enrollment experience for the next patient. PI and RC should include additional training needs for study staff, ED staff, PICU/floor staff, endocrinologists or any other parties involved. If additional study needs are identified, please communicate with the CDMCC as your ideas may help others!

In addition to reviewing the patient's study process, PI and RC should review the following data topics:

1. Study source forms: GCS Log, Digit Span Packets, & CBCL
2. Discharge data
3. Specific treatments
4. IV fluid administration
5. Vitals and Lab
6. AEs and SAEs, Concomitant medications

15.3 What can be abstracted? What must be completed in real-time?

Data which must be completed in real-time with a patient/parent source include:

1. Screening and Enrollment worksheet (must be completed AT ENROLLMENT)
2. Physician Treatment Initiation worksheet (must be completed AT ENROLLMENT)
3. Parental Permission (must be completed AT ENROLLMENT)
4. Digit Span Recall Test packets
5. GCS Log (see below for two exceptions)
6. Baseline CBCL, Follow-up CBCL
7. Follow-up neurocognitive testing
8. Demographics
9. Caregiver Demographics

Data which should be attempted in real-time with patient/parent and treating medical staff, but can be abstracted later, if necessary:

1. Review of Medical Conditions worksheet
2. Physical Exam worksheet

3. GCS Log (only acceptable to be abstracted if one is missing or verification of 13 or less is standard)
4. Diabetes History
5. Discharge Data: Discharge Data
6. Follow-up Visit Basics

Medical record abstraction of the following worksheets is acceptable:

1. Vitals and Lab log
2. AE/SAE Log (note reporting time constraints)
3. Concomitant Med Log
4. Specific Treatment Log
5. Fluid Administration Log
6. Discharge Data: PI questions

15.3.1 Data entry timing

All study data should be entered into OpenClinica as soon as possible. Patient data for patient creation should be entered in OpenClinica within one day of study enrollment (randomization into the study). Study source data and all available data should be entered into OpenClinica within one week of enrollment. All remaining data from medical record abstraction should be entered into OpenClinica as soon as possible and available, but no later than two weeks after enrollment.

If the follow-up visit was not scheduled before the patient was discharged, it should be scheduled as soon as possible.

Here is a table that outlines the specific timelines for each form to be completed in OpenCliica. Please note: These are very tight deadlines which *must be* met, as FLUID is a FDA-regulated RCT with a DSMB. Data needs to be as complete and clean as possible throughout the study so its ready for regular DSMB reviews.

Queries should be attempted to be resolved within 7 days. It is understood that some queries will take a little longer and may take 7-14 days to resolve. Queries should not age more than 21 days. Contact the DCC with any questions or assistance needed.

Table 15.1: Form Data Entry Deadlines

Form	***Entered by***
Patient created in OpenClinica	24 hours after randomization
Screening & Enrollment	3 days after randomization
Demographics	3 days after randomization
Physician Treatment Initiation	7 days after randomization
Review of Medical Conditions	7 days after randomization
Physical Exam	7 days after randomization
Diabetes History (HbA1Cs may take more time)	7 days after randomization
Caregiver Info	7 days after randomization
GCS Log & Digit Span Log	7 days after randomization
Imaging form	14 days after randomization
Vital & Labs Log	14 days after randomization
Fluid Administration Log	14 days after randomization
Discharge Data	14 days after randomization
Cerebral Edema Log	14 days after randomization
Concomittant Medications	14 days after randomization
AE Log	14 days after randomization
SAE Report	Notify CDMCC in 24 hours; Report in 72 hours

15.3.2 Data entry checklist

A checklist walking the research team through these tasks appears on the Discharge Data worksheet. See A.17, labeled "for research team".

For research team:

- All AEs & SAEs reviewed by PI, forwarded to CDMCC as needed
- Specific Treatment Log completed by PI, if applicable
- GCS log, glucose/digit span log, and CBCL uploaded to OpenClinica
- Fluid Administration Log completed by PI and RC
- Space for follow-up visit reserved
- Reminder to remind patient/parent of follow-up visit placed
- All worksheets completed, data entered into OpenClinica

15.4 Study Source forms: GCS, Digit Span, CBCL

Ensure that these study source forms have been properly completed, entered, and uploaded to OpenClinica. For more information, see chapter 14 on page 167.

15.5 Discharge Data: PI Questions

Ensure that all study tasks have been completed. Use the checklist on the Discharge Data worksheet to guide you through (see A.17).

From the medical record the RC and PI should abstract the patient's weight at discharge, and date and time of discharge. For the FLUID study, weight must be a measured, actual weight, NOT an estimated weight. Weight must be measured with no shoes and the patient in pajamas or a gown. Weight should always be in kilograms. If the patient's weight is not routinely obtained at hospital discharge, ensure that patient's weight has been obtained and recorded on study source worksheets.

If the patient did have clinically-overt cerebral edema, as defined by the study and determined by the site PI, enter "yes" on the Discharge Data worksheet and in OpenClinica (DKA Treatment event, Discharge Data tab) and create and complete the Specific Treatment Log (see 15.6).

The PI should also review the medical record for any head CTs or MRIs that the patient may have received. If the patient did have a head CT or MRI, the report must be uploaded into OpenClinica (DKA Treatment Event, Imaging Reports tab). All head CTs or MRIs report should be de-identified and uploaded.

15.5.1 What if the patient died during hospitalization and so was not "discharged"?

In this case, please complete as much of the study data as is available. Enter "yes" on the Discharge Data worksheet and in OpenClinica on the DKA Treatment event, Discharge Data tab to the question "Did the patient die during hospitalization?". Use the date and time of death as the Discharge date and time.

If the patient died during hospitalization, please note this is automatically considered an SAE. Add what caused the death (not "death") to the AE log (both patient study file and in OpenClinica) and notify the CDMCC immediately. Complete the SAE report and fax to the CDMCC within 72 hours. See the AE/SAE section for more details, chapter 19 on page 240.

15.5.2 OpenClinica Data Entry: Discharge Data

On the DKA Treatment Event, Discharge Data eCRF, enter if the patient had clinically-overt cerebral edema (as defined by the study and determined by the PI). Enter if the patient died during hospitalization. Enter the date and time of hospital discharge, the patient's weight at discharge, the scheduled date for the follow-up visit, and if consent for future studies was obtained.

If the patient had any head CTs or MRIs, upload de-identified reports to DKA Treatment Event, Imaging Reports eCRF. Each CT or MRI report should be uploaded to its row with the date and time of the imaging test and the type of test done. Enter as many CTs and/or MRIs reports as are in the medical record.

15.6 Specific Treatment Log

If the PI determines that the patient had clinically-overt cerebral edema as defined by the study, a Specific Treatment Log (see A.19 for the worksheet) is required.

For the purposes of the study, clinically-overt cerebral edema is present if the patient received any one of these three treatments:

1. Mannitol
2. Endotrachael intubation
3. Hypertonic saline

Please note that for this study, "clinically-overt cerebral edema" is not based on GCS or any other diagnosis or test. It is based on the documentation and administration of any one of the three specific treatments listed above. Determination of clinically-overt cerebral edema must be made by the PI. If PIs have any questions about any cases, please contact the Study PIs or the CDMCC. Patients determined to have "clinically-overt cerebral edema" by the study defintion will likely be reviewed so sites should keep information and documentation about the determination of "clinically-overt cerebral edema" in the patient study file. If the patient did not have one of the three treatments, they did not have clinically-overt cerebral edema according to the study definition. The PI should complete this log indicating which of the three treatments the patient received and start and stop date and times of the treatment. This log is only needed for patients who had one of

these treatments (treatments which defined clinically-overt cerebral edema; answered as "yes" on the Discharge Data Worksheet for clinically-overt cerebral edema).

Please note: In most cases, cerebral edema is likely to be considered an AE/SAE, per the PI's clinical judgment. Add "cerebral edema" to the AE log (both patient study file and in OpenClinica) and notify the CDMCC immediately. Complete the SAE report and fax to the CDMCC within 72 hours. See the AE/SAE section for more details, chapter 19 on page 240.

15.6.1 OpenClinica Data Entry: Specific Treatment Log

Enter on the DKA Treatment event, Cerebral Edema eCRF in OpenClinica. If the patient received more than one treatment, use a new row for each treatment. This log is only needed for patients who had one of these treatments (treatments which defined clinically-overt cerebral edema; entered as "yes" on the Discharge Data tab for clinically-overt cerebral edema).

15.7 Fluid Administration Log

Together, the PI and RC should review the complete medical record to calculate the IV fluid volume intake totals for the patient. PIs should work with RCs to ensure the correct dates, times, and fluid amounts are abstracted. If you need any help determining these totals, please contact the CDMCC for assistance. The Fluid Administration Log worksheet can be found here: A.18.

The process for calculating fluid totals at each site **must be documented in the site specific workflow** or as a separate study document (See 8.2). This document should include source hierarchy, data point location in the MR, site specific review process, and the method for double checking fluid rates and types. These documents should be written so that a person coming into the study (auditor or new staff) could recreate the fluid calculations for each patient enrolled in the study. This documentation should include any and all assumptions made by the site in calculating fluid totals.

Each site should use a simple, clear Excel spreadsheet for documenting fluid totals that will become a part of each study file. Most sites have already developed this; the DCC will provide a suggested template with all the best practices incorporated. (Template is here: `https://www.nedarcssl.org/eRoom/NDDP/StudyDiabeticKetoacidosis/0_63a47` or in the appendix A.37) Sites may opt to use the DCC template or integrate into

their own already existing method. But, each site should clearly document which fluid was used and how totals were calculated for each individual patient.

The Fluid Admin Log provides an excellent opportunity to review each patient enrollment to **check for arm compliance or any issues that may have occurred during the patient's enrollment.** Calculations should be reviewed regularly with the PI. If there are items that are not self-evident, or could be difficult for another person to identify, sites should write a Note-to-file (NTF) that explains specific decisions or interpretations so that another person could clearly see how the totals were calculated. The NTFs should be placed in the patient study file.

Communication with floor staff is critical to verification of study treatment arm compliance, as well. Medical record abstraction of fluid administration amounts is complex and sometime inaccurate. To ensure that all patients are receiving the study treatment arm as assigned via randomization, study staff must follow-up with the patient's treatment team to verify on arm compliance. Any issues discovered during conversation should be documented in the patient study file with a Note-to-file (NTF). Any systematic issues uncovered must be documented in the EDB with a CAPA.

15.7.1 Fluid Administration Log Sources

Sites are using a variety of sources, and most sites reference two or more sources to calculate fluid totals. Most commonly used are the MAR to assess DKA resolution, IV start time, IV study rate start time, rates ordered and then I and O flowsheets to calculate fluid totals with start and stop times of rates or changes in fluid (dextrose content titration).

Documentation errors and/or missing documentation in site medical records or MARs often make it difficult to accurately find total fluid amounts. All sites have had to make key assumptions about amounts of fluid infused when documentation is incomplete. (Examples include lack of documentation of fluid infused during the transition from the ED to the floor). These assumptions must be documented in the Site Specific Workflow for each site. link

The DKA resolution time point can be especially difficult to isolate from the medical record. For some patients at all sites IV insulin stop date and time is not always clearly documented. If DKA resolution is not clearly identified for a particular patient, a Note-to-file (NTF) is required for that patient study file explaining how DKA resolution was determined. If this

happens systematically at a site, the Site Specific Workflow must include documentation about how this important data variable is determined. Site methods for obtaining and documenting DKA resolution time vary, but some ideas are:

- Adding the DKA resolution time point to the GCS Log or other study worksheet
- Ask the RC to record DKA resolution time point while in the room with the patient

As this is the end point of the study, it will be important to work out an accurate and consistent method of recording at all sites, for all patients.

Because many sites have found that fluid intake recorded in the medical record can be inaccurate and prone to error, it may be helpful to use a bedside (written) fluid log to record fluid administration, or at least arm deviations. *Unless medical record fluid records at your site are routinely accurate and easy to interpret, we highly recommend using these bedside logs.*

15.7.2 Dates and Times on the Fluid Administration Log

IV Fluid Start Date and Time: This is the date and time that the patient first received an IV with fluid of any kind. If the patient's IV fluid started at an outside hospital, enter the date and time the outside hospital started it.

DKA Resolution Date and Time: This is the date and time that DKA resolved. DKA resolution is defined for study purposes as the date and time when the IV insulin drip is stopped.This is the time the IV insulin was stopped for the last time (ie. in the case where a patient's IV insulin may have been stopped and then restarted, use the last time the IV insulin was stopped). DKA Resolution should be the actual time the that IV insulin was actually stopped. Sites may need to review their study processes and possible add this to real-time data collection to ensure that is the time recorded.

Study Treatment (Study Arm Calculated IV Fluid Rate) Start Date and Time: This is the date and time that the IV fluid rate the patient was randomized to was started. It is when the treating team initiated the study IV fluid rate they calculated according to the study arm the patient was randomized to. If the patient received an additional bolus after randomization (e.g., the extra 10 cc/kg called for in the A arms), still use the time

that the study calculated IV fluid maintenance rate was initiated. This date and time is the moment that the IV maintenance rate calculated using the FLUID calculator was initiated with the 1/2 NS or NS fluid.

For example, suppose a patient was assigned to arm A1 and immediately after randomization, then the additional 10 cc/kg bolus started first. During administration of the bolus, the clinician calculated the IV fluid rate for arm A1, the order is placed, and the correct maintenance IV fluid with 0.45% NS IV is received in the ED. Once the additional bolus is completed, the treating team started the study arm A1 calculated IV fluid maintenance rate. This moment is the date and time this IV study treatment fluid rate starts; it is the date and time that should be entered under the Study Treatment Start Date and Time.

Study Hour 12 and Study Hour 24: You do not need to enter these times into OpenClinica, but you will need to know them to complete your total fluid amounts. Study Hour 12 is 12 hours after randomization time; Study Hour 24 is 24 hours after randomization time.

15.7.3 How do I calculate fluid totals for the Fluid Administration Log?

First, you will need to figure out the three time periods requested. Second, you will need to figure out the total amount of fluid the patient received through those three time periods. Third, you will need to determine what types of fluid make up those amounts. See diagram A.36 on page 347 for a picture of what's needed.

Best practices include:

- Double check of calculations by an separate RC or PI who independently calculates and then comparing the two, resolving discrepancies
- Using a spreadsheet to do the math for you
- Using this calculation process to find OOPs and places for process improvement at the site.
- Document the process for calculating at your site, including any assumptions made and the source hierarchy for each data point.
- Total volume may be calculated by adding up the ccs or by applying the rate of fluid over the time frame in which that order was running. A best practice is cross-referencing the other method to ensure that no fluid is left out of the totals and that the treatment arm is being followed.

Step One: Time Periods

Three IV fluid totals are requested:

1. Total fluid the patient received from the IV Fluid Start Time (when the IV was placed and fluid began) to Study Hour 12.
2. Total fluid the patient received from the IV Fluid Start Time (when the IV was placed and fluid began) to Study Hour 24.
3. Total fluid the patient received from the IV fluid start time (when the IV was placed and fluid began) to DKA Resolution.

Recall that Study Hour 0 is randomization. So to determine when Study Hour 12 is, add 12 hours to the Randomization Time. To determine Study Hour 24, add 24 hours to the Randomization Time. DKA resolution is defined for study purposes as the date and time when the IV insulin drip is stopped.. Determine these three times.

If DKA resolves before Study Hour 12 or 24, still calculate the fluid total for all three time points. It is possible that all three points would be the same totals. However, once DKA is resolved, fluid may still continue and this additional fluid should be included in the Study Hour 12 or 24 totals. If the patient is discharged prior to Study Hour 12 or 24, include all IV fluid the patient received through their discharge.

Step Two: Fluid amounts given

For each of the above time periods, calculate how much IV fluid the patient received. We are looking for the IV fluid volume received by the patient from fluid initiation (either at an outside or PECARN hospital) to the three specific time points listed above. Make sure that your calculations include all fluid from the ED as well as the anywhere else in the hospital or outside hospital. Total fluid amount calculations should include all IV boluses given including any IV boluses given at an outside hospital. IV insulin drip fluids or prep and IV flushing fluids do not need to be included in the Fluid Administration Log calculations.

Fluid volumes should be calculated regardless of dextrose or other additives (1/2 NS or 0.45% NS includes "D5 .45" or "D10 .45"). All fluid volumes should be entered into OpenClinica in mls (1 ml = 1 cc).

Step Three: Type of fluid

Fluid is classified on the log as either:

1. 0.45% NS
2. 0.9% NS
3. Other

All fluid amounts must fit in one of these categories. For example, "D5 .45" and "D10.45" would be added under the 0.45% NS totals. Boluses given with 0.9% NS should be added under the 0.9% NS totals. Most fluid given will fit into category 1 or 2; however if a fluid type neither contained normal saline nor half normal saline, enter it as "other". If the patient did not receive a particular type of fluid (e.g. all fluid given contained only 0.9% NS and no other fluid type was given), enter 0 mL into OpenClinica for the 0.45% NS totals and Other Fluid totals.

When you enter the three different fluid amounts for the three types of fluid in a specified time period, OpenClinica will automatically calculate the total received for that time period for you.

Examples

A patient comes to the ED in DKA and has IV fluid started at 3:30 PM, prior to randomization. This patient was then randomized at 4:00 PM to B1 (requiring no additional boluses) and the study treatment IV fluid rate was started at 4:30 PM. Study Hour 12 would be 4:00 AM and the fluid total at Study Hour 12 would be whatever fluid including boluses he received prior to randomization through Study Hour 12, or through 4:00 AM. IV Start Time would be 3:30 PM and Study Treatment Start time would be 4:30 PM.

Suppose another patient who weighed 50 kg was given 500 cc of 0.9% NS IV fluid at 9:00 AM, prior to randomization, and then was randomized at 10:30 AM to arm A1. The patient then received the study treatment arm additional bolus of 500 ccs of 0.9% NS IV fluid at 10:35 AM and the study treatment arm IV fluid calculated rate of 257 ml/hr 0.45% NS (for the first 12 hours) was started at 11:00 AM. If, by 12 hours after randomization (10:30 PM is Study Hour 12) the patient had received only the study calculated treatment at the correct rate, the patient would have received an additional 2956 cc of 0.45% NS. The fluid calculations would be 1000 cc total of 0.9% NS given as boluses plus 2956 cc total of 0.45% NS given per study treatment arm calculation and no "other" fluid type. Thus, the fluid total (for all three types) at 12 hours would be 3956 mls. The IV Start Time in this example would be 9:00 AM and the Study Treatment Start Time would be 11:00 AM.

15.7.4 OpenClinica Data Entry: Fluid Administration Log

On the Fluid Administration eCRF enter the IV Fluid Start Date and Time, the Study Treatment Start Date and Time, the DKA Resolution Date and Time, and the IV fluid totals for each of the three specified study time periods (12 Hour, 24 Hour and DKA Resolution) and each of the three types of IV fluid (0.9% NS, 0.45% NS, and Other). Once entered and the eCRF is saved, OpenClinica will calculate the total fluid amount for each of the specified study time periods.

15.8 Vitals and Labs

For this study, we will collect all standard of care vitals and labs listed below:

1. First ketone test result, either urine or blood
2. Hourly glucose
3. Hourly vitals: blood pressure, respirations, heart rate (only needed for the first 24-hours)
4. Serum electrolytes (every 2-4 hours): Sodium, Potassium, Chloride, Bicarb, BUN and Creatinine
5. Serum Calcium, Serum Magnesium, Serum Phosphate (every 4-8 hours)
6. Blood gases (every 2-4 hours): pH & pCO_2

Every lab result in the medical record should be entered into OpenClinica. With the exception of ketones, all lab values should be entered through hospital discharge (even if this is after IV insulin has been discontinued, or after the 24-hour study period). Vitals need to only be entered during the 24 hour study period. The only ketone test to be abstracted on the Vitals and Lab Log should be the first one done at the ED visit (or in the hospital). *The first labs and vitals should be the results first documented, even if these are from an outside hospital.* The time entered should be the time the lab was drawn.

All of these tests should be standard of care for DKA patients and therefore are not study labs. The timelines provided are guidelines for the sites as to when these tests are typically done and how often they should expect to see them in the medical record. However, every lab result should be entered, regardless of these time lines. Enter all results that are available in

the medical record. If one part of a row of data is missing from the medical record, leave it blank (e.g. you may have serum calcium and serum magnesium but no serum phosphate; enter the serum calcium and magnesium, leave phosphate blank). A missing lab value does not count as a protocol deviation.

Because all labs are required to be entered into the database, abnormal labs do not need to be entered as AEs, unless certain criteria are met. (See chapter 19 on page 240 for more AE details.) it is very important that ALL lab results required for the study done during hospitalization and recorded in the medical record are to be entered into Labs & Vitals Logs.

Below are some specific tips to remember for each lab result. PIs should spend time with RCs to ensure that RCs are looking at the correct lab results. If PIs or RCs have any questions, please contact the CDMCC ASAP.

15.8.1 Ketones (positive or not):

Typically, a ketone test is done when patients with suspected DKA enter the ED. These tests can be done on urine or blood (usually urine), and may be a point-of-care test. RCs should look for the first documented ketone test result (whether in the ED or hospital or transferring hospital), answer if it was positive (ketones present) or not, and enter the date and time of the first ketone test only. If there is no documented ketone test result, enter "test not done." Either blood or urine ketone results are acceptable. We do not want ketone tests done at home; it's thought that a ketone test will likely be done again once they reach a hospital. That is the ketone test result we'd want. If no ketone test is done at the hospital or doctor's office, enter the test as not done. No OOPs entry is required for a ketone test that is "not done".

Ketones may be referred to in the medical record as: Serum ketone; Plasma ketone; Beta-hydroxybutyrate; Ketone bodies; Beta-hydroxybutyric acid; Acetoacetate; Acetoacetic acid; Acetone. Urine Ketones are likely done with a urinalysis test strip and may appear with several other results (typically, specific gravity, pH, protein, glucose, blood, leukocytes, nitrites, bilirubin, and urobilinogen).

15.8.2 Glucose (mg/dL):

For patients with DKA, serum glucose is typically measured every hour. Enter all blood glucose results, whether from lab results or point-of-care results. If both lab and i-STAT or other point-of-care glucose values are

available from the same date and time, please enter the lab serum result as the study-preferred result. If a point-of-care glucose is within 15 minutes of a lab glucose, only the lab glucose needs to be entered. If the only result at that date and time is from an i-STAT or point-of-care test, it should be included.

Enter every result in the medical record from ED evaluation through hospital discharge. Some point-of-care glucose meters may read values above the maximum (usually between 500-600 mg/dL) as "Hi" or "high". If anything other than a numerical value is recorded in your medical record, please do not enter that glucose test (missing data). Only glucose tests with numerical value results should be entered into OpenClinica. However, documentation of any non-numerical results should be kept in the patient study file. If a glucose result reads ">*a number*" please enter the number and create an OOPs entry so we are award of the issue. For example, if a glucose result is ">700", enter "700" on the glucose log and create an OOPs entry that says "glucose result on *date and time* of >700 entered as 700 per MOO." When entering a ">" glucose result, be sure to include the date and time of the result in the OOPs entry.

15.8.3 Vital Signs (blood pressure, respiratory rate, heart rate):

For patients with DKA, vital signs are typically obtained every hour. Vitals should be entered for the 24-hour study period only (from randomization) and should also include the initial vital signs done at ED evaluation. Vital signs to enter include: systolic blood pressure, diastolic blood pressure, respiratory rate, and heart rate. Blood pressure may be referenced in the medical record as "BP", uses mm Hg as units, and may appear as systolic blood pressure/diastolic blood pressure (e.g. 120/80). Respiratory rate (RR) should be the number of breaths the patient took in one minute. Heart rate (HR) should be the number of heart beats in one minute. RR and HR may be counted for a shorter period of time and then calculated to the standard one minute; the one minute rate is what should be documented in the medical record. PIs should clarify these findings, if needed.

15.8.4 Electrolytes (NA, K, Cl, Bicarbonate, BUN, Creatinine):

For patients with DKA, serum electrolytes are typically collected every 2-4 hours. Electrolyte lab results should be entered from ED evaluation through

hospital discharge. Some results may appear in the medical record in mEq/L or mmol/L; RCs should note these are the same unit of measurement.

See table below for other names and units of each electrolyte:

Electrolyte	Units	Additional Names
Sodium	mEq/L	Na
Potassium	mEq/L	K
Chloride	mEq/L	Cl
Bicarbonate	mEq/L	HCO_3, total CO_2, TCO_2, or Bicarb
BUN	mg/dL	Urea nitrogen, Blood urea nitrogen, urea
Creatinine	mg/dL	Creat, Cre, Blood creatinine

NOTE: We are looking for serum electrolyte results. Some of these results may be confusing to locate in the medical record. PIs should ensure that RCs are abstracting the correct data.

Potassium (K) results may be "hemolyzed". These results do not need to be entered into OpenClinica (no date, time or result required).

15.8.5 Serum calcium, serum magnesium, serum phosphate:

For patients with DKA, serum calcium, serum magnesium, and serum phosphate are typically collected every 4-8 hours. Serum calcium, serum magnesium, and serum phosphate lab results should be entered from ED evaluation through hospital discharge. See table below for other names and units of each lab:

Lab	Units	Additional Names
Serum Calcium	mg/dL	Ca, should be *total* calcium (not ionized)
Serum Magnesium	mEq/L	Mg, Mag
Serum Phosphate	mg/dL	P, PO_4, phosphorous

15.8.6 Blood gases (pH and pCO_2):

For patients with DKA, blood gases are typically collected every 2-4 hours. Blood gas lab results should be entered from ED evaluation through hospital discharge. Blood gas results may be either venous or arterial for the study, though most are expected to be venous (and venous are preferred for study purposes). All blood gas results should be entered. Please indicate the route (venous or arterial) of each test. If the blood gases were capillary, please enter them as venous. PIs should ensure that RCs know which tests are

commonly done at their site and how they would know if the route was different for a particular test. Blood gases of study interest are pH and pCO_2. Blood pH is a value between 6 and 8 and should be reported to the first decimal (e.g. 7.6). $pCO_2$is not pO_2 (partial pressure O_2) and is not total CO_2 and is not O_2 Sat (Oxygen Saturation). $pCO_2$is partial pressure carbon dioxide and should be reported in mm HG units. Blood gases may also be called ABGs, or arterial blood gases. PIs should ensure RCs are abstracting the correct values.

15.8.7 OpenClinica Data Entry: Labs & Vitals

All labs and vitals should be entered on the DKA Treatment Event, Laboratory Data & Vital Signs Log eCRF in OpenClinica. Each set of labs or vitals has its own tab on the Laboratory Data & Vital Signs Log eCRF. Each row of data requires a date and time and the lab or vital result. Units of measurement used are indicated in OpenClinica and so only numerical values need to be entered for results. If at a given date and time, the medical record only contains some of the requested data, enter that available data and leave the rest blank (e.g. record has results from 1/1/10 at 13:10 for Serum Magnesium and Serum Calcium but no Serum Phosphate; enter the values for Serum Magnesium & Serum Calcium leaving Serum Phosphate blank).

15.9 AE/SAE, Concomitant Medication Review

PI & RC should review the patient's AE log and SAE to ensure all AEs and SAEs have been properly identified and entered into OpenClinica. For more information see AE and SAE chapter 19 on page 240. Ensure that the Review of Medical Conditions and Physical Exam worksheets and forms are complete, as well (see worksheets A.6).

Additionally, review the Concomitant Medication log to ensure that all concomitant medications from randomization through hospital discharge have been included. For more details on the Concomitant Medication Log, see 13.8.4 on page 165.

15.10 Patient data entry completion

At this point, all inpatient data for the patient should be complete. One exception to this rule may be the past twelve months of HbA1c for patients

with existing diabetes, if they see an outside endocrinologist or diabetes healthcare provider. Sites should develop a plan for tracking this data, including following-up with outside providers, if necessary. Once data is received, it should be entered into OpenClinica promptly.

Chapter 16

Step 9: 3 month follow-up

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16.1 Worksheets & Sources

Time point: Three months following the DKA episode, follow up visit

- *Follow-up Worksheet:* RC completes with parent/patient interview
- *CBCL:* parent completes
- *Digit Span Recall Test worksheet (one forward; one backward):* RC completes with patient interaction
- *Neurocognitive Testing materials:* RC completes with patient interaction

16.2 General

All patients need vital status (i.e. dead or alive) at 3 months as well as documentation of any episodes of thrombosis (blood clots of arms, legs, lungs, etc) since discharge.

- For patients ages 3 and up who come to a follow-up visit, these data should be collected at the follow-up visit with parent/patient interaction.
- For patients under 3 or who do not come to a follow-up visit, the PI will need to review your institution's medical records looking for any repeat visits resulting in death or thrombosis.

Complete the History & Status section of the 3 Month Follow-up worksheet (A.21) for all patients.

Follow up neurocognitive testing should be completed only for patients ages 3-18 (at the time of the follow up visit). For patients who come to the follow-up visit, information about severe hypoglycemia events and any

additional DKA episodes since discharge should also be collected with parent/patient interaction by completing the Follow Up Visit History and Follow Up Visit Screening sections of the 3 Month Follow-up worksheet (A.21). For patients who do not have a follow-up visit, severe hypoglycemia and additional DKA information is not needed. For a diagram of which patients need what, see A.22.

At the time that follow-up data is collected, sites should review the patient study file to ensure that study data were completed. The following study worksheets can be completed with the patient at the time of follow-up, if they were previously missed:

- Future Studies Form
- Patient Demographics
- Caregiver Demographics

Please note: every effort should be made to complete all of these study worksheets and tasks before the follow-up.

16.2.1 A note about age

During the inpatient stage of the hospitalization, the patient's age at that time should be used to calculate age-appropriate testing. However, *the patient's age at follow-up should be used to determine which age-appropriate tests apply at follow up.* Therefore, if a patient was 2 years and 10 months old during hospitalization, they should be scheduled for the follow-up visit at 3 years and 1 month and be given the test for a 3 year old. If a patient was 5 years and 11 months during hospitalization, at follow-up, they should be given the testing for a 6 year old.

16.3 Follow-up History and Status: All patients

For patients with no follow-up visit because they are either less than 3 at time of follow-up, non-English speaking, or they do not come to the visit, PIs need to review the medical record looking for return visits to your hospital. This would also include patients who do not speak English or who were re-enrolled prior to completing appointment. Both types of patients are unable to complete the follow-up visit. The PI should look for any visits resulting in death or thrombosis. PIs should review all medical visits through 3 months after the ED visit. If no visits are found, it should be assumed that the

patient is still alive and had no episodes of thrombosis. If a visit is found and the patient was again discharged alive, it should be assumed that the patient is still alive. *Please note: this review MUST be done by the PI.* See 16.4.3 for more information about thrombosis for study purposes. Answers to vital status and thrombosis questions should be documented on the 3 Month Follow-up worksheet in the History & Status section.

16.3.1 OpenClinica Data Entry: Follow-up History and Status

All patients must have the 3-Month Follow-up Event scheduled in OpenClinica. For patients who will not come to a follow-up visit (either because of age or don't show up), on the 3-Month Follow-up Status & History eCRF, Status tab, for 'Was a patient history obtained at 3 months?' answer "yes" if the PI completed the review and continue with data entry. If not, answer "no" and provide a detailed response explaining why not.

To the question 'Did patient complete in person 3-month follow-up visit', pick the pull down menu which option best applies to your patient.

- Patient is under 3 years of age at the time of 3-month follow-up
- Patient is non-English speaker/reader
- Patient re-enrolled in the study before or during the 3-month follow-up window
- Patient death
- Patient withdrawn from study (withdrawal form completed) -Any patients who were withdrawn by the physician OR patients/parents who specifically state they would like to be withdrawn from the entire study.
- Lost to follow-up (Describe) -All patients that do not come back for follow-up, who do not fall into one of the categories listed above will be included in this category. Patients that express they will not be coming back for the follow-up are also included in this category. An Oops entry will be required for all patients who do not complete follow-up.

On the 3-Month Follow-up Event, History and Status eCRF, History tab enter the data from the History & Status section of the worksheet, including the patient's vital status at the time of follow-up. For the date of the History was obtained, if multiple calls or visits were done, use the last phone call

or visit. (Note: History should NOT be updated if the patient re-enrolls or after the neurocognitive visit is done. If you have questions on timing and updating History, please contact the CDMCC.) If the patient was seen since discharge for medical care outside of regular diabetes care, enter all dates and reasons for visits. Once medical records from those visits are reviewed by the PI, enter the response for thrombosis, as appropriate. If the patient did die and the cause of death is unknown, enter "unknown".

For patients under 3 at the time of follow-up visit (or who don't show up), no follow-up visit should be done. HOWEVER, the 3-month history should still be obtained and entered; data entry in OpenClinica is now complete.

16.4 Follow-up visit: Patients ages 3-18

An in-person follow-up visit is required for all enrolled patients ages 3 and older (at the time of the follow-up visit). These visits typically take 2-3 hours and should be planned in advance so that all materials are ready.

Follow-up evaluation rooms should have:

- A restroom nearby
- Area for breaks
- Area for patients to wait in
- Quiet with good lighting, limited distractions
- A desk or table, enough chairs
- Outlet and space for the study provided laptop, the study staff, and the patient
- Juice boxes and other carbohydrate snacks to treat hypoglycemia

16.4.1 Scheduling the Follow-up

The follow-up visit should be scheduled 3 months $\pm$ 4 weeks after the ED visit. This means it should occur sometime between two months and four months after the ED visit. Scheduling the visit earlier will allow for more time for rescheduling and reminding, but it should not be scheduled sooner than 2 months after the ED visit. We recommend scheduling the follow-up visit for roughly 10 weeks from the ED visit (2 $\frac{1}{2}$ months) in order to account for scheduling difficulties.

Ideally, the follow up visit should be scheduled prior to the patient leaving the hospital (prior to discharge). Ensure that you have appropriate contact information to follow-up and remind the patient and family of the visit. Remember that the patient will need to bring:

- Parent to complete the CBCL
- Ketone testing kit
- Glucose

See also 14.5.

16.4.2 Preparing for the Follow-up Visit

Reminder to the patient:

As your institution allows, remember to remind patients of their follow-up visit. Each site should create a log system that tracks scheduled follow up visit dates and a system that tells you when to remind patients of their follow-up visit. A suggested schedule of reminders that has worked for the lead site include a call to the parents one week before to ensure that the date and time still work (or possibly rescheduling), and then, the day before, call again to confirm.

At the reminder call, patients need to bring:

1. Ketone testing kit (ask the patient/parent to check the expiration date as these often expire before completely used)
2. Glucose testing kit
3. Snacks, if they like

Provide directions to the follow-up visit location.

Appointments may be rescheduled as often as needed (as long as it stays within the 3 months ± 4 weeks since the ED visit window).

Some example reminder language is provided here: A.23.

Practice, practice, practice the neurocognitive tests and materials before the visit.

Site Preparation Checklist:

For preparation, sites should complete the following:
√ Patient/guardian reminded of visit
√ Practice, practice, practice the neurocognitive tests and materials before the visit. Do you have enough age-appropriate testing materials?
√ Collect other items: laptop, charger cord, stop watch, break materials, juice/snacks, follow-up worksheet, one digit span recall test form, CBCL for parent completion, IQ test materials
√ Space reserved and available, quiet with good lighting & the correct number of chairs & table
√ Check to be sure that patient has not been enrolled in the study a second time since the first ED visit. If the patient has been enrolled again since their first enrollment, reschedule the visit for three months following their second ED enrollment discharge. See Repeat Enrollment (12.5) for more details.

Tips for improving Lost-to-Follow-Up rates

Getting patients to return to complete the follow-up visit is a critical issue for this study. Tips for improving follow up rates include:

1. In past studies, families seemed to have a very low threshold for dropping out with even the slightest inconvenience. For example, families often were unwilling to do the follow up if it could not be scheduled on the childs clinic day or even if they had to go to a different building for the testing. So scheduling the follow up at the time of the childs clinic visit and (if possible) doing the testing at the clinic is helpful.

2. Some RCs keep weekend hours frequently, that is more convenient for families.

3. If the RC cannot get the family on the phone, consider just having the RC show up in the clinic at the time of the childs visit and try to do the testing that day (if timing is right) or schedule a separate visit at that time.

4. If the family has to walk from the clinic to another building, have someone show up in clinic to accompany them.

5. Involve the diabetes nurse or diabetes educator in the process (or ask your endocrinology collaborator to involve them). The diabetes team

often knows the families very well and even has experience trying to get them to come to clinic when they have missed appointments in the past, etc.

6. Work with your endocrinology colleagues, as appropriate

16.4.3 On the day of the Follow-up Visit

Welcome the patient and parent(s) to their visit. Ensure they feel comfortable. Start by including the parent and the patient as you address the follow-up history questions.

Follow-up Status & History questions

The RC should obtain the following data from the patient &/or parent/guardian. PIs are responsible for ensuring that RCs understand these terms. RCs should ask for PI assistance, if needed. All of these questions should be answered by patient &/or parent interview at the beginning of the follow-up visit. The Follow-up Status & History questions may be addressed by telephone for parents who are unable to come to the follow-up visit in person.

Begin by asking the History & Status questions on the 3 Month Follow-up worksheet. Obviously, if the patient is present for a follow-up visit, they have not died. RCs will need to find out, since the patient's discharge from the hospital for their DKA episode, if the patient has had (and if so, how many episodes):

1. Any medical care received by the patient outside of regular diabetes care

2. Thrombosis (blood clots)

Medical care outside of regular diabetes care
Medical care outside of regular diabetes care since the time of the patient's discharge from the hospitalization for the study-related DKA visit will likely be rare. If the patient or parent indicates the patient has received care since discharge, ask for the main reason for the visit. The FLUID study is concerned with capturing any complications from the DKA episode (e.g. so not regular endocrinology check-ups or vaccination visits). If the patient did have a medical care visit for anything outside of regular diabetes care since the study DKA episode, please ask the date of the care, and where the care was received. Please also ask if the patient was rehospitalized.

If parents or patients indicate the patient did have medical care outside of regular diabetes care, medical records of that visit will need to be reviewed to ensure that all thromoboses &/or severe hypoglycemia &/or additional episodes of DKA are correctly identified. RCs should ask where the care was received. If it was received within your hospital system are medical records are accessible, no additional action by the parents is needed.

If the care was received outside your hospital system, request a medical release of information from the parent. After the follow-up visit is concluded, RCs should review the patient with their PI to determine if the medical release should be sent and medical records should be requested. Medical records need to be requested only for medical conditions, not trauma related, that may be related to diabetes or complications of diabetes, but are not routine visits for diabetes outpatient care. Conditions that are obviously not related to DKA or diabetes like asthma or appendicitis don't need to be reviewed. RCs should get as much detail as possible, get the release signed, then talk with PIs to determine if the records should be requested for review. If needed, follow up with the medical care provider to receive the medical records of visits since hospital discharge. All medical care should be entered into OpenClinica, even if the medical records are not requested; date of visit can be blank if you don't have an exact date of visit for the additional medical care.

The RC and PI should review medical records together to ensure correct complication data is recorded in the patient study file and in OpenClinica. If thrombosis or severe hypoglycemic episode(s) or DKA is confirmed by the medical record review, update the Follow Up Status & History &/or Follow-up Visit History to accurately reflect the medical records.

If the patient has received medical care more than once since their DKA study-related hospitalization discharge, then record all visits on the Follow-up worksheet. To enter more than one visit into OpenClinica, answer "yes" to medical care, enter all dates of additional visits, and enter a description for each visit.

If any diagnosis of re-hospitalization sounds concerning, or significant, you may wish to consult your Study PI to be certain there is no reason to cancel the follow-up visit. This would be rare but if the child had a stroke, re-scheduling might be appropriate.

Some prompting for determining these questions might go something like this: "We would like to be sure your child did fine after he/she was sent home from the hospital. Did your child need to come back to the hospital or did your child need to see his/her doctor for any reason after being sent home? " If yes..." Could you explain why he/she needed to come back to

the hospital or be seen by his/her doctor?" The parents might not know that what the child had was a "blood clot"; they might only know that they had a swollen leg or had trouble breathing or some related concerns.

Thrombosis

Thrombosis is another word for blood clots. A patient may have had a blood clot in some part of their body. This would be a significant event that would likely send them to the hospital. The clot could have been in the leg, arm, or in severe cases the brain which would be a stroke. Parents may also recall this as a swollen leg or trouble breathing. If the parent or patient answers "yes" they have had a "thrombosis", please request the date of the medical visit related to the thrombosis. Note: A finding of thrombosis MUST be verified by the PI by reviewing the appropriate medical records. Please make sure those records are available.

Follow-up Visit History questions

The RC should obtain the following data from the patient &/or parent/guardian. PIs are responsible for ensuring that RCs understand these terms. RCs should ask for PI assistance, if needed. All of these questions should be answered by patient &/or parent interview at the beginning of the follow-up visit. The Follow-up Visit History questions may be addressed by telephone for parents who are unable to come to the follow-up visit in person.

Ask the Follow-up Visit History questions on the 3 Month Follow-up worksheet. RCs will need to find out, since the patient's discharge from the hospital for their DKA episode, if they've had (and if so, how many episodes):

1. Any severe hypoglycemia events (with loss of consciousness or mental status changes)
2. Any additional DKA episodes since the study episode

The Follow-up worksheet will walk you through these questions. If the parent/patient indicated that the patient had no additional medical care since the study DKA episode, it can be assumed that the patient has not had additional DKA episodes or severe hypoglycemic events.

Severe Hypoglycemia

Severe hypoglycemia means severely low blood sugar. It may be normal for patients with diabetes to experience episodes of mild hypoglycemia throughout the day. However, for this question, we are interested only in severe

episodes, meaning with loss of consciousness or substantial change in mental status like the patient could not swallow or stand. These type of episodes should be fairly memorable to the patient &/or parent/guardian. If they answer "yes" to having experienced severe hypoglycemia, please ask them how many episodes (1, 2, or more than 2) they've experienced since discharge. Since the three months since discharge, most patients should say none or maybe just 1; 2 will be rare and more than 2 very rare.

Additional DKA episodes

DKA means Diabetic Ketoacidosis and is the condition this study is researching. For this question, we are interested in any additional DKA episodes the patient may have suffered since discharge from the study DKA episode. Do not count the study DKA episode. These type of episodes should be fairly memorable to the patient &/or parent/guardian. If they answer "yes" to having experienced additional DKA, please ask them how many episodes (1, 2, or more than 2) they've experienced since discharge. Since the three months since discharge, most patients should say none or maybe just 1; 2 will be rare and more than 2 very rare. If the patient had an additional DKA episode following discharge and was re-enrolled in the study, complete this question only at the follow-up visit (for the second DKA episode, for the second enrollment). If the patient was rehospitalized for DKA, check to see if they were re-enrolled in the study for that second DKA visit.

- If the patient was enrolled in the study a second time, stop the follow-up visit and reschedule it for the timeframe from the second enrollment (3 months ± 4 weeks from the second DKA hospitalization).

Follow-up Visit Screening

Screen the patient to make sure they are able to complete the follow-up neurocognitive testing. Ask the patient to test their own glucose (blood sugar) using their own glucose meter.

- If the glucose level is <70 mg/dL, the patient should be treated for hypoglycemia and the follow-up visit rescheduled. Talk with the parent. The patient/parent should have some juice or a snack and know how to handle low blood sugar. Or you may supply some snacks or juice, as well.
- If the glucose level is >350 mg/dL, the patient will need to test their ketones using their own ketone testing kit brought from home. These

can be either urine or blood test kits. Direct the patient to the bathroom, if needed.

- If the patient tests negative for ketones, complete the follow-up visit.
- If the patient tests positive for ketones, the patient needs medical attention. Refer the patient to a physician immediately. The follow-up visit will need to be rescheduled.

If at any time during the testing you are unsure of ketone or glucose values or outcome of the testing by the parent, please call your site PI or other ED attending contact. Record the glucose and ketone findings on the Follow-up Worksheet (only the glucose result should be entered into OpenClnica on the Follow-up event).

Uncommonly, a patient may have a hypoglycemic event (i.e. low blood sugar) during the follow-up neurocognitive testing. If that occurs, please stop the testing until blood sugar normalizes with food, etc, but then resume testing. The reason that we dont want to stop and reschedule the testing at that point is that there is evidence that the neurocognitive testing can be learned and if the patient has experienced the testing before, their performance on the next testing will be enhanced.

See Follow-up screening diagram, A.35.

What if the patient forgets their glucose or ketone testing kit? If the patient brought their glucose meter but forgot their ketone kit, ask them to screen for glucose. If their glucose is more than 70 or less than 350, complete the follow-up visit. If their glucose is less than 70, treat for hypoglycemia and reschedule the follow-up visit. If their glucose is greater than 350, the patient will need to test their ketones. Patients may use the ketone kits provided by the study at the September 2010 training session (patients must test using the ketone kit; RCs cannot do the testing). If a ketone kit is unavailable, refer to a physician and reschedule the follow-up visit.

If the patient forgot their glucose meter, glucose testing may done in the diabetes clinic (if nearby, convenient, and possible). If this is not possible, reschedule the appointment at the patient/parents next available convenient time and ask them to return with both the glucose meter & the ketone kit.

What if the patient no-shows their Follow-up?

Contact the patient and parent immediately to reschedule the visit ASAP. Remind the patient of the study and the need for the follow-up visit.

Remember that the follow-up visit is very important to the study and do your best to get them in; do you need to relocate the visit? Do you need to provide better directions? Is parking a problem? Try to do whatever is possible and appropriate to ensure that the patient completes the follow-up visit.

Try to get at least the Follow-up Status & History section of the worksheet answered via telephone.

If it's already outside the 4 month since ED visit window, do your best to schedule your visit as soon as possible. This follow-up data will still be used. If the patient cannot come in, try to get answers to the Follow-up Status & History section of the worksheet, at minimum. This will be a protocol violation (follow-up done outside the protocol timing); follow protocol deviation procedures (18.2). If, after every attempt, the patient still does not come to a follow-up visit, see 16.3 on page 195 for data that must be entered (History & Status section of the Follow Up worksheet).

16.4.4 What if the patient died before their follow-up visit (but after hospital discharge)?

Schedule the Follow-up event in OpenClinica. Answer just the Status & History questions (on the Follow-up worksheet). If cause of death is unknown, enter "unknown". No SAE Report needs to be created as AE/SAEs are only followed through discharge.

16.4.5 What if the patient is 18 years of age at the time of the follow up visit?

If the patient has turned 18 years of age since their ED visit, they are now of legal consenting age and must be consented as an adult to complete the follow up portion of the study. Use the Informed Consent document approved by your IRB for 18 and over patients. See 10.3 on page 106 for more information on informed consent.

A parent must still complete the CBCL for these patients. Please ensure that a parent comes with them to do so.

16.4.6 Compensation: $50 for coming to the follow-up

The study budget allows for compensation of $60 per patient. $10 should be given for the inpatient portion of the study, $50 for showing up to the follow-up. Note: the follow-up visit does not need to be fully completed for the patient to receive the $50. Distribution of the compensation money should follow site policy and procedures. IRBs should be aware of this and the compensation amount should appear in all consent documents, as required by your institution. If the patient completes a partial follow-up and is rescheduled for a whole new visit, they still should only receive $50 for follow-up. If a patient fails the follow up screening and reschedules the visit, they still get $50 for the follow-up (not $50 per visit).

16.4.7 OpenClinica Data Entry: Follow-up History and Status, Follow-up Visit History

All patients must have the 3-Month Follow-up Event scheduled in OpenClinica. On the 3-Month Follow-up Status & History eCRF, Status tab, enter the information from the History & Status section, including the patient's vital status at the time of follow-up. For 'Was a patient history obtained at 3 months?' answer "yes" if the parent/patient answered any of the History questions. If you were not able to obtain any History data, enter "no" and provide a detailed explanation. Answer 'Did patient complete in-person 3-Month Follow-up visit?' as "yes", indicating a follow-up visit was done if any portion of the neurocognitive testing was started. If no part of the neurocognitive testing was done, answer "no" and then choose one of the reasons from the pull-down menu. If patient is categorized as 'Lost to Follow-up', you will provide a detailed explanation.

On the 3-Month Follow-up Event, Status & History eCRF, History tab enter the data from the Follow Up Status & History section of the worksheet. For the date of the History was obtained, use the date of the follow-up visit in most cases. If calls or multiple calls or visits were done, use the last phone call or visit. (Note: History should NOT be updated if the patient re-enrolls or after the neurocognitive visit is done. If you have questions on timing and updating History, please contact the CDMCC.) If the patient was seen since discharge for medical care outside of regular diabetes care, enter all dates and reasons for visits. Once medical records from those visits are reviewed by the PI and the RC, enter the responses thrombosis, as appropriate. If the patient did die and the cause of death is unknown, enter "unknown".

On the 3-Month Follow-up Event, Follow Up Visit eCRF, Screening tab

enter the data from the Follow Up Visit History and Screening sections of the worksheet with the patient's age at the visit and glucose result. For the date of the visit, use the date of the follow-up visit in most cases. If more visits were done, use the last visit. If the patient was seen since discharge for medical care outside of regular diabetes care, once medical records from those visits are reviewed by the PI and the RC, enter the responses severe hypoglycemia and additional DKA, as appropriate.

16.5 Neurocognitive Tests and Tips

There are four tests to be done at the follow-up visit:

1. Digit Span Recall Test
2. CBCL by parents
3. Memory span test
4. WASI or WPPSI (IQ tests)

16.5.1 Tips for testing

When performing the neurocognitive follow-up tests, here are a few tips to keep in mind.

- Make eye contact and be enthusiastic!
- Pay attention to where patient is sitting. For the IQ testing, the patient should sit across the table from you so all materials are shown correctly. For memory testing, ensure the patient can see the computer screen.
- Spinning or swivel chairs will likely be too distracting. Pick a stationary chair where the patient can allow their feet to touch the floor. Place a heavy box in from of the chair, for example, so the patient can comfortably rest their feet as if they were touching the floor. This should help with wiggling.
- Provide reinforcement, acknowledgment and clarification of answers but try not to praise right answers.
- Be "kind but firm" when you are encouraging the child to continue with the testing; friendly and professional

- Provide break activities, if possible: some examples include games, potty breaks, books, but nothing too energetic or thoughtful
- Remain blinded to the study arm that the patient received; don't go back and look up the patient's fluid treatment assignment
- If unsure, prompt patient with "Tell me more". Don't read into any answers. Don't answer for the patient!
- All timed tests should be recorded in seconds, if possible. Whatever unit of time is used (mm:ss or ss), be consistent.
- If at all possible do not break between the WASI subtests. Its recommended to put a break between the main tests (i.e. between the Memory Task and the WASI). This will allow you time to get things setup, the child to relax a little and spend time with his/her family. Should a break be needed in the middle for some reason, its recommended that it come between the block design and similarities. The break between the memory task and WASI shouldnt exceed 15 minutes; breaks between subtests in the WASI should not exceed 5 minutes if possible. With older individuals the best thing you can do is get the session moving and keep it rolling. Too much down time and you will lose their attention.

16.5.2 Digit Span Recall Test

Perform one forward and one backward Digit Span Recall Test. Use the next Digit Span Recall test in the patient's packet. For example, if the last Digit Span Recall Test that the patient completed while hospitalized for their DKA episode were pages 6 and 7, use pages 8 and 9 for the follow-up Digit Span Recall Test. For more information see 12.3 on page 136.

16.5.3 CBCL

After all the questions for parents have been asked, ask the parent to complete a CBCL regarding the patient's behavior since their hospital discharge. This will be the second CBCL completed for this patient; one at the ED visit and one now at the follow-up visit. If patient is 18 years of age or emancipated and no guardian is present at follow up, CBCL is not required. For more information see 13.8.3 on page 164.

Once the parent completes the CBCL, review their answers. Ask for clarity on any questions where handwriting is illegible, there is no answer,

or two answers have been selected. Use GCP to indicate the correct answer or a Note-to-File, as needed.

Upload the completed CBCL from the follow-up visit to OpenClinica on the Follow-up event, CBCL tab. Please remember to completely de-identify the CBCL (the patient's name, date of birth, and parent name). Also clearly label the CBCL with the study subject ID and "Follow up". Name the upload "Follow up CBCL xxxxxx" (xxxxxx = study subject ID).

16.5.4 Memory Span Test

Perform the age-appropriate memory test with patient using the study-provided laptop and software. The memory test requires children to memorize drawings appearing on the screen surrounded by different color frames (color task) or at different location (spatial test), using the study laptop. The length of the memory test will vary with the patient's age. This test measures both item-color and item-space all within one script. Each part of the memory test consists of a section showing the patient items (encoding), a break interval (5 minute break), followed by the patient's recall of the items (retrieval). This happens for both color and space related tasks.

Memory tests vary based on condition (1 or 2) and version (A or B). Conditions vary with each patient. Two versions have been provided in case something catastrophic happens (e.g. the computer malfunctions and turns off) and the testing needs to begin again. These are automatically assigned for you by the study laptop when you begin a session. You will only need to reference these in case of a need to manually start the software.

To allow for re-testing of the same child in case of interruption of the memory test when the child has already viewed some drawings, two versions of the tasks were created (version A and B), which use different sets of drawings. To ensure that our findings hold across drawings, each version is further differentiated into two conditions (Condition 1 and 2). For example, Condition 1 and Condition 2 of Version A use the same drawings in the retrieval test, but what changes is what half of those drawings was actually viewed during encoding. Thus, if a child needs to be tested again, the person administering the test will need to use a different version of the task, NOT a different condition.

While administering the Memory Span test, notes about the patient or session can go on the Memory Span worksheet printed from eRoom^{TM}, found here: https://www.nedarcssl.org/eRoom/NDDP/StudyDiabeticKetoacidosis/0_6120f. Handwritten notes are ok; please write clearly. Please make sure you've used the correct Memory Span worksheet (age, condition and ver-

sion).

Once completed, find the patient's file and upload it to Follow-up Event in OpenClinica. The data file can be found here on your study laptop:

1. double click the "Data" icon on the study laptop desktop (C:\DKAconditionChoose\dka\Dat
2. find the patient file folder,
3. open the patient file folder. The primary data file we want is the *patient id.csv* file. This file is a study source document.

Upload the Memory Task worksheet with any handwritten notes addressing any issues encountered during the testing session. Attach a note-to-file to the worksheet upload and your patient study file, if needed, to explain a particular situation. Please use the Memory Span paper notes to record only issues that need to be corrected on the computer files. So, please record *only* mis-keyed answers or if the patient changes their mind after the answer has been entered into the computer. When in doubt, please include a note on the paper form. Please include clear, concise, and complete notes, if needed. But, every single answer the patient gives does not need to be included. Review your notes immediately following the neurocognitive testing session to clarify anything while it is fresh in your mind.

What if the patient is color blind?

Please note this on the Memory Span worksheet but conduct all tests possible.

Scoring of Memory Span Testing

After follow-up testing is uploaded to OpenClinica, it will be reviewed by the CDMCC to ensure completion, correct de-identification, placement of Study Subject IDs, and any other readability issues. Uploaded memory span scores will be scored by the neurocognitive team at UC Davis and stored at the CDMCC in the study data warehouse. Scores will not be available to sites.

Using the study laptop for memory testing

Your study laptop has been set up to make administration of the memory tests as easy as possible. Do not change the username on your laptop; the assigned username is necessary for the memory testing software.

Steps to starting a testing session:

1. Login. No password is needed.
2. Ensure the internet connection is turned off.
3. All tests are icons on the desktop. Double click the age-appropriate test to begin a testing session.
4. Enter the patient's OpenClinica Study Subject ID. Check it. Click ok.
5. Note the assigned Condition and Version number in use. Use the correct Memory Task Worksheet for your session notes.
6. Follow the instructions on the screen for completing the testing session.

If you have difficulty with the study laptop, please contact the CDMCC who will follow up with UC Davis, if needed.

Please keep your study laptop in a locked study cabinet. The study laptop should be used only for FLUID memory test administration. No patient identifying information should be stored on the laptop. No other study materials should be stored on the laptop.

Tips to prevent laptop failure

The neurocognitive team has recently reviewed a couple of the laptops that have been sent to UC Davis due to some kind of technical issue. The following are recommended:

- When there's an interruption during the first task or the 20 min break between the two memory tasks, you're asked to enter a subject ID that is different than the original ID. Please do this!! Otherwise the system will overwrite the original file if it has the same name and only a partial file will be created.
- Use the Esc key when stopping a task for any reason. Using Ctrl+Alt+delete or closing the laptop lid will not allow the file to be written.
- Turn off sleep mode and any power saving features or screen savers. These can lead to the laptop crashing during the evaluation.
- Some sites have experienced the laptop having issues when it gets too hot. Switching the power cord was found to be and easy solution to this problem.

What if the computer crashes?

If something catastrophic happens (e.g. computer crash), you may need to restart the session manually. You may need to use the same version and condition or a different version of the test depending on when during the test the problem occurred.

Please keep detailed notes of when in the testing this happened. There is a flowsheet found here A.25 in the Appendix that can help you keep track of what happened when.

If the patient has encoded some of the drawings when the computer crashes, or has seems some or all of the drawing but is no longer interested in participating and wants to reschedule to another time, then you will need to follow the instructions below and enter a DIFFERENT VERSION (B if originally A and A if originally B) of the test, and you will enter the same Condition .

If you started the retrieval phase and the computer crashes, if you are at least 50% through the color retrieval test, you may stop there and manually enter the same VERSION and the same CONDITION for the spatial task only. If you are at least 50% through the space retrieval test, you may stop there and continue with IQ testing. If something happens during the interval between Color encoding and retrieval, you can manually open up the task and enter the SAME version and SAME Condition, advance (out of the child's view) to the end of encoding phase and continue the retrieval phase. If something happens during the interval between Spatial encoding and retrieval, you can manually open up the task starting from space only and enter the SAME version and Condition, then you will advance (out of the child's view) to the end of encoding phase and continue the retrieval phase.

NOTE: You should almost never need to do this! If you feel you should do this process but aren't certain, please contact the CDMCC for clarification.

To start a test manually:

1. Double click the "Manually Enter Test Setting" icon on the study desktop

2. Enter the patient's OpenClinica Study Subject ID. Check it. Click ok.

3. Enter the year number age of the patient (e.g. "7"). Check it. Click ok.

4. Enter the SAME CONDITION that the patient was previously assigned (that you documented on your Memory Task worksheet. (either "1" or "2") Check it. Click ok.

5. Enter the VERSION LETTER, either "A" or "B" (must be capitalized) as described above. Check it. Click ok.

6. You may need to run just the last memory test section, the spatial section. If the patient made it completely through the color test before the interruptions, you can complete just the spatial version manually. To do this, click "No". If the patient still needs to complete both the color and the spatial test, click "Yes" to both. If the patient started the spatial test but completed the color test, they need to complete just the spatial test only.

Once you've completed the testing session, contact the DCC for data entry of the notes and csv files. This process will create two csv files for this one testing session (when done correctly). The DCC will open a JIRA ticket for you to upload both files, the files will be combined at Davis into one file, the one file will be returned to you via the JIRA ticket for uploading into OpenClinica. You will also be asked up upload a complete NTF, indicating the exact moment the computer crashed and any ideas you may have about what happened to both the JIRA and OpenClinica. You are welcome to include the diagram found here: A.25 as part of your NTF.

16.5.5 WASI or WPPSI (IQ testing)

Perform the age-appropriate IQ test (WASI for ages 6 and up; WPPSI for 3 through 5 year olds). This test uses the WASI/WPPSI manual, color blocks, puzzle, Record forms. For detailed instructions of each test, see the test-specific materials and instruction manuals. Once completed, scan the complete record form into OpenClinica (de-identified and with the OpenClinica Study Subject ID included on each page). Any issues noted during the testing session should be written on the Record Forms. Attach a note-to-file, if needed, to explain a particular situation.

DETAILED INSTRUCTIONS INCLUDING THE ACTUAL SCRIPT AND WORDS YOU SHOULD READ ARE IN THE TEST MANUAL.

Steps for administering the IQ tests are:

1. Read the instruction out loud from the manual

2. Read the text next to the testing item for the age of the patient

3. Write the patient's answer in the Record From while the patient is speaking (please write clearly!)

4. After the answer is recorded, score the answer based on the manual

Scoring is done on the age-appropriate paper Record Form (given to sites at the September 2010 training and found in eRoom^{TM} here: https://www.nedarcssl.org/eRoom/NDDP/StudyDiabeticKetoacidosis/0_611c1). Each item has particular scoring details found in the manual. Tests have starting and stopping points, as indicated in the manuals.

If an answer the patient gives has a "Q" next to it in the manual, it requires further explanation. Ask the patient "Tell me more" and record that response after a written "Q" on the Record Form.

Rules for Reversal are also indicated in the manuals. These rules are used if a patient gets a score of 0 (incorrect). In this case, where indicated in the manual, you should ask the patient preceding test items in reverse order until two consecutive perfect scores are obtained. See manuals for details and more information.

The scripts are standardized such that they should give the best chance of success for the participant to understand the task. You have to build a cold heart to administer this test correctly at times. Many of the children will fail at a some of the tasks in the WASI/WPPSI, that is simply the reality of the test. This is why it is so important to build the rapport before and during the testing session. Using the down time between the end of one subtest and the beginning of another is a great time to recapture any ground lost during the test. In general, do not deviate from the script in the manuals. They are your best resources.

What's the difference between the WASI and the WPPSI?

The WASI is used for patients age 6 and up *at the time of their follow-up visit* and the WPPSI is used for patients ages 3 through 5 *at the time of their follow-up*. (For more information on age at follow-up, see 16.2.1.) Each test has its own Record Form; please ensure you use the correct Record Form for the correct test (WASI's is purple, WPPSI's is red.) Here's a summary of the main differences between the two tests:

Table 16.1: Differences Between WASI and WPPSI IQ Tests

WASI	WPPSI
Age 6 and up	Age 3 through 5
Vocabulary, Block Design, Similarities, Matrix Reasoning	Receptive Vocabulary, Block Design, Information, Object Assembly, Picture Naming
Need manual, WASI stimulus book and blocks	Need manual, WPPSI stimulus book, blocks, puzzle pieces
Stimulus book is larger, red	Stimulus book is smaller, purple
9 red and white blocks in a grey labeled box	4 red and white blocks, 4 white blocks, 6 red blocks in a red labeled box
	Large white Object Assembly box with puzzle pieces
Age specific stopping points	NO stopping points
Block design uses 2D pattern reproduction, has instruction of *I am going to put these blocks together to make a design. Watch me.* And, block rotation of 30 degrees or more is a fail	Block design uses 3D block models, has instructions that are step-by-step and no degree or rotation is penalized
No querying during the picture portion subtest	Querying during the picture portion subtest ok

Scoring of IQ Tests

After follow-up testing is uploaded to OpenClinica, it will be reviewed by the CDMCC to ensure completion, correct de-identification, placement of Study Subject IDs, and any other readability issues. Then, they will be scored by neurocognitive specialists at UC Davis. Once scores are completed by the specialists, the scores will be added into OpenClinica, though unavailable to sites. If a parent asks for the IQ score, explain that these are shortened tests that require neurocognitive specialists to score. Parents will be alerted in the case of a particularly low score and encouraged to seek additional testing.

Low IQ Scores

If a patient scores below 85 on the WASI or WPPSI, sites will be notified via the query system to alert the parents. You should send the parents a letter suggesting they get additional testing. A sample letter can be found here A.24. Please note: low scores on study tests may not indicate a low IQ. These are shortened tests for our study outcome that have not been administered by trained neuropsychologists. A low score on our tests may indicate no issues for the patient; however, parents should seek additional testing, if they choose.

Common Mistakes

- Forgetting introduction script at the start of the WASI
- Paraphrasing or dropping of essential words when recording verbal responses. Do not paraphrase a participant's response. The only acceptable changes to what is written include dropping of words such as: something, someone, a, who, that, etc. Never drop a word that would cause the meaning of the sentence to change. When in doubt, write everything.
- Starting timing after participant has started a trial. It is essential to start timing as soon as you give the last word of a prompt. This should coincide to the time when a participant starts a trial. (see next item)
- Assuming participant will wait for the RC to be ready before beginning a trial. Never assume that a participant will wait for you to finish a script. Maintain control of all materials until you are ready for the participant to begin a trial. In the block design this can equate to

holding onto the blocks until you have finished the script or preparing the blocks and turning the page to the next trial as you are administering the script. The preferred method would be to maintain control of the blocks, but both are acceptable solutions.

- Stumbling over common scripts. We can't stress practicing the scripts enough. The more you practice them, the easier they will come and the easier it will be for you to keep the test moving smoothly.

- Straying from scripts or omitting sections. Read all scripts verbatim. The most common script errors so far:

  - Omitted: WPPSI- Word Reasoning: "let's try another one" between each item.
  - Omitted: WASI - Introduction
  - Off script: WPPSI - Queries given were not among the allowed queries:
    * Can you tell me more?
    * Explain what you mean?
    * Test and item specific queries as described in the manual.
  - Take your time reading through the scripts. Highlighting scripts and tabbing the manual for commonly pages can help prevent these problems.

- Problems maintaining neutrality. The most common break of neutrality that has been seen during assessments and live testing is to laugh at a participant either due the type of response or being caught off guard at a participant that answers before an item has been fully administered. There is no end to the variability in responses you will get to the test questions. Do your best to not react as you may inadvertently cause a participant to withdraw and lose valuable rapport with them.

- Asking questions like

  - Are you ready for the next part?
  - Are you having fun?
  - These are great games, aren't they?

The honest answer for most children would be NO-so let's avoid putting yourself in the awkward position of giving unnecessary tough loveIf you feel the need to say something to push to the next test use lines like:

  - Let's go on to the next one!
  - Now let's play a different game!

- Determining if an item has greater than or less than a 30 degree rotation during block design. The manual's state that a rotation error is a *pronounced* rotation of 30 degrees or more. It is hard to tell if an item is rotated 25 degrees or 35 degrees unless you spend hours with a protractor. If it looks borderline to you give the participant the benefit of the doubt and assume that it is not over 30 degrees.

- Maintaining a good pace throughout the entire test. It is important to keep the test moving. If you notice a participant is squirming in their chair or starts to drum their fingers on the desk, these are clear signs the test may be taking too long. Most verbal sections allow for a maximum of 30 seconds per item. For timed sections, don't allow more than 1 minute of extra time for a participant to complete a construction, even if they are still working hard. This can cause the time for completion of the test to go out of control and cause the overall test to take far longer than it should.

- The only time a query would move a point value down, is if it directly violates the main principle being described. An example would be in the WPPSI asking: What is a leaf? (A) Part of a tree (1 point plus Q) the part that goes into the ground. This would be scored zero points as the response from the query shows a complete lack of understanding of the concept leaf. If the reply to the query simply adds nothing to the original answer, then the point value remains the same.

- For all WASI block designs, please remember to record all designs in the incorrect design column regardless of whether the design was constructed correctly or incorrectly. This will help the Davis team to grade the forms more accurately.

Marking your WASI and WPPSI for easier use

During test administration having important pages marked and having scripts highlighted can make it easier to administer the WPPSI and WASI. The

WPPSI already has its main sections tabbed for your convenience. However, to help guide you through marking the WASI and WPPSI for easy administration, we have prepared a standardized method of marking the testing booklets. Highlight the introduction scripts for each section as well as item prompts The WASI is already color coded to help differentiate scripts from instruction text. However, highlighting these pieces may make finding the scripts slightly easier. Highlight responses which require queries in a different color.

WASI

Tab the age specific start points:

- General testing guidelines, Page 35
- Introduction, Page 53
- Vocabulary, Page 58, Item 5 (6-8 year old start point); Page 60, Item 9 (9-89 year old start point)
- Block Design, Page 90 Design 1 (6-8 year old start point); Page 92, Design 3 (9-89 year old start point)
- Similarities, Page 100 Item 1 (6-8 year old start point); Page 102, Item 5 (9-11 year old start point); Page 103 Item 7 (12-89 year old start point)
- Matrix Reasoning, Page 120 Section introduction and general start point

WPPSI

Tab Start points:

- Block Design Page 63 Part A Item 6 (4/5 year old start point)
- Information Page 72 Item 11 (4/5 year old start point)
- Matrix Reasoning Page 82 Sample A
- Vocabulary Page 91 Item 6 (4/5 year old start point)
- Picture Concepts Page 108 Sample A
- Word Reasoning Page 118 Sample A
- Coding Page 125 Introduction Script

- Block Design (3 year old) Page 181 Part A Item 1
- Information (3 year old) Page 190 Item 1
- Object Assembly Page 205 Item 1

16.5.6 What if a patient doesn't complete the neurocognitive testing?

Complete the Follow-up worksheet with as much information as possible. If the patient got more than halfway through the memory testing materials, consider the visit complete. However, the IQ testing still needs to be completed so if that has not been fully completed, the patient will need to be rescheduled for a second visit to complete the IQ portion of the visit. The IQ testing needs to be fully completed at one time, so either at the first visit or completely at a rescheduled second visit. If the patient got less than halfway through the testing materials, try to reschedule the patient for a re-visit (all materials will need to be re-completed at the second visit; the patient must start over).

Update OpenClinica testing portions once the patient has completed all testing materials. If the patient returns for a second visit, complete the follow-up event with the complete data after the second visit (including completed testing from the first visit, if applicable).

Uploaded notes

If there are not any notes associated with neurocognitive tests a blank page should be uploaded that states there were no notes associated with test. This helps to clarify if there were truly not any notes or if they were forgotten. Additionally, If patient does not complete neurocognitive testing, a NTF should be written and kept in patient binder. The NTF should be uploaded in place of testing not done. Additionally, if there is anything unusual or different that occurs during testing please include it in a NTF and upload it with the other testing notes.

16.5.7 What if a patient changes their mind on an answer?

If it's during the Memory Span testing, make a note on the Memory Test worksheet. If it's during the IQ (WASI/WPPSI) testing, make a note on the Record Form. Continue testing.

16.5.8 OpenClinica Data Entry: Neurocognitive Tests

On the 3-Month Follow-up Event, 3-Month Follow-up Visit eCRF enter all data and uploads from the follow-up visit. Enter the follow-up screening data on the Screening tab (follow up visit date, age of patient, and glucose level).

On the 3-Month Follow-up Event, 3-Month Follow-up Visit eCRF, enter the Digit Span forward and backward scores on the Digit Span tab. Enter Memory span data on the Memory tab, IQ testing on the WASI/WPPSI tab, the CBCL on the CBCL tab. If any of these tests were not completed, please provide as detailed as answer to "why not?" as possible. Uploads required at follow up are:

1. Memory span csv file to Memory Span tab
2. Memory span notes file to Memory Span tab
3. IQ Testing WASI or WPPSI scoring document to WASI/WPPSI tab
4. CBCL survey to CBCL tab

Prior to uploading any test to OpenClinica, review the electronic file to ensure that it has been properly de-identified by checking the following:

- OpenClinica ID appears on all pages
- Patients Name, Age, Ethnic Group/Race, DOB, Date of form, patients parents name and grade have been removed. De-identification does not apply to the computer generated .csv file output from the Memory Span tests.
- Review all handwriting to ensure it is clear and all forms have been correctly completed.
- The CBCL done during inpatient is labeled "CBCL #1" and is uploaded to Caregiver Information eCRF; the CBCL at follow-up "CBCL #2" and is uploaded to 3-Month Follow-up Visit eCRF

16.6 Video assessments of neurocognitive testing administration

Throughout the study, neurocognitive testing procedures will be re-evaluated at intervals during the trial to insure that each site continues to conduct

these procedures according to standardized methods. For quality purposes and when feasible, each Clinical Center investigator and/or research coordinator responsible for neurocognitive testing will be videotaped conducting the tests and the video tape will be reviewed by the collaborating neuropsychologist, Dr. Ghetti. Any deviations from the correct testing procedures will be reviewed with the individual conducting the tests and corrected. This same monitoring procedure will be followed later in the study, in the event of change in personnel requiring retraining.

Once a video session is requested, information about the process logistics can be found in eRooms. All RCs who are responsible for conducting the neurocognitive testing will be required to provide a recorded session before they are able to conduct the neurocognitive exam on real participants. In addition to the prior to first study participant video, you will be asked at different points throughout the study to provide on-going video sessions as well.

Prior to first study participant:

Prior to conducting the first session with a study participant, each person will need to send a video of a practice neurocognitive session to the neurocognitive team. This first practice video session should take place as soon as possible. The first session must be reviewed and approved by the neurocognitive team before an RC is able to administer the testing for a real study participant. Thus, this first session must be done on a willing volunteer, preferably a child. It is recommended that you DO NOT use your own child for this, as it might be difficult to conduct the session in a serious manner. If however, you are unable to find a willing volunteer CHILD participant, an adult volunteer would suffice. (NOTE: Make sure that the volunteer participant has provided the necessary consent before any neurocogntive session is recorded. As these are not live participants, consents for the mock sessions can be filed in a safe place at your site.)

It is possible that, following review by the neurocognitive expert team, an RC may need to repeat the test session before conducting a study visit. Thus, the video should be completed as soon as possible (i.e. not two days before the first subjects scheduled visit). Before the trial video session, the RC should practice, practice, practice! If any questions arise during practice be sure to ask them prior to the video recording. The practice participant video version should be your best effort!

On-going monitoring:

On-going reviews will also occur at regular intervals during the study. Sites will be notified when a video session is required. The ongoing reviews will be conducted with willing study participants, and should be done in a way that minimizes patients exposure. This means that the focal point of the camera should be pointed at the RC and the activities, and NOT directly at the participant. It is very important that you follow your sites policy regarding video release documentation. You will likely need to have the child complete a standard consent form per your hospital policy. All video consents must be filed with the patients study file for safe record keeping. NOTE: The video portion of the follow-up visit should not interrupt the neurocognitive visit. The priority is to complete the testing and not the video recording. If needed, (i.e. technical difficulties, etc) proceed with the neurocognitive session testing, and capture the required video session for ongoing review on the next patient.

Simona will be providing some one-on-one technical review and support to help you improve your skills and make sure we are all performing the highest quality test administration possible. Simona will contact each RC administering neurocognitive tests. Shell want to talk with the RC, briefly, about how things are going, answer any questions, and find out when the next testing session is planned. She will then want to observe the testing session, remotely. This will involve:

1. Talking with Simona prior to a visit. She will contact you for this brief (5-10 minute call).

2. Obtaining Consent/Assent from the patient/parent following your sites requirements. You should have worked this out with your IRB already. Some of you may have included this in the study consent/assent documents. Some of you need to find the additional documents that need to be completed. Work this out and refresh your memory on this process for you site now!

3. Alerting Simona to a scheduled date and time for the session.

4. Arranging for Simona to Skype in for the session. Set up an additional computer in the testing room, angle the camera at the table, check to make sure the volume works. Skype Simona prior to the testing session. Then ignore the computer as you complete the testing session. Simona will simply be an observer. If Skype wont work for your site, please let us know as soon as possible. Simona may be able to call in

on an open conference line and listen to the session. We do not need a video of these sessions, but if thats the only option, it is acceptable. Skype is the preferred method of observation.

5. Soon after the testing session, Simona will again contact the RC for a longer call (30 minutes or so) to discuss how the session went, any tips for future testing sessions, and again to answer any questions.

6. Simona will then send a brief email indicating completion of this activity to the DCC and the RC for study documentation of this process. Please view this as a helpful opportunity to hone your skills with Simona the expert!

Please note! This should not disrupt study flow or contribute to a reason for possibly losing a patient to follow-up. Schedule sessions at the patient/parents convenience. Simona will work with you to get this done during a session she is available for. If families do not want to be observed, conduct the session without Simona.

Methods of capturing the session:

There are various means by which this can be accomplished, and the video capturing process is intended to be fairly flexible as we recognize that sites vary in the availability of technological equipment. The neurocogntive follow up will last about 1-2 hours, so you will need to have a device that will at least hold 2 hours worth of video recording. Below are some options that are available for your site to explore:

1. Digital Files: any video recording device that can produce a digital video file. This can be a digital camcorder or alternative devices like the Flip, iPhone 4 (or 3GS), or a newer generation iPod touch. Most smart phones currently on the market will also provide this functionality. Please account for the length of time the device needs to record. The video quality can be minimal and DOES NOT have to be of HD quality. Upon the completion of the follow up session, the file will need to be downloaded and burned onto a DVD, and mailed to the neurocognitive team for evaluation.

2. VHS tapes: VHS analog recording is also an acceptable mean for you to capture video recording.

   All physical video formats must be mailed certified mail with the following requirements:

(a) tracking number and

(b) proof of delivery via signature.

This will ensure that the tapes arrive at the intended location.

Once the video is sent, it is very important that RC you provide the following information to the study CDMCC Project Manager:

(a) Certified mail tracking number

(b) Date that the package was sent to neurocognitive team

All videos can be addressed to: Attention: Dr. Simona Ghetti Center for Mind and Brain 202 Cousteau Place Davis, CA 95618

Once the neurocognitive team member reviews the video session for quality control, the videos will be stored in a safe and secure location for archiving.

3. Live Teleconference Monitoring: Live teleconference monitoring will allow for sites to provide live video feed of the neurocognitive follow-up tests to our neurocognitive study team.

   This can be accomplished by a web cam installed on a standard computer with an external microphone (if not already built into the computer or the webcam), and a third party host software such as Skype. Skype will allow you to make user to user video calling free of charge. Skype calls are encrypted with strong encryption algorithms ensuring upmost privacy for calls. Thus, Skype is a great alternative for video transmissions via internet. You can download the free software located here: http://www.skype.com/intl/en-us/features/allfeatures/video-call Once the free software has been installed on your computer, you will be asked to create a Skype ID and password. However, a Skype ID and password has already been created for each site. Your specific site ID and password can be found here: https://www.nedarcssl.org/eRoom/NDDP/StudyDiabeticKetoacidosis/0_62c37 Sign in according to the instructions provided by Skype. Note: It is not recommended that you use the study laptop for this purpose, as you will be utilizing the laptop to administer the memory test. Since this option is a live feed, appointments must be made with the neurocognitive team beforehand. Both neurocognitive study personnel and test administrator must be on simultaneously in order for video conferencing to begin. *Live teleconferencing Process:* RC will setup the neurocognitive follow-up appointment with the neurocognitive team. You

are able to set this up with either Clint Perry (csperry@ucdavis.edu) or Dr. Simona Ghetti (sghetti@ucdavis.edu). Once the appointment has been set please send the appointment details to the study PM Marci (Marci.Fjelstad@hsc.utah.edu) or Hai (Hai.Le@hsc.utah.edu). The following items should be included with all request:

(a) Date and Time of appointment (include the appropriate time zones)

(b) Site Skype ID

(c) Phone number this will be used to communicate directly with neurocognitive team if there are technical issues.

On the day of the appointment, RC and a member of the neurocognitive team will do an equipment and software check 20 minutes before the actual appointment start time to insure that everything is working appropriately. Skype sessions will be recorded by the neurocognitive expert team at Davis, so all applicable precaution to minimize participants exposure should be taken. This means that the focal point of the webcam should not be on the patient but instead directed at the activities related to the neurocognitive testing, and the RC who is administering the test. Again, please follow your sites policy regarding video and media release.

How to submit your recording materials to UCD: Formats that the UCD team can handle

1. General digital media

   (a) DVD/CD: Either as a playable disc or simply including the movie files

   (b) *.AVI

   (c) *.MPEG (1-4)

   (d) *.MOV

   (e) Any other video codec can be downloaded

   (f) Flash drives containing any of the above movie types

   (g) VHS tapes: This refers to standard size VHS tapes which can be played in any VCR without the need for an adapter. This does not include Mini-DV or other "mini" "digital" cassette. If your only recording device uses this type of media, please do us the

favor of exporting the video's on your side and burning them on to a CD.

2. Online Review
   (a) Skype
   (b) Gmail Video: The video and audio quality over this connection is relatively poor by comparison to Skype and should only be used if Skype is unavailable.
   (c) Other IM video chat: Depending on the IM software, we should be able to create a mock account and connect this way but only if Skype is unavailable.

Requirements to pass the video assessment

- Accurate reading of prompts and instructions
- Accurate recording of responses. Timing must be within 2 seconds of actual time. Verbal responses should be verbatim with allowed dropping of nonessential words. No words may be added. Word being dropped must not change the meaning of the sentence (e.g.: OK to drop something, anyone, and, the, who, etc.)
- Accurate application of age appropriate start and stop points
- Accurate application of discontinuation rules
- Accurate application of reversals
- Accurate application of Queries. No more than one missed query. No more than two excessive queries. Items that clearly do not need queries based on specific examples in the manual
- Use of appropriate materials. Correct forms used for correct tests. Appropriate stimuli presented for each trial.
- Test appropriate feedback. Feedback is neutral and is only as scripted in the testing manuals
- Maintenance of rapport. At least some attempt to maintain eye contact. Positive and engaging tone of voice used
- Testing room must be free of distractions. No excessive noise. No open windows in direct view of participant.

- Forms are easily legible
- Appropriate pace maintained throughout the tests. Non timed sections (around 30s per item), Timed sections (maximum of 2 minutes per item for 60s limits and maximum of 3 minutes for 120s limits). For digit span, the RC should maintain a standard pace throughout each trial and across trials, only very mild deviations in pace are acceptable.
- Accurate modeling of designs including scripts where appropriate

Follow-up sessions will only require RCs to repeat sub-tests which failed to meet passing criteria. If a general testing principle is violated, RCs may be required to complete the entire test. E.g. Failing to use correct start and stop points; inaccurate recording of responses, failure to apply a reversal, etc.

Chapter 17

Not Enrolled patients

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17.1 Patients who are not enrolled

In the FLUID study, there are several time points where patients may be excluded. These are referred to as "not enrolled" patients. Basic data for most of these patients are still requested in the protocol. Site IRBs may or may not have approved all these categories of data collection. Refer to your Site Specific Workflow for details about your site.

The categories of these patients are:

(a) Patients who meet inclusion criteria, but are excluded based on an exclusion criterion

(b) Patients who are eligible, but are not approached for the study

- This could happen because the treating physician does not want to enroll the patient, PI/RC study staff resources are scarce, or any other reason that the patient was known to be eligible but not approached
- This could also happen if it was impossible to consent/randomize the patient in 2 hours of maintenance IV fluid therapy or 4 hours of DKA therapy or both. This includes patients who were eligible,

but for whatever reason, were not recognized as eligible or screened at the time of the ED visit. For example, the patient presented at 3 AM and ED staff forgot about the study, so the patient was never considered for the study.

(c) Patients who are eligible, but whose parents refuse permission

(d) Patients who are eligible, for whom consent is obtained, but were not randomized

See the Pre-Enrollment Patient Flow Tree diagram for details, A.34 on page 345.

All these types of patients should be entered into OpenClinica with Demographics completed (see A.7).

All patients who are eligible but not enrolled should also have the Not Enrolled worksheet completed and data collected about diagnosis of diabetes, glucose, BUN, and pH during ED evaluation. These data should be the first tests done at your hospital (not an outside, transferring hospital). Therefore, this applies to groups B-D above; sites may or may not have IRB-approval for all three of these groups. Check your IRB-approval and your Site Specific Workflow for details.

Patients who are eligible, consented, but not randomized should also have the Randomization section of the Screening & Enrollment worksheet completed (see 10.4).

Sites should include their process for finding all four of these types of patients in their Site Specific Workflow. However, at a minimum, RC/PI should determine a set weekly schedule to review eligible patients and strategize about ways to limit the numbers of missed patients for the future. RC(s) should review ED logs for patients who came in to ED, who were diagnosed with DKA, and who were not approached for enrollment screening. Please note that logs should be reviewed for DKA diagnosis. There is no need to review medical records for every patient with diabetes who is evaluated in the ED; they should be there for DKA as their primary concern (e.g. no need to include a patient with diabetes who was in a car accident unless DKA was diagnosed).

For patients who are eligible but not approached (group b), the difference between "Site investigator or coordinator resources inadequate" and "Impossible to consent/randomize patient within two hours of DKA" is probably going to be a little bit grey at times. The "impossible to consent/randomize" relates more to time and the "resources inadequate" relates more to what the site is able to accomplish. "Resources inadequate" is meant to include things like the site study staff know about the patient, but no one is able to

get to them or the study staff are already following too many patients on the study and just don't have the capacity for another. The "impossible to consent/randomize" should be more for the patients who are eligible as they present to the ED but the time limits run out before they can be enrolled.

17.1.1 OpenClinica Data Entry: Not Enrolled

Not Enrolled patients need three eCRFs complete:

1. Screening and Enrollment Event, Screening & Enrollment eCRF
2. Screening and Enrollment Event, Demographics eCRF
3. Unscheduled Event, Not Enrolled eCRF

No other additional data is needed for these patients, including the 3-Month Follow-up Visit Status & History eCRF.

On the Unscheduled Event, Not Enrolled eCRF, enter if the patient has new onset diabetes or not, the initial ED serum glucose in mg/dL, serum BUN in mg/dL, and pH. If these tests were not done, indicate "no" for not done. If the results were not documented, enter "Not documented." These data should be the first tests done at your hospital (not an outside, transferring hospital).

A GCS for all Not Enrolled patients is required to complete the Screening & Enrollment eCRF, ideally the GCS done at the time of the initial ED evaluation. If a GCS is not documented in the medical record, staff should attempt to follow up with treating clinical staff to see if one can be recalled. If not, the PI should review the medical record and attempt to assign a GCS. For example, if the patient was "alert and oriented" or similarly noted, a GCS of 15 can be assumed (for Not Enrolled patients only). The clinical staff's recollection or the PIs decision should be documented in the patient study file with a Note-to-File.

If a patient was eligible but not approached for consent (category B above, for any of the reason listed above), on the Screening and Enrollment Event, Screening & Enrollment eCRF, Eligibility tab, after the Inclusion and Exclusion criteria answers, indicate "yes" the patient is eligible. Please note: Inclusion and exclusion criteria should be evaluated based on the patient's condition at the time of ED presentation. On the Screening and Enrollment Event, Screening & Enrollment eCRF, Permission tab, answer "was the parent approached for consent" as "no" and select the reason why from the drop down list. If the treating physician believed a specific fluid or electrolyte regimen (including a plan for subcutaneous insulin) was warranted, select

"Treating physician believes a specific fluid & electrolyte regimen is warranted. If the site PI &/or RC are unavailable to assist with the patients enrollment, select "Site investigator or coordinator resources inadequate". If the patient was not considered for study enrollment at the time of their ED presentation, select "impossible to consent/randomize the patient in 2 hours of IV fluid or 4 hours of DKA therapy or both." Or, if the parent was not approached for any other reason, select "Other" and enter a detailed description. Complete Demographics and the Not Enrolled eCRF as above.

Sites that do not obtain IRB-approval for the waiver of consent for not enrolled patients and so do not have access to a date of birth for eligible patients not approached should alert the CDMCC and request an alternate plan.

Chapter 18

CAPA, OOPS, & NTF

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18.1 General

This chapter will discuss CAPA (Correction And Preventive Actions Plan), OOPS (Outside of Protocol Specifications), and NTF (Note to Files). This chapter will describe each one of these essential GCP tools and when to use which one.

18.2 What is an OOPS?

The protocol and the Manual of Operations are designed to guide clinicians and coordinators through the steps of the trial. Ideally, every step of the study is conducted according to the protocol, applicable regulations and IRB requirements to assure safety of the patient and integrity of the trial. However, errors, omissions, misinterpretations or protocol deviations will likely happen during the course of the study. It is important to report these problems and devise ways to correct them.

Protocol deviations/violations will be known in this study as activities that are Outside of Protocol Specifications (OOPS). If a clinician, research coordinator or other person becomes aware of something that deviated from the protocol or was an error or mistake at any point during the trial, it is required that you report these using an OOPS form. OOPS forms are available in the electronic database and are self explanatory.

18.2.1 What do I do if something goes wrong during the eligibility, consent, study procedures, or follow up portions of the study?

Examples of protocol deviations would be: enrolling a patient that was ineligible, administering the study fluid differently than is stated in the protocol, failing to take vital signs or lab procedures as specified, failing to consent/assent a patient or doing so incorrectly, completing a follow-up visit outside the follow-up period. Essentially anything that is done differently than the protocol states is, by definition, a protocol deviation/violation. If any of these things happens, complete an OOPS entry on the OOPS log and enter the OOPS into OpenClinica on the Unscheduled event, OOPS tab. Please be as clear, concise, and complete as possible in your descriptions of the event.

18.2.2 What if a decision was made to do something different from the protocol? Is this still a protocol deviation?

Yes. A clinician should always do what is best for the safety of the patient. If a clinician makes a decision to do something differently than the protocol specifies for safety reasons, this is a protocol deviation, but one that was necessary in the judgment of the physician. These should still be reported. This does not mean that anyone did anything wrong; it simply needs to be reported.

18.2.3 What if someone innocently forgets to get a set of vital signs or order a lab and it does not affect the patient in any way? Is this a protocol deviation?

Yes. Sometimes protocols can be difficult to follow or may found to be impractical or difficult as sites begin to enroll patients. Reporting these types of problems might generate the need for a protocol change, or for re-education among nurses, physicians or others in the study. Protocol deviations can also affect the data, and therefore it is important for us to be aware of how often they happen. Protocol deviations may need to be reported to your IRB. Check with your IRB to find out local requirements of reporting protocol deviations.

18.2.4 Is it a bad reflection on me or my site if we have protocol deviations?

Not necessarily. Obviously a site with poor performance needs to have re-training or other interventions. But protocol deviations are common in complicated trials. A report of a protocol deviation at one site will likely help avoid that same error at another site. It is better for a site to report OOPS than for a site monitor to find an unreported OOPS during a monitoring visit. Sites are responsible for reporting OOPS completely so that site monitors can determine that sites were aware the deviation occurred. Additional, reporting OOPS will help identify trends in the study that may need improvement or further training.

18.2.5 OpenClinica Data Entry: OOPS

Enter any and all OOPS into OpenClinica on the Unscheduled Event, OOPS eCRF. Please enter the date the OOPS was identified by study staff and the date the OOPS occurred. Please chose the study phase that is best

associated with when the OOPS occurred. Please be as clear, concise, and complete as possible in your descriptions of the event. A complete OOPs entry should include the what, when, how long and why of the deviation. If you need assistance completing this data, please contact the CDMCC. If you are unsure if you should enter a suspected OOPS, please enter it. All OOPS entries will be reviewed by the CDMCC and if it is not needed, you will be asked to remove it. CAPA and NTF do not need to be entered into OpenClinica.

18.3 What is a CAPA form?

A CAPA form is a way to document how an error will be avoided in the future. This form has become very important from a regulatory standpoint. While reporting a protocol deviation (OOPS) is helpful, setting up a system to avoid it in the future is even more important. A CAPA form documents what actions an individual or a site will take to avoid the mistake in the future. This avoids the situation of a site making an error repeatedly and simply reporting it as opposed to preventing re-occurrence. Errors in clinical trials can affect the study results, the safety of the patient, and can violate Federal regulations. For these reasons it is essential that a site take every precaution to avoid repeating errors.

CAPA forms can make a huge difference in assessing site performance in case of a federal agency or monitoring visit. For example, assume two sites had the same number of protocol deviations during the first year of the trial. Site A completed CAPA forms for each protocol deviation detailing how they will correct the problem and detailed ways to avoid each error in the future. This helps assure an auditor/monitor that the site has a sound quality assurance program. Site B has not documented anything and has made no obvious efforts to fix system problems that resulted in procedural errors. Even if site B actually did take steps to correct problems, the site investigator or coordinator failed to document these efforts. In FDA audits, Site B might receive a warning letter or be required to suspend enrollment until problems were fixed. Site A will likely fare better.

18.3.1 When do I fill out a CAPA form?

Almost any protocol deviation will generate the need for a CAPA form. On the CAPA form, the investigator or the coordinator should detail how the error happened and what actions were or will be taken to avoid the protocol deviation in the future. CAPAs do not need to be entered into OpenClinica.

18.4 What is a NTF?

A NTF (note to file) is simply a written note that describes any unusual situation or problem that happened during a trial. If you have already completed an OOPS form and a CAPA form, you do not likely need to complete a note to file. Notes to file have become replaced by OOPS and CAPA forms. In the event that something unusual happens that is not a protocol deviation, then a note to file would be the best way to document what happened so that a monitor or other person could understand it. For example, during a blood pressure monitoring after administration of the study fluid, a blood pressure machine went haywire and gave a reading of 240/100. The nurse on the floor immediately replaces the machine with one that functions. The next reading is 100/74 which seems correct. There is no protocol deviation here because the BP was taken at the right time. But there will be a piece of data that looks unusual. A note to file will simply explain why this one blood pressure value was outside the usual range. NTFs do not need to be entered into OpenClinica.

18.5 What is the difference between a protocol deviation (OOPS) form, a note to file and a CAPA form?

To summarize, a protocol deviation is a mistake or error in the way something was done and is in conflict with the MOO or the protocol or the site specific workflow. Protocol deviations are recorded in the database on the OOPS form. CAPA forms are used to indicate how an error or problem will be avoided in the future and should outline steps that will be taken to avoid or correct problems. CAPA forms should be completed and stored in your Essential Document Binder. A note-to -file is an explanation of something unusual or a situation that might be difficult to recall in the future. Note-to -files should also be retained in your Essential Document Binder.

Chapter 19

AE & SAE

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19.1 Adverse Events (AEs)

This section outlines the specifics of AE reporting for the FLUID study. For a summary of AE and SAE instructions, see A.12. For a diagram of this process, please see A.15 on page 317. If you are ever unsure about any adverse event reporting issue, please call the CDMCC for help.

19.1.1 What is an Adverse Event?

An adverse event (AE) is a new event, disease, sign, symptom, or worsening of pre-existing conditions that happens to a subject in the FLUID study. An event constitutes a disease, a set of related, signs or symptoms, or a single sign or symptom. The term adverse event encompasses all adverse events that occur in a patient during the time period of AE reporting outlined by the study protocol. Severe adverse events are a subset of adverse events and are described below.

An Adverse Event name should be entered as the symptom, not the effect. So, "respiratory arrest" should be the adverse event, not "intubation".

19.1.2 Who is responsible for reporting AEs?

Each Site Investigator has primary responsibility for the safety of the individual subjects under his or her care. All adverse events will be evaluated by the Site Investigator, and will be classified as noted in this section. All adverse events occurring after study randomization through hospital discharge will be recorded and entered into the electronic data entry system

provided by the CDMCC. Research coordinators may assist with this process and may complete AE forms under the supervision of their PI. Relatedness/Relationship of the AE to the study must be determined by the PI. If you have questions about this, contact CDMCC.

19.1.3 What are some examples of adverse events?

Onset of a rash, abdominal pain, irritability, a fall, a respiratory arrest, seizure, vomiting, would all be AE. An adverse event could also be a pre-existing symptom that worsened after randomization or during study treatment. For example, if the patient had a cough before they were randomized into the study, and the cough gets worse, this would be an adverse event. If pneumonia develops on a chest x-ray and it was absent at prior to randomization, it is an adverse event.

Pre-existing conditions that stay the same are not adverse events because they existed prior to the study start (randomization) and did not get worse during the study. For example, if a patient has a history of abnormal liver enzymes prior to randomization, and their first set of labs came back with abnormal liver enzymes similar to what they had before, this would NOT be an adverse event because it was pre-existing and did not worsen. However, if the patient had a history of asthma but was not wheezing on ED arrival, and then began wheezing after being randomized into the study, then this would be an adverse event because although the child had a history of asthma, the child was not wheezing on arrival. It could be that a study treatment aggravates asthma and we would want to know this.

An Adverse Event name should be entered as the symptom, not the effect. So, "respiratory arrest" should be the adverse event, not "intubation".

19.1.4 When do I start reporting adverse events?

Report (enter in to the database) any adverse event that happens after randomization. Randomization is the starting point for adverse event reporting. RC and PI should review the medical record and talk with floor staff on a daily basis to identify adverse events.

19.1.5 What does "prior to randomization" mean?

Prior to randomization refers to the time period that is reflected by the data on the Review of Medical Conditions and the Physical Exam (PE) form. These documents reflect the patient's condition prior to randomization. This form should be completed as close to randomization as possible. Forms

may be completed right after randomization, but should reflect the patient's status/condition prior to randomization. Any sign or symptom, disease or lab value that differs from what is documented on these forms is considered an adverse event.

The only exception to this is if a symptom or disease was missed on the Review of Medical Conditions or PE form and it is discovered that the patient did really have this history or condition before randomization. For example, the mother forgot to tell the doctor that the patient has a history of difficulty swallowing and has been seen by a doctor for it. After randomization, the child has difficulty swallowing his food. In this case, you would add this to the Previous Medical History form and make a note to file that this was added and why. In this case the difficulty swallowing would not be an adverse event.

After patient randomization, adverse events (including serious adverse events), whether expected or unexpected, related or not related, will be recorded in the AE log (A.13) according to the date and time of first occurrence, severity, and duration, as well as any treatment prescribed. Any medical condition present at the time of randomization, recorded in the patient's baseline history at study entry, which remains unchanged or improves, will not be recorded as an adverse event at subsequent evaluations. However, worsening of a medical condition that was present at the time of randomization will be considered a new adverse event and reported.

19.1.6 When do I stop reporting adverse events?

For the FLUID study, adverse events will be reported between randomization through hospital discharge. Specifically, events that occur following parental permission to participate in the study, but prior to actual randomization, will be not be reported as adverse events. These should be recorded as baseline conditions. Events that occur following discharge from the hospital will not be reported as adverse events. Adverse events will be followed until the resolution of the AE or hospital discharge, whichever is earlier. Adverse experiences (serious, related, or unexpected) that begin after discharge from the hospital will not be reported as study adverse events.

19.1.7 How do I find Adverse Events?

On each study day, the Site Investigators will determine if the subject has experienced any new adverse events or has had any events worsen or resolve. If the adverse event is new and has not previously been documented in the

study, you must record the AE on the adverse event record form. The nature of each experience, date and time (where appropriate) of onset, outcome, course, and relationship to treatment should be established and recorded. RCs may complete the adverse events form with supervision from the PI to assure that they are recognized and reported appropriately. Relatedness must always be completed by the PI.

What if a symptom is reported as an adverse event to me by the nurse, but it was already on the Review of Medical Conditions or Physical Exam Form?(Meaning that it existed before randomization occurred)

If a symptom existed prior to randomization and is listed on the Physical Exam or Review of Medical Conditions form, it is not an adverse event, unless it has worsened, or unless for some reason the PI feels it qualifies as an AE. Generally, symptoms or signs reported prior to randomization and recorded on the Review of Medical Conditions form or reported at the time of randomization on the Physical Exam form, are not adverse events because they were pre-existing.

19.2 Serious Adverse Events (SAEs)

The seriousness of clinical adverse events and laboratory abnormalities will be recorded by the site PI and categorized. The RC may determine this with oversight by the PI. A serious adverse event (SAE) is an adverse event that:

- Results in death; or
- is life-threatening (the patient was, in the view of the Site Investigator, in immediate danger of death from the event as it occurred); or
- requires inpatient hospitalization or prolongs an existing hospitalization; or
- results in persisten or significant disability or incapacity; or
- results in congenital anomaly/birth defect); or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

All serious adverse events must be reported to the data center within 24 hours of the study personnel becoming aware of the event. You may report the SAE to the CDMCC by phone or fax. A detailed report should be completed using the SAE reporting form and sent to the CDMCC within 72 hours by fax.

19.2.1 Does a Serious Adverse Event have to be related to the study treatment in order to be considered serious?

No, a serious adverse event is simply an adverse event that meets one of the 6 above conditions. The PI must then determine if the SAE was related or not using the definitions as described here 19.3 on the next page.

19.2.2 How soon do I need to report an SAE to the CDMCC?

Site Investigators and/or research coordinators will report every serious adverse event (SAE) to the CDMCC within 24 hours of discovery of the SAE. A detailed completed report will be required to be sent to the CDMCC within 72 hours of the event, and the medical monitor (at the CDMCC) will assess all serious adverse events (SAE) reported from sites. For each of these serious adverse events, the Site will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the trial. The medical monitor will sign each SAE report after review. All SAE reports will be retained at the CDMCC, and all SAE reports will be available for review by DSMB members and NICHD via the eRoom^{TM} facility.

DO NOT WAIT! You do not need to wait until 24 hours to report an SAE or 72 hours to complete the form. Report any SAE as soon as possible, but not later than 24 hours!

19.2.3 Follow-up of Serious, Unexpected and Related Adverse Events

All serious, unexpected and related adverse events, that are unresolved at the time of the patient's termination from the study or discharge from the hospital, will be followed by the Site Investigators until the events are:

- Resolved, subject is lost to follow-up, the adverse event is otherwise explained or has stabilized; OR
- 3 months has passed from the time of randomization.

19.3 Relatedness: How do you know if an adverse event is related to the study treatment?

This is an important part of SAE and AE reporting. The suspected relationship between study interventions and *any* adverse event will be determined by the Site Investigator using the following criteria. **Relatedness may not be assessed by a research coordinator, and must be assessed by the site PI.**

- *Not Related:* The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.
- *Possibly Related:* The event happened in a reasonable time sequence such that it could have been related to the assigned study intervention, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.
- *Probably Related:* The event happened in a reasonable time frame from the time of beginning the assigned study intervention, and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

19.4 Expectedness of the Event: How do I determine expectedness of events?

All adverse events, including serious adverse events, will be evaluated as to whether their occurrence was expected or unexpected. This is a very important determination. An unexpected adverse event requires specific action on the part of the CDMCC and the NIH. Please make this determination carefully. An adverse event is considered expected if it is known to be associated with:

- Diabetic ketoacidosis
- the underlying medical condition of the subject,
- is directly related to study outcome (e.g. cerebral edema, somnolence), or is otherwise mentioned in the protocol, informed consent, or other study documents.

For the FLUID protocol, **expected events** include:

- Death
- Thromboses (clots)
- Renal failure
- Cerebral edema (brain swelling)
- Cerebral infarction, cerebral thrombosis (stroke)
- Seizures
- Gastrointestinal necrosis
- Pancreatitis
- Hemolytic anemia (premature destruction of red cells)
- Cardiac arrhythmias (irregular EKG)
- Rhabdomyolysis (rapid breakdown of muscle tissue)
- Pulmonary edema (fluid in the lungs)
- Somnolence (sleepiness)
- Hyperchloremic acidosis (metabolic acidosis and increased chloride levels)

It is up to the investigator to determine if an adverse event is "expected" because it is known to present with diabetes or diabetes treatment, or if it is an event that is unexpected. This simply means that we know these diagnoses are already known to occur in patients with DKA and therefore we will categorize them as expected. Every AE or SAE will be categorized as expected or unexpected.

19.4.1 What is an unexpected SAE?

An unexpected SAE is one that is not listed above as expected. It can also be an event that the clinical investigator judges to be unexpected based on the patient's condition.

19.4.2 What if I find that an SAE is unexpected?

The Site Investigator will report all serious adverse events (SAE) to the CDMCC within 24 hours. A serious adverse event (SAE) that is also unexpected, and study-related should therefore, be reported to the CDMCC as soon as possible but within 24 hours. This type of SAE may have serious implications and should be reported as soon as possible. A detailed completed report will be required to be sent to the CDMCC within 72 hours of the event. After receipt of the complete report, the CDMCC will report such serious, unexpected, and study-related adverse events to the NICHD Program Official or Project Officer in an expedited manner (within 24 hours). In accordance with local IRB requirements, the Site Investigator may be required to report such events to their IRB in addition to notifying the CDMCC. Please consult the CDMCC about this if unsure.

In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and NICHD staff cannot be reached expeditiously, the CDMCC will notify the study investigators (Drs. Kuppermann and Glaser) and all Site Investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NICHD staff after discussion with the DSMB.

19.4.3 Can regular adverse events (not SAE) also be considered unexpected?

Yes, but an unexpected SAE is of greater concern in the study. For example, a rash would likely be an adverse event (if not present at randomization) and it might be unexpected, but if it is not considered serious by the definition listed here 19.2, it does not require reporting within 24 hours. These would be simply recorded in the AE Log and in OpenClinica.

If an adverse event is judged to be serious, unexpected and related to the study treatment, the CDMCC will take special action. See 19.4.2.

19.5 How do I record intensity?

The intensity is a clinical judgment and reflects how bad the event (sign, symptom, disease) was. If the patient complained of a headache, it is important to report on the AE form if it was a mild, moderate or severe headache.

19.6 How do I record the treatment or action taken for each AE?

For each adverse event, the Site RC, with assistance of the PI, will record whether an intervention was required for each AE:

- Intervention: Surgery or procedure
- Med initiation, change, or discontinuation
- Other: please describe
- None: No action taken

For example, if the patient had a cough as an AE, and the physicians observed but there was no treatment, then the answer would be "none". If the patient had a seizure and medications were given to stop the seizure, then the answer would be "Med initiation, change, or discontinuation".

If patient has multiple treatments for one AE, then add a row and enter all treatments under that AE. Identify this as the same AE and that multiple treatments were given.

19.7 How do I summarize the clinical outcome of each adverse event?

The Site RC, with the help of the PI, will record the clinical outcome of each adverse event as follows:

- Death
- Recovered and the patient returned to baseline status
- Recovered with permanent sequelae (harm)
- Symptom persist

19.8 What about abnormal laboratory values? Are they adverse events?

Abnormal laboratory values that are clinically significant and are not included in 2.7.2 should be recorded as adverse events. It is not necessary to

record abnormal laboratory results for the tests listed in 2.7.2 because all values for these labs are being collected on a daily basis and will be entered into the database. Since we are recording the values, we do not need to enter them into the Adverse Event log. However, if an abnormality of a lab value in 2.7.2 is considered to be serious by the Site Investigator, then it will be necessary for the site to record and report the event as an adverse event and as a serious adverse event (SAE). Remember, laboratory values that are abnormal at the time of randomization and that do not worsen will not be recorded as adverse events. Abnormal vitals considered clinically significant by the PI and not present at baseline should be included as an adverse event.

If the patient had an electrolyte change that was enough of a concern to cause a change in the patients treatment, then we DO want it included on the AE Log as an AE, even though it is a lab result. Rule of thumb: if it was bad enough to cause someone to change the patients treatment, off the study protocol arm, then it should be appear on the AE Log and the change should be documented as an OOPs.

19.8.1 What about abnormal lab values that are not listed on Table 2? Do I report these as AE?

Since DKA is associated with a large number of lab abnormalities, for purposes of this study, abnormal lab values not listed 2.7.2 will be recorded as adverse events when the severity grade is grade 2 or higher on the Common Terminology criteria for Adverse Events v3.0 (CTCAE) lab page located here 19.1.

Adverse events will be coded using the MedDRA coding vocabulary. Coding will be done centrally at the CDMCC because this requires specific training.

19.9 OpenClinica Data Entry and Reporting Procedures: AEs & SAEs

Non-serious adverse events (those that are not SAEs) are recorded in OpenClinica but do not need specific reporting to the CDMCC. Record the AE on the AE Log in the Patient Study File. Enter the AEs into OpenClinica on the Safety Data Event, AE Log eCRF. Include the date the AE started and the date the AE ended (if not on-going). Enter the relationship, action taken, outcome, expectedness, and intensity. Indicate if this AE is also an

SAE.

Serious Adverse Events (SAE) must be reported directly to the CDMCC within 24 hours of the site becoming aware of the event. This can be a brief phone call or email notification. You can also create a ticket in JIRA (www.jira.dcc.utah.edu) that notifies the CDMCC that an event has occurred. ***A full report of the SAE must be provided to the CDMCC within 72 hours of the site becoming aware of the event.*** Complete the SAE Reporting Form (A.14) and submit it to the CDMCC within 72 hours. This is separate from completing data entry into OpenClinica.

Once the SAE has been reported to the CDMCC and the full report submitted, enter the SAE data into OpenClinica on the Serious Adverse Event Event, Serious Adverse Event Reporting eCRF, completing both the SAEs and Labs and Narrative tabs. Enter as many SAE Reports as needed for each patient. Do not use the DCC only tab.

In general, when entering AEs, more detail is better than less but entries should be as concise as possible. The type of something is important and if you have a diagnosis that is preferred over a symptom. Enter what the lab result or sign or symptom mean rather than the result of the lab (ex. not "GCS >8" but "altered mental status"). One entry with one diagnosis, sign, or symptom should be made for each term. If you enter a sign or symptom and later get a diagnosis, update the AE entry with the diagnosis instead of the sign or symptom. Enter the most severe diagnosis given. We do not need "rule out" type of exams but do include the sign or symptom that lead to the exam. Procedures are not an AE, but whatever required the procedure to be done may be. Use medical terminology but not abbreviations. This log is reviewed completely separately from other patient data like the OOPS Log, so the AE Log should be standalone entries. Spelling, punctuation, and capitalization for a SAE and its corresponding AE Log entry should be identical. If patient has multiple treatments for one AE, then add a row and enter all treatments under that AE. Identify this as the same AE and that multiple treatments were given.

If the patient had no AEs or SAEs, no data entry needs to be done. Indicate the physicians review of the data in the patient study file (printed data, initialed or signed and dated indicated a completed review; a certified copy), but the eCRFs in OpenClinica do not need to be created and the Safety Data Event does not need to be scheduled.

19.10 What is an Unanticipated Problem (UP) and how is it different from an SAE?

An unanticipated problem is an incident, experience, or outcome that is unexpected, related to participation in the FLUID study, and suggests that the research places subjects at a greater risk of harm than was previously known or recognized. To qualify as an UP, the event must meet 3 criteria:

1. unexpected (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied;

2. related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Reference: http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm#Q1
Please consult the CDMCC if you feel you have an UP.

The Site Investigator will report unanticipated problems to the CDMCC within 24 hours. A detailed completed report will be required to be sent to the CDMCC within 3 working days of the event. After receipt of the complete report, the CDMCC, not the site, will report these unanticipated problems to the NICHD Program Official or Project Officer in an expedited manner (within 24 hours). In accordance with local IRB requirements, the Site Investigator may be required to report such unanticipated problems to the IRB in addition to notifying the CDMCC. In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and NICHD staff cannot be reached expeditiously, the CDMCC will notify the study investigators (Drs. Kuppermann and Glaser) and all Site Investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NICHD staff after discussion with the DSMB.

After notification of the NICHD Program Official or Project Officer, and the DSMB chairperson, *of serious, unexpected, and study-related adverse*

events or unanticipated problems (UP), decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made to suspend enrollment in the trial, this will be reported to the study investigators (Drs. Kuppermann and Glaser) and all clinical investigators, who will be instructed to report this to their local IRB.

METABOLIC/LABORATORY						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4] Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY						Page 2 of 3
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY						Page 3 of 3
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

Chapter 20

Patient Study Withdrawal

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20.1 General

Study withdrawal may occur if a parent or patient requests complete removal from the study. If a study withdrawal request is made, RCs should complete the Study Withdrawal worksheet, indicating the phase of the study the patient was in and the complete details leading to the withdrawal.

The patient should still be monitored for AE/SAEs, as per the protocol and your site's informed consent documents and IRB. All adverse events leading to withdrawal of study interventions must be fully documented and followed up as appropriate. This is particularly important when adverse events are ongoing at the time of withdrawal, but the reason for withdrawal is not related to the adverse event.

If the study intervention is discontinued by the clinical care team because of adverse events, this does not constitute subject withdrawal from the study. Instead, this is considered a protocol deviation and an OOPS form must be completed. If the treating physician removes the patient from the fluid regimen without an adverse event, this does not constitute subject withdrawal from the study. Instead, this is considered a protocol deviation and an OOPS form must be completed (see 18.2 for more details on OOPS).

For study purposes, all cases randomized in this study will be analyzed

as an intention-to-treat. Please notify the CDMCC if you have a study withdrawal. Contact your IRB for specific instructions they may have regarding study withdrawal.

20.2 OpenClinnica Data Entry: Study Withdrawal

On the Unscheduled Event, the Withdrawal eCRF, enter the date and time consent was withdrawn. Enter the phase and who withdrew the patient. Provide clear details as to the circumstances of the withdrawal. Please also notify the CDMCC.

Part IV

Reference Materials

Chapter 21

Relevant Publications

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21.1 Purpose of Articles

These papers are provided as supplemental material for the interested reader. It is not necessary for research investigators or coordinators to read and completely understand these manuscripts in order to successfully participate in this protocol.

21.2 Description of PECARN Network

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The Pediatric Emergency Care Applied Research Network (PECARN): Rationale, Development, and First Steps*

The Pediatric Emergency Care Applied Research Network†

Abstract

Since its formal recognition as a medical specialty, the field of pediatric emergency medicine has made substantial advances with respect to its scope and sophistication. These advances have occurred in clinical practice as well as in the research base to improve clinical practice. There remain, however, many areas in emergency medical services for children (EMSC), in the out-of-hospital as well as the emergency department (ED) and hospital settings, that suffer from a lack of data to guide practice. In an effort to expand the quality and quantity of research in pediatric emergency care, the Pediatric Emergency Care Applied Research Network (PECARN) was created in October 2001. PECARN is the first federally funded national network for research in EMSC. PECARN is the result of Cooperative Agreement grants funded through the Health Resources and Services Administration (HRSA) with the purpose of developing an infrastructure capable of overcoming inherent barriers to pediatric EMSC research. Among these recognized barriers are low incidence rates of serious pediatric emergency events, the need for large numbers of children from varied backgrounds to achieve broadly representative study samples, lack of an infrastructure to test the efficacy of pediatric emergency care, and the need for a mechanism to translate study results into clinical practice. PECARN will serve as a national platform for collaborative research involving the continuum of care within the EMSC system, including out-of-hospital care, patient transport, ED and in-hospital care, and rehabilitation. This article describes the history of EMSC, the need for a national collaborative research network in EMSC, the organization and development of PECARN, and the work plan for the Network.
Key words: emergency medical services for children; pediatric emergency care; PECARN; research. ACADEMIC EMERGENCY MEDICINE 2003; 10:661–668.

BACKGROUND

Systematic out-of-hospital triage and care did not broadly impact the civilian population in the United States until 1966, when a seminal treatise issued by the National Research Council identified trauma as "...the neglected disease of modern society."[1] Its publication led to the development of modern-day emergency medical services (EMS) and the idea that patients could benefit from coordinated systems of field triage and transport. The EMS Act of 1973 provided state and local governments with the resources to implement their own EMS systems. The early years of EMS development were focused primarily on field training and hospital coordination to form regionalized networks of care. The care of children in these systems was largely integrated into adult models using principles and approaches extrapolated from adult experience with insufficient early attention to different processes, resources, or provider skill sets for children.[2] As a result, while adult outcomes improved dramatically, similar improvements were not observed among children.[3]

Emergency Medical Services for Children. In 1984, federal legislation (PL-98-555) was passed establishing the EMSC program under the Health Resources and Services Administration (HRSA).[4] Over the past 18 years, the federal EMSC program has provided grants for program development in all 50 states, the District of Columbia, and six territories. In accordance with the recommendations of the 1993 Institute of Medicine report on EMSC, the programmatic priorities have focused on four areas: 1) education and training; 2) equipment and supplies; 3) regulation and funding; and 4) evaluation and research.[5] EMSC is organized on state, regional, and local levels in order to meet the varying emergency care needs of children in their communities. It includes a wide spectrum of services ranging from prevention and out-of-hospital care to stabilization, definitive acute care, and rehabilitation.[5]

The Need for EMSC Research. Over the past several decades, the scope and sophistication of

*This article is being simultaneously published, with slight variation, in *Pediatric Emergency Care*.

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†The members of PECARN and their institutional affiliations are listed in Appendix A at www.aemj.org as a Data Supplement. Appendix B (also a Data Supplement) lists PECARN contact information.

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pediatric emergency services have expanded greatly, presenting unique challenges, needs, and opportunities for rigorous, collaborative research.[6] Annual emergency department (ED) visits have increased from 81 million in 1988[7] to 102.8 million in 1999,[8] and the rate of rise in annual ED visits is also escalating.[9] Children account for approximately 30% of ED visits, 12% of EMS transports for injuries, and 5.5% of EMS transports for medical conditions.[10] Despite the frequency of pediatric ED use, the impact of emergency medical care on pediatric health outcomes remains largely unevaluated. There have been few attempts to measure the quality or efficacy of EMSC in spite of wide variations in training and practice.[11] For example, emergency transport practices for children are not standardized with respect to safety requirements.[12] In the ED itself, management of common pediatric disorders often varies[11] and often complies poorly with evidence-based practice guidelines.[13,14] This may be due in part to gaps in knowledge about EMSC quality of care, which were identified in the 1993 Institute of Medicine report[5] and were prioritized by a consensus panel of EMSC experts convened in 1999.[15]

Investigations of optimal therapeutic regimens in the out-of-hospital setting have been particularly lacking, despite the fact that when they have been performed, rigorously conducted studies in this setting have altered clinical practice considerably. One example is a study showing that endotracheal intubation offers no benefit over bag-valve-mask-assisted ventilation for children with respiratory compromise in an urban out-of-hospital setting.[16] To our knowledge, this is the only published randomized controlled trial of a major clinical intervention for children in this environment. Additional examples of important issues for EMSC research in the out-of-hospital setting include the role of out-of-hospital fluid resuscitation[17–19] and the provision of advanced life support for injured children in the field.[20–22] These and other important questions about EMSC care can be studied only with rigorous multicenter participation.

Barriers to Research. Despite the need to expand research in EMSC, there are several barriers limiting the ability to conduct valid and generalizable studies. First, serious adverse outcomes are uncommon in pediatrics, limiting the opportunities for patient enrollment, particularly in a single institution or a small group of institutions. In a recent, multicenter study of children with diabetic ketoacidosis, for example, only 61 cases of cerebral edema were identified, despite a 15-year study period at ten major pediatric centers.[23] Similar limitations were experienced in a recent large study involving decision rules for computed tomography (CT) scanning of the brain in mild-to-moderate head injury. Despite the prospective enrollment of 1,044 children from four hospital EDs, and 83 (7.9%) "positive" CT scans, fewer than 1% of children with minor head injury required neurosurgical intervention. Because of the small numbers of children with serious adverse outcomes, a clinical decision rule developed from these data will likely suffer from the data demonstrating unacceptably wide confidence intervals.[24]

Second, EMSC research is typically conducted in tertiary care centers or in EDs with strong pediatric staffing. Such facilities, however, care for a minority of children in the United States. Only 9.4% of EDs are located in specialty pediatric hospitals[25] and most pediatric ED visits occur in nonpediatric specialty hospitals. Therefore, to ensure generalizable results, a research program in EMSC must include patients treated in nonpediatric specialty hospitals.

Third, informed consent for research is difficult to obtain in the setting of life-threatening emergencies. True informed consent is unlikely in an emergency situation and is especially difficult for clinical trials. Historical approaches to this problem have included a brief scripted summary of the study with delayed full consent,[26] or randomization by odd–even medical record number or day of the month without a consent process.[16,19] Clarification of federal regulations, published in 1996, made the requirements for emergency research more stringent, but nonetheless allow a waiver of informed consent in certain emergency circumstances.[27] Studies implementing the use of the waiver must involve the community in early consultation and dialogue prior to study initiation.[28] Study investigators must keep the community abreast of progress and results.[29,30] Therefore, an effective research program in EMSC will require substantial input from the communities involved.

Other important barriers to research in EMSC include:

- Difficulty in tracking patients along the continuum of out-of-hospital to hospital care. There is often limited documentation of EMS providers' field assessments, inconsistent patient identifiers used in out-of-hospital and hospital records, and an absence of a central repository for patient information. As a result, there are lapses in exchange of vital patient information between out-of-hospital and hospital providers.
- Difficulty in maintaining data quality, integrity, and consistency. Emergency personnel must attend to patient needs under hurried and stressful circumstances. Legibility, accuracy, and comprehensiveness of data collection are problematic and data gathering must be planned to minimize burdens on the practitioner.
- The need for an increased number of research studies focused on improving EMSC care and services and the lack of consistent, significant funding for EMSC research.[6]

- The need to recruit and enroll sufficiently diverse patient populations. Results of studies should ideally be applicable across broad groups of patients and therefore participation in research protocols must be sufficiently representative.
- The need for severity adjustment. Interventional trials or observational studies of patient health outcomes must control for baseline differences in severity of illness. A general severity of illness measurement tool, that is applicable to both traumatic and medical conditions, is required.[31,32]
- The need to develop methodologically sound outcomes measures in order to identify the effectiveness of EMS interventions.[33]
- Translating science into practice. There has been no significant infrastructure to facilitate translation of evidence-based knowledge into EMSC practice.

CONCEPTION AND DEVELOPMENT OF PECARN

Conception of PECARN. The barriers noted above led to national discussions in which PECARN was conceived. In 1998 and 1999, EMSC organizational leadership and the Ambulatory Pediatric Association (APA) held two sequential meetings, collectively called the "APA-EMSC Partnership for Children Workgroup Meetings to Address Barriers to Research in Pediatric Emergency Medicine (PEM)." This consortium of PEM/EMSC investigators, health service researchers, and administrators raised the various issues noted above and concluded that one of the most serious barriers to PEM research was the lack of a well-supported infrastructure to conduct multicenter collaborative studies.[34]

Precedents for a Collaborative Network. There are several examples of productive pediatric collaborative research networks in the United States as well as abroad.[35–37] Other pediatric specialties, experiencing similar barriers to research as those identified for EMSC, have created successful multicenter research infrastructure networks. These networks include: a) *The Vermont Oxford Network*, founded in 1988 as a collaboration of neonatal health care providers, which has grown to involve more than 270 neonatal intensive care units[38,39]; b) *The Pediatric Research in Office Settings (PROS) Network*, sanctioned by the American Academy of Pediatrics (AAP) in the 1980s to promote collaborative pediatric practice research, now including more than 470 practices[40]; and c) The *Children's Oncology Group,* established in March 2000, which is a clinical trials cooperative group supported by the National Cancer Institute. Although different in nature, setting, and scope, these collaborative pediatric research networks have successfully conducted and published important studies made possible by federal and private funding of their infrastructures. The general objectives of these networks are broadly applicable to those of a PEM/EMSC research network: to study the process, effectiveness, and costs of medical care of children, and to disseminate the results to the appropriate provider groups.

Within general EM, a few multicenter networks have been created to study disease-specific entities. The Emergency ID Net is an ED-based network dedicated to reporting and studying emerging infectious diseases.[41] The MARC collaborative group performs multicenter studies pertaining to respiratory illnesses.[42] Notable disease-specific collaborative research in the ED has addressed out-of-hospital airway management of children requiring bag-valve-mask ventilation,[16] and methods for ruling out cervical spine injuries.[43]

Within the academic PEM community, there exists a framework for a collaborative research network. The Section on EM of the AAP created the PEM Collaborative Research Committee (PEM CRC) in the 1990s to support and facilitate collaborative PEM research. Although the limited infrastructure of the PEM CRC is not funded, it has provided a platform for the conduct of several important collaborative research projects.[23,44–46] With the exception of the PEM CRC, however, there are no collaborative research networks dedicated to PEM/EMSC.

Development of PECARN. In June 2001, the HRSA, Maternal and Child Health Bureau (MCHB), invited proposals from established clinical investigators to participate in the cooperative agreements with the HRSA/MCHB to establish the EMSC Network Development Demonstration Projects (NDDP). The purpose of the EMSC NDDP is to "demonstrate the value of an infrastructure or network designed to be the platform from which to conduct investigations on the efficacy of treatments, transport, and care responses, including those preceding the arrival of children to the hospital" (HRSA/MCHB Guidance for Cooperative Agreements for EMSC NDDP).[47] Pursuant to the Public Health Service initiative "Healthy People 2010," which is a statement of national priorities developed by the Department of Health and Human Services, the EMSC NDDP is designed to address the issues of injury and violence prevention, access to quality health services, and, in particular, the need for public health infrastructure for EMSC-related research. The EMSC NDDP-supported network is designed to eliminate barriers currently limiting progress in establishing EMSC "best practice" guidelines and improve and measure the quality of EMSC care.

STRUCTURE OF PECARN

The NDDP is charged with promoting high-quality, high-priority, and diverse research in EMSC, with a focus on forming collaborative research partnerships

among various academic and community-based hospitals. The network currently consists of four regional node centers (RNCs), located at diverse sites across the country and collectively organized in accordance with the federal guidance as the Pediatric Emergency Care Applied Research Network (PECARN).

Each RNC has entered into a cooperative agreement with HRSA/MCHB to engage in collaborative clinical research. In order to develop its own infrastructure, each RNC hosts a regional network of Hospital Emergency Department Affiliates (HEDAs) for a total of 25 sites across the United States, including the RNC itself. The HEDAs have agreed to participate in observational studies and controlled trials to be conducted either regionally as pilot studies or as part of the national PECARN. The Central Data Management and Coordinating Center (CDMCC), based at the University of Utah, will manage data generated from the network under a cooperative agreement with MCHB. The CDMCC will provide a central repository for data generated by the PECARN research projects. The CDMCC also will work with the entire network to implement standards for data collection and analysis in order to ensure uniformity and quality of the data, and provide safety and regulatory guidance to ensure the timely progress of PECARN studies.

PECARN is overseen by a steering committee, with equal representation from each of the nodes and with membership from the CDMCC, acting as the primary governing body. PECARN has bylaws that outline its purpose, structure, membership, policies and procedures, and code of ethics. The PECARN steering committee has responsibility for reviewing and approving specific PECARN research proposals, as well as formulating and monitoring policies and procedures guiding the research activities of the Network (Figure 1).

PECARN Subcommittees. The PECARN subcommittees were established by the PECARN Steering Committee to carry out specific PECARN-related tasks and are advisory to the Steering Committee.

- **Protocol Concept Review and Development Subcommittee (PCRADS):** Reviews and makes recommendations regarding specific research concept(s) and protocol(s) for the PECARN network.
- **Safety and Regulatory Affairs Subcommittee (SRAS):** Assists the principal investigators (PIs) and the Steering Committee to ensure compliance with all institutional, local, state, and federal government regulatory laws, guidelines, and policies. One of the main responsibilities of this committee is to assist with network-wide institutional review board (IRB) proposal preparations and submissions.
- **Quality Assurance Subcommittee (QAS):** Ensures research protocol design, development, and implementation are in compliance with standards for protection of human subjects, rigorous research practices, and accurate and consistent data collection.
- **Data Analysis and Management Subcommittee (DAMS):** Assures the quality of data management activities, facilitates the exchange of information with investigators on matters related to the design

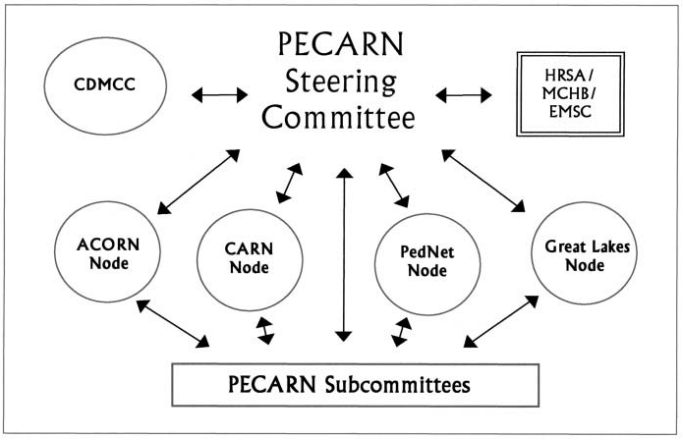

Figure 1. The Pediatric Emergency Care Applied Research Network (PECARN) organizational structure. CDMCC = Central Data Management and Coordinating Center; ACORN Node = University of California–Davis Medical Center; CARN Node = Children's National Medical Center, Washington, DC; PedNet Node = Columbia University/Harlem Hospital Center; Great Lakes Node = University of Michigan; HRSA/MCHB/EMSC = Health Resources and Services Administration/Maternal and Child Health Bureau; Emergency Medical Services for Children.

and operation of data acquisition systems, and helps to develop and monitor processes involving statistical analysis and reporting of results.

- **Grant Writing and Publication Subcommittee (GWAPS):** Assists PIs in developing, and offers critique of, research grant applications submitted for external funding. This subcommittee also reviews research documents for presentation and publications, and reviews, facilitates, and ensures timely submission and dissemination of research results to scientific and nonscientific communities. Finally, the GWAPS is charged with creating an authorship plan and authorship agreements, reviewing authorship of manuscripts and ensuring equitable participation and attribution.

The subcommittee members are made up of both voting PECARN members and nonvoting HEDA representatives. There is equal nodal representation on all the PECARN subcommittees. These subcommittees serve as working groups of the Steering Committee, with membership based on experience, interest, and expertise. The five subcommittees work in an integrated fashion to facilitate the conduct of PECARN research.

Within the PECARN Subcommittees there are substantial expertise and senior level participation. Overall, Subcommittee participants of PECARN include 17 chairs, directors, or chiefs of emergency medicine or pediatric emergency medicine, and 19 directors or chiefs in a variety of areas, including research and research centers, trauma, intensive care, and residency programs. The PECARN subcommittee expertise extends over the entire spectrum of EMSC research and related areas, including out-of-hospital EMS transport safety, alcohol and drug-related injuries, psychiatric emergencies, rural ED issues, clinical decision rules, cost–effectiveness, medical education, special needs children, disaster preparedness, and intensive care practices. Many subcommittee members also serve on an array of scientific, clinical practice, research operations, community advisory, bioethics, biostatistics, and National Institutes of Health (NIH) grant review committees and panels. In addition, many subcommittee members contribute to the professional association boards of PEM, AAP, APA, the American College of Emergency Physicians (ACEP), and the editorial boards of major pediatric, emergency, and PEM journals.

HEDAs Participating in PECARN. The hospitals participating in PECARN serve a large and diverse population across the country in urban, suburban, and rural locations. These hospitals provide differing levels of care and services that are representative of EMSC across the United States. Additionally, across the country, EMSC is delivered in different physical settings and institutional organizations, and this is reflected in the disparate settings of PECARN HEDAs. For these reasons, the research findings from PECARN will be generalizable to the many sites and settings across our country that provide EMSC.

A detailed resource survey was completed by each HEDA to define the EDs and their patient populations. The 25-site PECARN network annually treats 808,454 patients, up to 21 years of age. Participating hospitals are diverse in organization, location, range of services offered, and university affiliations. The racial composition of the patients served is likewise diverse, with 46.6% African American, 43.3% white, 1.6% Asian or Pacific Islander, 0.6% Native American or Alaskan Native, and 7.6% unknown. Nine percent are of Hispanic ethnicity (a category separate and distinct from race). Approximately 48% of patients have some form of government insurance, 39% have private insurance, and 11% are self-pay.

The organization of the 25 participating hospitals and their geographic locations are diverse as well. These hospitals serve urban, suburban, and rural patients. All are nonprofit and include a variety of academic, community, general, and freestanding children's hospitals (the latter designation includes approximately a third of the HEDAs). Of the 25 hospitals, 17 are Level 1 trauma/pediatric centers, 20 have pediatric intensive care units that treat 22,546 patients annually, and 22 have neonatal intensive care units that treat 31,390 patients annually. The ED practice environments of the participating HEDAs also represent those found across the United States. Seventeen are physically distinct pediatric EDs, five have a pediatric area within a general ED, and three are general EDs without separate pediatric facilities. Most of these hospitals have university affiliations, and PEM is typically situated in divisions of pediatrics or emergency medicine. Many of these institutions also have training programs that include emergency medicine and pediatric residencies, pediatric emergency medicine fellowships, and physician assistant (PA), nursing, emergency medical technician (EMT) and EMT-P training programs.

Anticipated Work Flow/Protocol Review Process. PECARN nodal investigators or outside investigators prepare draft research proposals and submit them to the Concept/Protocol Review Subcommittee (PCRADS). PCRADS reviews the proposals for their scientific quality and their appropriateness for implementation in the PECARN network and provides the Steering Committee with recommendations. The proposals are then reviewed and voted on by the Steering Committee. Those proposals that receive Steering Committee approval are then developed into robust proposals by the investigator(s) and simultaneously submitted to the four other subcommittees (Safety, Quality, Data Analysis, Grants and Publications). These subcommittees review, critique, offer technical

advice, and recommend changes to the protocols. The investigator makes the recommended revisions to the protocols and submits the amended protocols to the Steering Committee for final review and approval. Once approved by the Steering Committee, the nodal lead investigators and their teams submit the approved research protocol to federal or nonfederal agencies for funding. When funding is secured, the research protocols will be implemented.

FIRST STEPS

HRSA/MCHB funding for the EMSC NDDP cooperative agreement is intended to support the initial development of PECARN research infrastructure, including startup hardware and administrative costs as well as the production of nodal research proposals. Funding to *implement* the proposals approved by the PECARN Steering Committee will be sought extramurally through other government, foundation, or alternate private funding sources.

To initiate the research process, the PECARN Steering Committee required two pre-proposal submissions from each of the Regional Nodes, each of which were expected to be broadly relevant to published EMSC research agendas[6,15,48] and to have the potential for widespread impact on a national level. The PCRADS members reviewed the pre-proposals according to standardized review criteria and assigned specific criteria scores as well as overall scores. After reviewing the recommendations of the PCRADS, the Steering Committee organized the pre-proposals into two categories. The first category consisted of proposals that could be implemented in PECARN using existing PECARN resources. The second category consisted of proposals that would need extramural funding to be implemented. The Committee recommended that two proposals, both that sought to characterize the populations served by participating PECARN hospitals through the collection of ED-based epidemiological surveillance data, be combined as the first project implemented using existing PECARN resources. The combined proposals became the ''PECARN Core Data Project.'' This project will establish and test an ED-based data collection and surveillance system by determining the number and characteristics of all visits to participating sites and identifying core data elements through existing electronic databases and chart review. This study will develop an infrastructure to collect, manage, and transfer data, measure agreement between electronic and medical records data, and map these data using Geographical Information Systems (GIS) software, designed to create geographical maps of disease/injury incidence. Two other proposals were approved for development into extramural funding proposals: 1) ''Clinical Decision Rules for Identifying Children at Low and High Risk for Traumatic Brain Injuries after Mild Blunt Head Trauma'' is a protocol designed to develop and validate a clinical decision rule for performing head CT in children with minor head injury. 2) ''Use of Ultrasonography to Evaluate Pediatric Blunt Abdominal Trauma'' is a protocol aimed at determining the sensitivity and specificity of ED-based ultrasonography to detect intra-abdominal injury in children.

FUTURE GOALS OF THE NETWORK

PECARN has been established by the EMSC-NDDP to achieve the following goals by the end of its initial three-year funding period:

1. To establish a well-conceived and fully operational infrastructure to conduct clinical trials and observational studies on EMSC priority topics, using rigorous study designs and methodologies;
2. To develop a consensus-derived and well-informed research agenda used to guide the network activities;
3. To institute a research and development process within the network to develop proposals and carry out fully developed investigations with the help of MCHB or other federal agencies;
4. To design and implement a plan to study and encourage the transfer of network findings to EMSC practices; and
5. To foster a collaboration of EMSC personnel, nurses, practitioners, and researchers in order to provide opportunities for bidirectional education and exchange of ideas and information between the treatment and academic communities.

One of the goals of the network is to expand on the current initial infrastructure to include additional HEDAs and outside specialists and consultants. Ultimately, our aim is to establish and maintain a cohesive consortium of clinical researchers to produce a volume of high-quality studies in the area of EMSC.

LONG-TERM SUSTAINABILITY

Following PECARN's initial three-year funding period, the original NDDP awardees will have the opportunity to apply for an additional year of funding. The NDDP will also consider funding two additional nodes (for a total of six) through a competitive grant process. PECARN plans to continue to implement network-wide research that increases and expands its scope, and its ability to promote evidence-based EMSC practices. PECARN will continue to receive infrastructure funding from HRSA/MCHB, pending availability of funds, and seek extramural funding for PECARN research projects. In this way, capabilities will be expanded and partnerships developed as this national research network matures and evolves.

External Participation with PECARN. Recognizing the broad EMSC expertise available beyond the PECARN nodes, the network is open to all investigators, regardless of affiliation with PECARN in general or a specific PECARN node. Investigators interested in using the PECARN structure may submit pre-proposals for PECARN consideration through two mechanisms: 1) they may submit the proposal to one of the PECARN nodes by contacting the node PI directly; or 2) they may submit the proposal directly to PECARN through the PECARN Steering Committee Chair (currently Nathan Kuppermann), who will direct the investigator to the most appropriate PECARN node for project development and collaboration. Individual investigators otherwise unaffiliated with PECARN who submit proposals that are endorsed by PECARN will be admitted to PECARN as associate members and maintain lead management for their proposal as appropriate. Additionally, PECARN members will solicit participation from recognized experts, as appropriate, to contribute to various research proposals.

CONCLUSIONS

Historically, there have been several barriers to effective EMSC research. These include the infrequency of certain pediatric diseases and adverse events in children, the need to include diverse patient populations, the difficulty of obtaining informed consent in emergency settings, and the need for an infrastructure to conduct multicenter research and translate research findings into clinical practice. The PECARN network was established by EMSC/MCHB to address many of these barriers. The conceptual model developed by PECARN capitalizes on the unique research resources of multiple EDs serving the emergency care needs of a broad diversity of children. This network has great potential to conduct meaningful research with the goal of improving the practices and outcomes of EMSC.

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21.3 Risk Factor for Cerebral Edema in Children with Diabetic Ketoacidosis

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RISK FACTORS FOR CEREBRAL EDEMA IN CHILDREN WITH DIABETIC KETOACIDOSIS

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ABSTRACT

Background Cerebral edema is an uncommon but devastating complication of diabetic ketoacidosis in children. Risk factors for this complication have not been clearly defined.

Methods In this multicenter study, we identified 61 children who had been hospitalized for diabetic ketoacidosis within a 15-year period and in whom cerebral edema had developed. Two additional groups of children with diabetic ketoacidosis but without cerebral edema were also identified: 181 randomly selected children and 174 children matched to those in the cerebral-edema group with respect to age at presentation, onset of diabetes (established vs. newly diagnosed disease), initial serum glucose concentration, and initial venous pH. Using logistic regression, we compared the three groups with respect to demographic characteristics and biochemical variables at presentation and compared the matched groups with respect to therapeutic interventions and changes in biochemical values during treatment.

Results A comparison of the children in the cerebral-edema group with those in the random control group showed that cerebral edema was significantly associated with lower initial partial pressures of arterial carbon dioxide (relative risk of cerebral edema for each decrease of 7.8 mm Hg [representing 1 SD], 3.4; 95 percent confidence interval, 1.9 to 6.3; $P<0.001$) and higher initial serum urea nitrogen concentrations (relative risk of cerebral edema for each increase of 9 mg per deciliter [3.2 mmol per liter] [representing 1 SD], 1.7; 95 percent confidence interval, 1.2 to 2.5; $P=0.003$). A comparison of the children with cerebral edema with those in the matched control group also showed that cerebral edema was associated with lower partial pressures of arterial carbon dioxide and higher serum urea nitrogen concentrations. Of the therapeutic variables, only treatment with bicarbonate was associated with cerebral edema, after adjustment for other covariates (relative risk, 4.2; 95 percent confidence interval, 1.5 to 12.1; $P=0.008$).

Conclusions Children with diabetic ketoacidosis who have low partial pressures of arterial carbon dioxide and high serum urea nitrogen concentrations at presentation and who are treated with bicarbonate are at increased risk for cerebral edema. (N Engl J Med 2001;344:264-9.)

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DIABETIC ketoacidosis occurs in 25 to 40 percent of children with newly diagnosed type 1 diabetes mellitus[1,2] and may later recur in association with illness or noncompliance with treatment. Clinically apparent cerebral edema occurs in approximately 1 percent of episodes of diabetic ketoacidosis in children and is associated with a mortality rate of 40 to 90 percent.[3-6] Cerebral edema is responsible for 50 to 60 percent of diabetes-related deaths in children.[7,8]

The pathophysiologic mechanism underlying the cerebral edema associated with diabetic ketoacidosis is controversial. Clinical studies to date, most of which have been small, have provided little information about predictive factors. In this case–control study of children with diabetic ketoacidosis, we evaluated the associations between cerebral edema and the following factors: demographic characteristics and initial biochemical characteristics, therapeutic interventions, and changes in biochemical values during treatment.

METHODS

Study Subjects

Cerebral-Edema Group

We identified all the children (persons ≤18 years of age) in whom cerebral edema related to diabetic ketoacidosis developed between 1982 and 1997 at any of 10 pediatric centers. To identify these children, we reviewed the records of all the children who had been admitted because of diabetic ketoacidosis and whose records indicated that they had had cerebral edema, cerebral infarction, coma, seizures, or death, or that they had undergone computed tomographic scanning, magnetic resonance imaging, intubation, or treatment with mannitol. The records of all children who died (with or without type 1 diabetes) at these 10 centers during the study period were also reviewed to ensure that no cases of cerebral edema related to diabetic ketoacidosis had been missed.

To be included in the study, children identified as having cerebral edema were required to meet all the following criteria: the

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presence of diabetic ketoacidosis (defined as a serum glucose concentration >300 mg per deciliter [16.7 mmol per liter], a venous pH <7.25 or a serum bicarbonate concentration <15 mmol per liter, and the presence of ketones [acetoacetate] in the urine); alteration in mental status (obtundation or disorientation); and either radiographically or pathologically confirmed cerebral edema or specific treatment for cerebral edema (hyperosmolar therapy or controlled hyperventilation) that was followed by clinical improvement.

Because cerebral infarction may occur as a consequence of cerebral edema or impending herniation,[9,10] radiographic studies of children with cerebral infarction were also reviewed by a neuropathologist. Six patients whose radiographs revealed patterns of infarction consistent with the consequences of cerebral edema were included in the cerebral-edema group.[9]

Control Groups

For each child with cerebral edema, we identified six other children who were designated as controls, three in each of two control groups. One control group (the "random controls") consisted of children with diabetic ketoacidosis (as defined above) who were randomly selected with use of a computer-generated list of numbers from among all the children admitted for diabetic ketoacidosis at each center during the study period. The second control group (the matched controls) consisted of children with diabetic ketoacidosis (as defined above) who were matched with the children with cerebral edema according to age (within two years), onset of diabetes (established vs. newly diagnosed disease), venous pH at presentation (within 0.1), and serum glucose concentration at presentation (within 200 mg per deciliter [11.1 mmol per liter]). If pH values were not available, children were matched according to serum bicarbonate concentration (within 3 mmol per liter). If more than three matched controls could be identified for a child with cerebral edema, the controls whose dates of admission most closely approximated that of the child with cerebral edema were chosen.

Data Collection

The following data from the record of each child were recorded by one investigator at each center: demographic characteristics, initial biochemical values, treatment regimen, and changes in laboratory values during treatment. We calculated other variables according to the following formulas[11-14]: corrected serum sodium concentration = measured serum sodium concentration + ([(serum glucose concentration − 100) ÷ 100] × 1.6), with the serum glucose concentration expressed in milligrams per deciliter; osmolality = (2 × serum sodium concentration) + (serum glucose concentration ÷ 18) + (serum urea nitrogen concentration ÷ 2.8), with the serum sodium concentration expressed in millimoles per liter and the serum glucose and serum urea nitrogen concentrations in milligrams per deciliter; arterial pH = venous pH + 0.05; and the partial pressure of arterial carbon dioxide = the partial pressure of venous carbon dioxide − 6. Information from nursing records about treatments given during each hour was used to calculate the rates of administration of fluid, sodium, and insulin. In the cerebral-edema group, these rates and changes in biochemical variables during treatment were calculated for the interval between the initiation of therapy (defined as the first intravenous administration of fluids or insulin) and the onset of symptomatic cerebral edema; in the control groups, these values were calculated for the same interval.

To assess interrater agreement in the recording of data, 10 percent of the records were randomly selected and reexamined by a single investigator. Interrater agreement with respect to eight variables (the initial serum glucose and sodium concentrations, the initial venous pH value, the use or nonuse of a bolus dose of insulin, the rates of insulin and fluid administration during the first hour of treatment, the use or nonuse of bicarbonate therapy, and the dose of bicarbonate, if used) was evaluated with use of the weighted kappa statistic. The consistency of the recording of data among investigators was excellent, with a median kappa statistic of 0.9 (range, 0.6 to 1.0).

The study was approved by the institutional review board of each participating institution.

Statistical Analysis

We compared data from the cerebral-edema group with data from both of the control groups by one-way analysis of variance for continuous variables and the chi-square test for categorical variables. The Kruskal–Wallis test was used when variances were unequal among the groups. The Scheffé[15] and Bonferroni[16] procedures were used to adjust for multiple comparisons in the analyses of variance and chi-square tests, respectively.

We compared the cerebral-edema group with the random control group by means of a logistic-regression analysis that included the demographic variables and initial biochemical variables. We compared the cerebral-edema group with the matched control group by means of a conditional logistic-regression analysis that included the demographic variables and initial biochemical variables as well as the therapeutic variables and changes in biochemical variables during therapy. Because the odds ratio approximates the relative risk of diseases with a low incidence, we computed the odds ratio to estimate the relative risk. If two or more variables were collinear, only the variable that was measured most frequently was included in the multivariate analysis. For continuous data, missing values (12 percent of the continuous data points) were imputed.[17]

Using bootstrap methods, we performed 1000 iterations of the multivariate analyses to assess their stability.[18,19] We considered the association of a variable with cerebral edema to be validated if a significant association with cerebral edema was found in more than 50 percent of the 1000 repeated analyses.[19] All the statistical computations were two-tailed and were performed with Stata statistical software[20] (version 6.0, Stata, College Station, Tex.).

RESULTS

Incidence of Cerebral Edema

Clinically apparent cerebral edema occurred in 61 of 6977 hospitalizations for diabetic ketoacidosis during the study period (0.9 percent; 95 percent confidence interval, 0.7 to 1.1 percent). The diagnosis of cerebral edema was based on deterioration in mental status accompanied by radiographic evidence in 32 of the 61 children (52 percent), by changes in mental status that improved after therapy for suspected cerebral edema in 27 children (44 percent), and by postmortem findings in 2 children (3 percent). Neurologic deterioration occurred a median of 7 hours (range, 0 to 25) after the initiation of therapy for diabetic ketoacidosis (Fig. 1), but in three of the children (5 percent), all of whom had radiographically apparent cerebral edema, it occurred before the initiation of therapy.

Of the 61 children with cerebral edema, 35 (57 percent) recovered without sequelae, 13 (21 percent) survived with permanent neurologic dysfunction, and 13 (21 percent) died. During the study period, only two other children died as a result of diabetic ketoacidosis, both owing to cardiac arrest associated with hypokalemia and hypocalcemia.

Demographic and Initial Biochemical Variables

The 61 children in whom cerebral edema occurred were younger, more likely to be white, and more likely to have newly diagnosed diabetes than the 181 children in the randomly selected control group (Ta-

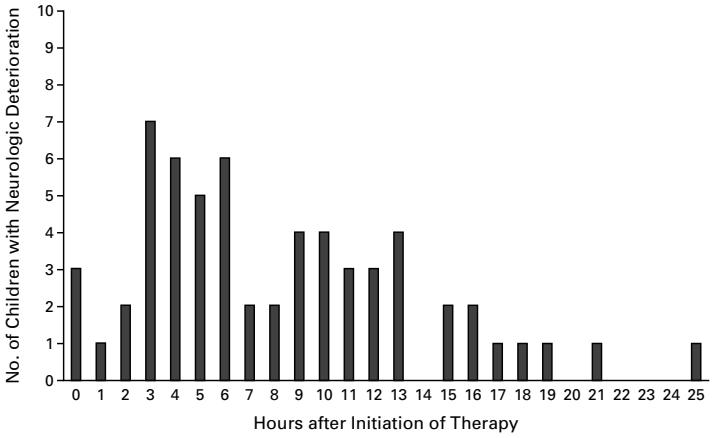

Figure 1. Time between the Initiation of Therapy and Neurologic Deterioration in Children with Diabetic Ketoacidosis and Cerebral Edema.

ble 1). The children with cerebral edema also had more severe acidosis and hypocapnia and higher serum glucose, urea nitrogen, and creatinine concentrations at the time of presentation than the randomly selected controls.

The 61 patients in the cerebral-edema group and the 174 children in the matched control group were well matched: there were no significant differences between these groups with respect to age, the proportion with newly diagnosed diabetes, serum glucose concentrations, and arterial pH values at the time of presentation (Table 1). However, the children with cerebral edema had significantly higher serum urea nitrogen concentrations and significantly lower partial pressures of arterial carbon dioxide than the matched controls. Eighty-five percent of the children in the cerebral-edema group had initial partial pressures of arterial carbon dioxide of less than 18 mm Hg, as compared with 54 percent of the random control group and 69 percent of the matched control group.

Comparison of the Children with Cerebral Edema and the Random Controls

In the multiple logistic-regression analysis, the only variables that were associated with cerebral edema, after adjustment for other covariates, were the serum urea nitrogen concentration and partial pressure of arterial carbon dioxide at the time of presentation (Table 2).

Because both arterial pH values and serum bicarbonate concentrations are measures of the degree of acidosis and thus are collinear, we included only the latter in the main multivariate analysis. Likewise, we excluded the initial serum osmolality values from the multivariate analysis because of collinearity. When serum osmolality was substituted for the serum sodium, glucose, and urea nitrogen concentration in a subanalysis, it was not a significant predictor of the risk of cerebral edema. However, the initial partial pressure of arterial carbon dioxide continued to be a significant predictor of the risk of cerebral edema (data not shown).

Comparison of the Children with Cerebral Edema and the Matched Controls

In the conditional logistic-regression analysis, both a higher serum urea nitrogen concentration and a lower partial pressure of arterial carbon dioxide were independently associated with cerebral edema (Table 3). A smaller increase in the serum sodium concentration during therapy and treatment with bicarbonate were also significantly associated with cerebral edema.

We evaluated the timing of bicarbonate administration in relation to the onset of symptoms of cerebral edema in order to investigate the possibility of bias in bicarbonate administration. We sought to ensure that physicians were not administering bicarbonate in response to deteriorating mental status, thus creating a misleading association between this intervention and cerebral edema. Of the 23 children in the cerebral-edema group who were treated with bicarbonate, only 3 (13 percent) received the first dose within two hours before the onset of neurologic deterioration. By comparison, of the 43 children in the matched control group who were treated with bicarbonate, 4 (9 percent) received their first dose during this interval ($P = 0.69$). Thus, no bias in the use of bicarbonate was detected.

TABLE 1. CHARACTERISTICS OF THE CHILDREN AT THE TIME OF PRESENTATION.*

VARIABLE	CHILDREN WITH CEREBRAL EDEMA (N=61)	MATCHED CONTROLS (N=174)	RANDOM CONTROLS (N=181)	P VALUE†
Age (yr)	8.9±4.2	9.0±4.2	11.3±5.0	<0.001
Male sex (%)	57	54	41	0.02
White race (%)	73	67	53	0.009
Newly diagnosed diabetes (%)	66	64	39	<0.001
Serum bicarbonate (mmol/liter)	5.9±2.7	6.5±2.9	7.9±3.6	<0.001
Serum urea nitrogen (mg/dl)	27±14	21±11	20±9	0.002
Serum creatinine (mg/dl)	1.5±1.1	1.3±1.2	1.1±0.7	0.04
Serum glucose (mg/dl)	758±330	700±286	614±244	0.002
Arterial pH‡	7.06±0.10	7.09±0.10	7.12±0.11	<0.001
Partial pressure of arterial carbon dioxide (mm Hg)§	11.3±6.5	15.1±8.4	17.9±7.8	<0.001

*Plus–minus values are means ±SD. To convert the values for serum urea nitrogen to millimoles per liter, multiply by 0.36; to convert the values for serum creatinine to micromoles per liter, multiply by 88.4; and to convert the values for serum glucose to millimoles per liter, multiply by 0.056.

†P values are for the comparison among all three groups. There were no significant differences among the three groups in the following variables at presentation: serum sodium concentration, corrected serum sodium concentration, initial serum potassium concentration, and serum osmolality (data not shown). After adjustment for multiple comparisons by the Scheffé or Bonferroni procedure, there were no significant differences between the cerebral-edema group and the matched control group in any of the variables except the serum urea nitrogen concentration and the partial pressure of arterial carbon dioxide; the cerebral-edema group and the random control group remained significantly different with respect to all the variables.

‡Arterial pH values were calculated according to the following formula[13]: arterial pH=venous pH+0.05.

§The partial pressures of arterial carbon dioxide were calculated according to the following formula[14]: partial pressure of arterial carbon dioxide=partial pressure of venous carbon dioxide−6, with all values in millimeters of mercury.

Validation of Multivariate Analyses

With bootstrap analysis, the results of the multivariate regression analyses were validated. All the variables that were found to be associated with cerebral edema in the original analyses were significantly associated with cerebral edema in more than 75 percent of the 1000 iterations of the multivariate analyses.

DISCUSSION

In this study, the children with diabetic ketoacidosis who had higher serum urea nitrogen concentrations and more severe hypocapnia at presentation than other children with diabetic ketoacidosis were at increased risk for cerebral edema. Smaller increases in the serum sodium concentration during therapy also indicated a greater likelihood of cerebral edema. Of the therapeutic factors analyzed, only treatment with bicarbonate was associated with cerebral edema. Neither the initial serum glucose concentration nor the rate of change in the serum glucose concentration during therapy was associated with the development of cerebral edema, after adjustment for other covariates; the same was true of the rates of fluid, sodium, and insulin administration.

In the current study, symptomatic cerebral edema occurred in approximately 1 percent of the episodes

TABLE 2. MULTIVARIATE ANALYSIS OF RISK FACTORS FOR CEREBRAL EDEMA IN THE CHILDREN WITH CEREBRAL EDEMA AS COMPARED WITH THE RANDOM CONTROL GROUP.*

VARIABLE†	RELATIVE RISK (95% CI)	P VALUE
Male sex	0.9 (0.4–1.8)	0.68
New onset of diabetes	1.3 (0.5–3.1)	0.57
Age (per 1-yr increase)	0.9 (0.9–1.0)	0.20
Initial serum sodium concentration (per increase of 5.8 mmol/liter)	0.8 (0.6–1.1)	0.19
Initial serum glucose concentration (per increase of 244 mg/dl)	1.0 (0.7–1.5)	0.98
Initial serum urea nitrogen concentration (per increase of 9 mg/dl)	1.7 (1.2–2.5)	0.003
Initial serum bicarbonate concentration (per increase of 3.6 mmol/liter)	1.3 (0.7–2.4)	0.41
Initial partial pressure of arterial carbon dioxide (per decrease of 7.8 mm Hg)	3.4 (1.9–6.3)	<0.001

*In this analysis, the cerebral-edema group was compared with the random control group by means of logistic regression. CI denotes confidence interval. To convert the value for serum glucose to millimoles per liter, multiply by 0.056, and to convert the value for serum urea nitrogen to millimoles per liter, multiply by 0.36.

†The increase or decrease used in the analysis of each continuous variable (except age) represents a change of 1 SD in the variable in the randomly selected control children with diabetic ketoacidosis.

TABLE 3. MULTIVARIATE ANALYSIS OF RISK FACTORS FOR CEREBRAL EDEMA IN THE CHILDREN WITH CEREBRAL EDEMA AS COMPARED WITH THE MATCHED CONTROL GROUP.*

VARIABLE†	RELATIVE RISK (95% CI)	P VALUE
Male sex	0.6 (0.3–1.4)	0.27
Age (per 1-yr increase)	0.9 (0.6–1.3)	0.53
Initial serum sodium concentration (per increase of 5.8 mmol/liter)	0.7 (0.5–1.02)	0.06
Initial serum glucose concentration (per increase of 244 mg/dl)	1.4 (0.5–3.9)	0.58
Initial serum urea nitrogen concentration (per increase of 9 mg/dl)	1.8 (1.2–2.7)	0.008
Initial serum bicarbonate concentration (per increase of 3.6 mmol/liter)	1.2 (0.5–2.6)	0.73
Initial partial pressure of arterial carbon dioxide (per decrease of 7.8 mm Hg)	2.7 (1.4–5.1)	0.002
Rate of increase in serum sodium concentration during therapy (per increase of 5.8 mmol/liter/hr)	0.6 (0.4–0.9)	0.01
Rate of decrease in serum glucose concentration during therapy (per decrease of 190 mg/dl/hr)	0.8 (0.5–1.4)	0.41
Rate of increase in serum bicarbonate concentration during therapy (per increase of 3 mmol/liter/hr)	0.8 (0.5–1.1)	0.15
Administration of insulin bolus	0.8 (0.3–2.2)	0.62
Treatment with bicarbonate	4.2 (1.5–12.1)	0.008
Rate of infusion of intravenous fluid (per increase of 5 ml/kg of body weight/hr)	1.1 (0.4–3.0)	0.91
Rate of infusion of sodium (per increase of 0.6 mmol/kg/hr)	1.2 (0.6–2.7)	0.59
Rate of infusion of insulin (per increase of 0.04 unit/kg/hr)	1.2 (0.8–1.8)	0.30

*In this analysis, the cerebral-edema group was compared with the matched control group by means of conditional logistic regression. CI denotes confidence interval. To convert the values for serum glucose to millimoles per liter, multiply by 0.056, and to convert the value for serum urea nitrogen to millimoles per liter, multiply by 0.36.

†The increase or decrease used in the analysis of each continuous variable (except age) represents a change of 1 SD in the variable in the randomly selected control children with diabetic ketoacidosis.

of diabetic ketoacidosis. Asymptomatic cerebral swelling, however, is thought to occur more frequently.[4,21] Whether these conditions represent a spectrum of disease presentation or whether they are manifestations of different pathophysiologic processes is unknown. Equally controversial is whether specific therapies contribute to the development of cerebral edema. In the current study as well as several previous investigations,[8,22,23] symptomatic cerebral edema developed in a few children with diabetic ketoacidosis before the initiation of therapy. This observation suggests that although variations in treatment may exacerbate an ongoing pathologic process, cerebral edema is not necessarily caused by therapeutic interventions.

Previous investigations of cerebral edema in children with diabetic ketoacidosis cited younger age, a new diagnosis of diabetes, and the rate of fluid administration as factors associated with cerebral edema.[5,6] In these studies, however, children with cerebral edema were not compared with controls, and there was no adjustment for possible confounding factors. In the current study, the differences associated with these three variables were not significant after adjustment for other covariates. The results of our study agree with those of a recent study in which the initial partial pressure of arterial carbon dioxide was found to be an important predictor of the risk of cerebral edema.[24]

We found that smaller increases in the serum sodium concentration during therapy were associated with cerebral edema, in agreement with previous studies.[3,5,25,26] The rates of fluid or sodium administration, however, were not associated with the risk of cerebral edema, after adjustment for other covariates. In children with cerebral edema, failure of the serum sodium concentration to rise during therapy may not be the result of excess administration of free water. Physiologic responses to cerebral injury, such as cerebral salt wasting, may alter sodium homeostasis in these children.[27,28]

It has been hypothesized that cerebral edema in children with diabetic ketoacidosis may be caused by the accumulation of osmolytes in brain cells exposed to hyperosmolar conditions. A rapid decrease in extracellular osmolality during treatment would then result in osmotically mediated swelling of the brain.[25,29-31] The current data do not fully support this theory, since none of the relevant variables — the serum glucose concentration at presentation, the change in serum glucose concentration during therapy, or the rate of fluid or sodium administration — were associated with the risk of cerebral edema.

Although osmotic factors and other mechanisms may play a part in the development of cerebral edema, our data lend support to the hypothesis that cerebral edema in children with diabetic ketoacidosis is related to brain ischemia.[24,32] Both hypocapnia, which causes cerebral vasoconstriction, and extreme dehydration would be expected to decrease perfusion of the brain. In addition, bicarbonate therapy causes central nervous system hypoxia in laboratory animals with diabetic ketoacidosis.[33] Hyperglycemia superimposed on an ischemic insult increases the extent of neurologic damage, blood–brain barrier dysfunction, and edema formation.[34,35] This interaction might help to explain the occurrence of neurologic damage in association with minor degrees of cerebral hypoperfusion. Blood–brain barrier dysfunction and vasogenic edema may occur several hours after an ischemic insult as a result of the release of vasoactive substances and mediators of inflammation.[34,35] The occurrence of cerebral edema several hours after the initiation of therapy thus correlates well with the hypothesis that the basis of this complication is ischemia. Finally, the more frequent occurrence of cerebral edema in children than in adults may be explained in part by the fact that children's brains have higher oxygen require-

ments than adults' brains and are thus more susceptible to ischemia.[10,36]

Although large in comparison with previous studies, our study was nonetheless limited in its ability to detect associations of smaller magnitude; in addition, within the 95 percent confidence intervals for the risks associated with several variables were values that indicated associations that were potentially relevant clinically. We therefore cannot definitively conclude that variables that were not associated with cerebral edema in this study are in fact unimportant in its pathogenesis. In addition, several children in the cerebral-edema group who met the clinical criteria for cerebral edema did not have radiographic or postmortem documentation of its presence. We cannot be certain that the observed neurologic decompensation in the latter children was due to cerebral edema; however, other causes of their neurologic abnormalities could not be identified, and the results of initial radiographic studies in children with cerebral edema may be normal, despite profound neurologic depression.[6,10] Because data were not available for every variable of potential interest, we also cannot exclude the possibility that confounding factors that were not analyzed may have influenced the detected associations, particularly those related to the use of bicarbonate treatment.

We conclude that children with diabetic ketoacidosis who present with high initial serum urea nitrogen concentrations and low partial pressures of arterial carbon dioxide are at increased risk for cerebral edema. In addition, the lack of an increase in the serum sodium concentration during therapy is associated with an increased probability of cerebral edema. Children with these biochemical features should be monitored extensively for signs of neurologic deterioration, and hyperosmolar therapy should be available for immediate use in case early signs of cerebral edema occur. Finally, treatment with bicarbonate is associated with an increased risk of cerebral edema and should be avoided in most circumstances.

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21.4 Correlation of Clinical and Biochemical Findings with Diabetic KetoacidosisRelated Cerebral Edema in Children Using Magnetic Resonance Diffusion-Weighted Imaging

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Correlation of Clinical and Biochemical Findings with Diabetic Ketoacidosis–Related Cerebral Edema in Children Using Magnetic Resonance Diffusion-Weighted Imaging

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Objective To determine clinical and biochemical factors influencing cerebral edema formation during diabetic ketoacidosis (DKA) in children.

Study design We used magnetic resonance diffusion-weighted imaging to quantify edema formation. We measured the apparent diffusion coefficient (ADC) of brain water during and after DKA treatment in 26 children and correlated ADC changes with clinical and biochemical variables.

Results Mean ADC values were elevated during DKA treatment compared with baseline (8.13 ± 0.47 vs $7.74 \pm 0.49 \times 10^{-4}$ mm^2/sec, difference in means 0.40, 95% CI: 0.25 to 0.55, $P < .001$). Children with altered mental status during DKA had greater elevation in ADC. ADC elevation during DKA was positively correlated with initial serum urea nitrogen concentration (correlation coefficient 0.41, $P = .03$) and initial respiratory rate (correlation coefficient 0.61, $P < .001$). ADC elevation was not significantly correlated with initial serum glucose, sodium or effective osmolality, nor with changes in glucose, sodium or osmolality during treatment. Multivariable analyses identified the initial urea nitrogen concentration and respiratory rate as independently associated with ADC elevation.

Conclusions The degree of edema formation during DKA in children is correlated with the degree of dehydration and hyperventilation at presentation, but not with factors related to initial osmolality or osmotic changes during treatment. These data support the hypothesis that CE is related to cerebral hypoperfusion during DKA, and that osmotic fluctuations during DKA treatment do not play a primary causal role. *(J Pediatr 2008;xx:xxx)*

Cerebral edema (CE) associated with diabetic ketoacidosis (DKA) is an important cause of death and disability in children with diabetes.[1-5] The mechanism of this complication, however, is not well understood, and proposed explanations have been controversial. Various protocols for DKA treatment have been promoted on the basis of the assumption that specific management regimens can minimize the risk of CE, yet data to support these recommendations are lacking.

Rapid changes in serum osmolality during DKA treatment have been suspected to play a causal role in DKA-related CE.[6-10] Recent studies of risk factors for DKA-related CE, however, suggest that other factors, such as the initial severity of dehydration, acidosis and hypocapnia, may be more important.[3,11-13] Furthermore, case reports of CE occurring before initiation of DKA treatment cast doubt on the importance of osmotic changes and variations in treatment strategies.[3,12]

Magnetic resonance imaging (MRI) studies conducted by our group in an animal model of untreated DKA suggest that CE occurring before DKA treatment is cytotoxic and associated with decreased cerebral blood flow.[14,15] During DKA treatment, however, the apparent diffusion coefficient (ADC) of water on MR brain imaging is elevated, indicating increased extracellular fluid, and MR perfusion weighted imaging suggests

ADC	Apparent diffusion coefficient	DWI	Diffusion-weighted imaging
CE	Cerebral edema	GCS	Glasgow Coma Scale
DKA	Diabetic ketoacidosis	MRI	Magnetic resonance imaging

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increased cerebral perfusion.[16] These findings suggest that cytotoxic CE occurs during untreated DKA, followed by vasogenic edema during DKA treatment.

We hypothesized that DKA-related CE might be caused by cerebral hypoperfusion before treatment, with vasogenic edema occurring as a result of reperfusion injury. We also hypothesized that edema formation would be greatest in patients with greater degrees of dehydration and hypocapnia at presentation because these factors might affect pretreatment cerebral perfusion. Finally, we hypothesized that the degree of edema formation would not be associated with initial osmolality or with osmotic changes during treatment.

METHODS

Patient Population

We enrolled a convenience sample of children with type 1 diabetes and DKA. Children were eligible for participation if they were <18 years old, diagnosed with type 1 diabetes mellitus, and had DKA defined as serum glucose >300 mg/dL, venous pH < 7.25 or serum bicarbonate <15 mEq/L, and a positive test result for urine ketones or serum ketones > 3 mmol/L. The study was approved by the institutional review boards of the participating institutions.

Treatment Protocol

After obtaining written informed consent from guardians, we treated enrolled patients according to a uniform DKA protocol[16] that complied with recent international consensus guidelines for DKA treatment.[17] Vital signs were evaluated hourly during treatment. Neurologic status was assessed hourly with an age-appropriate Glasgow Coma Scale (GCS)[18] for all patients, and every 30 minutes for patients with headache or altered mental status. Abnormal mental status was defined as a GCS score below 15 at any time during treatment. Serum electrolyte concentrations, venous pH, and P_{CO_2} were measured at presentation and every 3 hours for the first 24 hours of treatment. Effective osmolality was calculated as 2(serum Na) + serum glucose (mg/dL)/18. For patients transferred from outside hospitals, the study protocol was initiated as soon as possible, either at the referring hospital, during transport, or on arrival to the participating institutions.

Imaging Procedures

Patients underwent MR diffusion-weighted imaging (DWI) at 2 time points: (1) during treatment for DKA (2 to 12 hours after the initiation of therapy), and (2) after recovery from DKA (≥72 hours after initiation of treatment).

Diffusion MRI

Images were obtained using a 1.5 Tesla Horizon EchoSpeed LX 8.3.5 imaging system (General Electric Medical Systems, Milwaukee, Wisconsin) and a standard quadrature head coil. A 3-plane localizer was done acquiring T_1 images in 5 slice locations for each orthogonal direction (TR 40 ms/TE 1.5 ms, 7-mm–thick sections), followed by a T_2 fluid-attenuated inversion recovery (FLAIR) sequence (TR 10 000 ms/TE 147 ms/ IR 2200 ms, 4.2 mm thick sections). Diffusion imaging was performed using a modified single-shot spin-echo echo planar imaging sequence. Axial images were acquired at 19 slice locations with TR 8000 ms/TE 90.4 ms, and 5-mm–thick sections. The b-value in each of the 26 diffusion gradient combinations used in the sequence was 900 s/mm^2. With a custom program (TensorCalc, Maj Hedehus, Stanford University, 2000), raw diffusion images were converted to diagnostically relevant B0, trace, ADC (mean diffusivity), isotropic DWI, fractional anisotropy, Coherence Index Anisotropy[19] and Lattice Index Anisotropy[20] image types.

For each DWI image, we recorded ADC values in 3 regions: basal ganglia, thalamus, and frontal white matter. These regions were found in previous studies to have the most consistent changes in ADC values during DKA treatment and to allow the most accurate ADC measurements.[16] We measured the ADC on both the right and left sides of the brain and used the mean of these 2 measurements as the value for that region of interest. Overall mean ADC values were then calculated by determining the mean ADC value for all 3 regions of interest.

We avoided pharmacologic sedation during the imaging procedures whenever possible. When necessary, sodium pentobarbital (2 mg/kg or less) or midazolam (0.1 mg/kg or less) was used.

Statistical Analysis

We compared ADC values measured during DKA treatment with those measured after recovery using the Wilcoxon signed-rank test. Bivariate correlations between clinical and biochemical variables and changes in ADC during treatment were assessed with Pearson correlation coefficients. We used the Wilcoxon rank sum test to compare children with and without abnormal mental status during DKA treatment with regard to clinical and biochemical variables and ADC changes. Finally, we used multiple linear regression to determine which clinical and biochemical variables were independently associated with changes in ADC and multiple logistic regression to assess independent associations with abnormal mental status during DKA treatment. Values for missing variables were imputed using regression[21] provided that <20% of the values were missing. We considered P values < .05 to indicate statistical significance, and values between .05 and .10 to indicate a trend. All statistical analyses were performed with Stata version 8.0 (College Station, Texas).

RESULTS

Twenty-six children with DKA completed the study protocol (Table I). Descriptive and DWI data for 12 of these children have been published.[16] Ten of the 26 children (38%) had abnormalities in mental status (GCS score below 15) at some point during treatment. Seven of these were mild mental status abnormalities with minimum GCS of 14. Three children, however, had minimum GCS of 12 (2 children) and 13 (1 child). All children recovered fully from DKA without any evident

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Table I. Clinical and biochemical values at presentation of DKA (n = 26)*

Age, years	12.0 (3.1)
Sex, % female	46%
New onset diabetes mellitus	50%
Initial serum glucose, mg/dL†	611 (225)
Initial serum sodium, mEq/L	132 (4)
Initial serum potassium, mEq/L	4.6 (0.9)
Initial serum bicarbonate, mmol/L	8.6 (3.7)
Initial serum urea nitrogen, mg/dL†	21 (9)
Initial pH	7.09 (0.09)
Initial P_{CO_2}, mm Hg	21 (9)

*Values presented as mean (SD) or percentage.
†SI unit conversion factors are as follows: Glucose (mg/dL) × 0.0555 = mmol/L; urea nitrogen (mg/dL) × 0.357 = mmol/L.

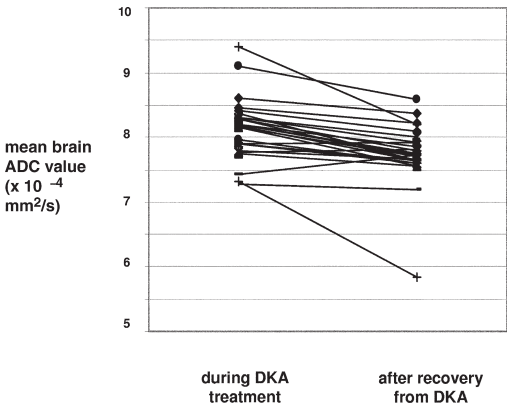

Figure 1. Mean brain ADC values measured during DKA treatment and after recovery from DKA.

neurologic deficits, and none had overt evidence of CE on MRI, although 1 child received treatment for suspected CE. This child had a minimum GCS of 13 and was treated with mannitol and hypertonic saline solution while awaiting MRI results. No overt evidence of CE was found on MRI, and the child regained normal mental status without further treatment for suspected CE. Children underwent imaging 6.1 ± 2.6 hours after the initiation of therapy. Four children required pharmacologic sedation for the initial imaging study, and 2 children required sedation for the follow-up study.

Mean ADC values were significantly higher during DKA treatment than after recovery, consistent with vasogenic edema during DKA treatment (8.13 ± 0.47 vs. 7.74 ± 0.49 × 10^{-4} mm^2/sec, difference in means: 0.40, 95% CI: 0.25-0.55, $P < .001$, Figure 1). Consistent changes were noted in all three brain regions used for mean ADC calculations (basal ganglia ADC: 7.87 ± 0.47 × 10^{-4} mm^2/sec [during treatment] vs 7.43 ± 0.57 × 10^{-4} mm^2/sec [post-recovery], $P <$ .001; thalamus ADC: 7.98 ± 0.66 × 10^{-4} mm^2/sec [during treatment] vs 7.51 ± 0.65 × 10^{-4} mm^2/sec [post-recovery], $P < .001$; frontal white matter ADC: 8.55 ± 0.49 × 10^{-4} mm^2/sec [during treatment] vs. 8.26 ± 0.72 × 10^{-4} mm^2/sec [post-recovery], $P = .01$).

As an index of the degree of CE formation in each patient, we calculated the difference between the mean ADC value during DKA treatment and the baseline ADC value measured after recovery. Children with altered mental status during treatment had significantly greater elevation in ADC values during treatment compared with those without mental status abnormalities (mean ADC difference in children with mental status abnormalities 0.63 ± 0.41 × 10^{-4} mm^2/sec, mean ADC difference in children without mental status abnormalities 0.25 ± 0.25 × 10^{-4} mm^2/sec, difference in means: 0.38, 95% CI: 0.11 to 0.64, $P = .007$). ADC elevation was also positively correlated with the initial serum urea nitrogen concentration (correlation coefficient 0.41, $P = .04$) and there was a non-significant trend toward a negative correlation with the initial pH (correlation coefficient −0.36, $P = .10$, Figure 2). There was also a nonsignificant trend toward negative correlation of the initial P_{CO_2} with ADC elevation (correlation coefficient −0.40, $P = .09$). The sample size for P_{CO_2}, however, was limited because P_{CO_2} often was not measured at presentation on patients transferred to the study centers from other hospitals. Because the initial respiratory rate was correlated with the initial P_{CO_2} (correlation coefficient −0.56, $P = .01$), we conducted an additional analysis using the initial respiratory rate as a proxy for the initial P_{CO_2}. In this additional analysis, the initial respiratory rate was strongly correlated with the ADC difference (correlation coefficient 0.61, $P < .001$, Figure 2).

In contrast to the previously noted correlations, measures related to effective osmolality were not significantly correlated with the mean ADC elevation (Figure 3). Neither the initial glucose concentration, nor the initial serum sodium concentration, nor the initial effective osmolality showed significant correlations with ADC change, although there was a non-significant trend toward greater ADC elevation with lower initial sodium concentrations. Furthermore, the absolute changes in glucose concentration (correlation coefficient 0.01, $P = .94$), sodium concentration (correlation coefficient 0.24, $P = .23$) or effective osmolality (correlation coefficient 0.19, $P = .36$) from the time of presentation until the time of imaging were not significantly associated with ADC elevation. Similarly, the hourly rates of change in glucose (correlation coefficient 0.20, $P = .32$), sodium (correlation coefficient 0.19, $P = .36$) or effective osmolality (correlation coefficient 0.30, $P = .13$) from the initiation of treatment until the time of imaging were not significantly associated with ADC elevation. The timing of the imaging study in relation to the initiation of treatment also was not significantly correlated with the ADC difference (Figure 4; available at www.jpeds.com).

To further explore the associations between biochemical values and ADC change, we conducted multivariable linear regression analyses to determine which factors were independently associated with ADC elevation during DKA treatment (Table II; available at www.jpeds.com). In these

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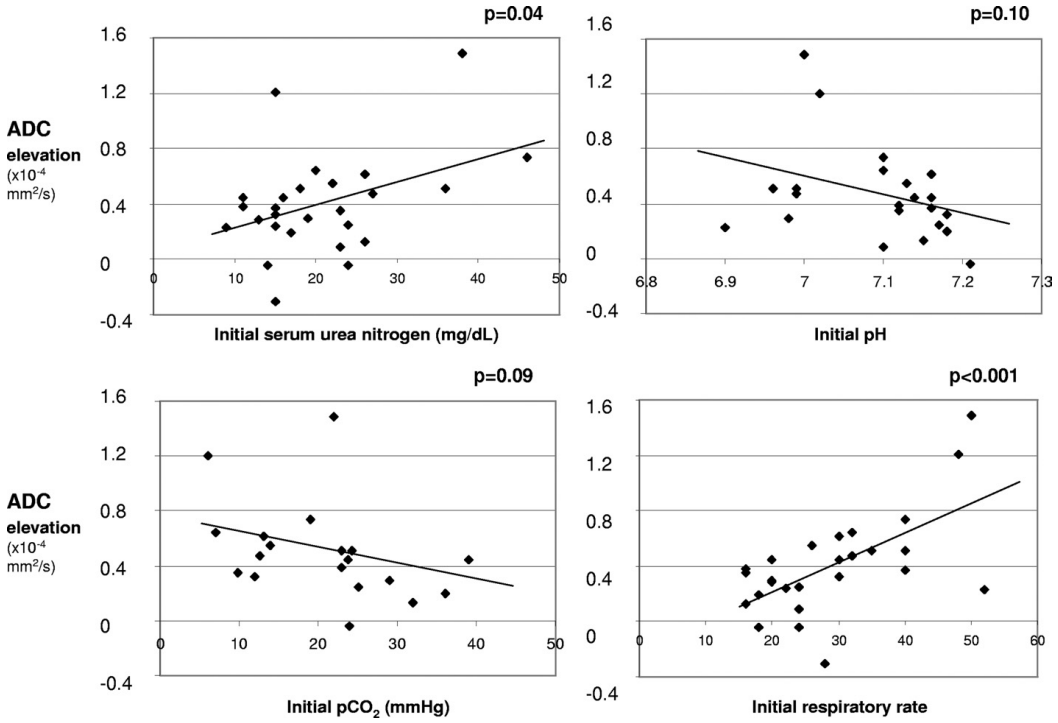

Figure 2. Correlation of ADC elevation during DKA treatment with clinical and biochemical measures at presentation of DKA.

analyses, we used the initial respiratory rate as a proxy for the initial P_{CO_2} level so that all available observations could be included. When we included the initial clinical and biochemical values in the model (Table II, A), only the initial serum urea nitrogen concentration and the initial respiratory rate maintained significant associations with ADC elevation. In a separate analysis, we included the initial effective osmolality and the change in effective osmolality during treatment as covariates in the model. (Table II, B) Neither of these variables were significantly associated with ADC elevation and, as in the previous analysis, only the initial serum urea nitrogen concentration and the initial respiratory rate maintained an independent association with ADC change.

Finally, we compared patients with and without abnormal GCS scores during treatment to determine which clinical and biochemical variables were associated with mental status abnormalities. In univariate analyses, the initial P_{CO_2} level was significantly lower (15 ± 6 vs 25 ± 9 mm Hg, difference in means: 10, 95% CI: 2 to 18, P = .02) and the initial respiratory rate significantly higher (36 ± 12 vs 24 ± 7, difference in means: 12, 95% CI: 4 to 19, P = .004) in children with mental status abnormalities. No other clinical or biochemical variables were significantly associated with abnormal mental status. Similarly, in a multivariable logistic regression model, only the initial respiratory rate was significantly associated with altered mental status (Table III; available at www.jpeds.com).

DISCUSSION

In this study, we confirm the results of a previous smaller study[15] demonstrating that brain ADC values during DKA treatment are elevated, indicating increased extracellular fluid consistent with vasogenic CE. More importantly, we demonstrate that higher initial serum urea nitrogen concentrations and higher respiratory rate at presentation are associated with ADC elevation. In contrast, we found that variables related to osmolality at presentation or to osmotic change during treatment are not significantly associated with ADC elevation. We also demonstrate that children with mental status abnormalities during DKA treatment have greater elevation in ADC. These findings are consistent with the hypothesis that DKA-related CE is related to cerebral hypoperfusion before DKA treatment, with subsequent vasogenic edema occurring during reperfusion. These findings also suggest that osmotic fluctuations during DKA treatment may not play a primary causal role in the pathogenesis of CE.

Although clinically-apparent cerebral injury occurs in less than 1% of DKA episodes, several studies have shown

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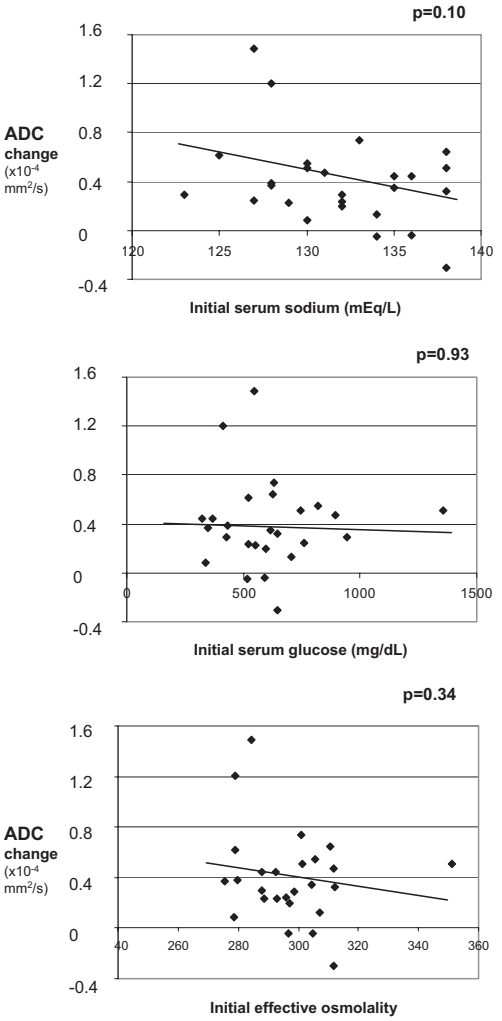

Figure 3. Correlation of ADC elevation during DKA treatment with variables related to osmolality at presentation of DKA.

that mild CE occurs commonly in children with DKA.[22-24] Recent data indicate that mild CE is present in at least half of children with DKA.[24] Mental status abnormalities are more common in children with evidence of mild CE and data obtained from MR spectroscopy studies suggest that subtle cerebral injury may occur during DKA as well.[25] Although associations between mental status abnormalities and mild CE do not necessarily indicate a causal relationship, these studies imply that DKA-related CE may represent a continuum, with the most severe manifestation resulting in overt cerebral injury or elevated intracranial pressure and milder forms resulting in subtle edema and possibly in modest mental status abnormalities.

A previous large epidemiologic study by our group demonstrated that children with higher initial serum urea nitrogen concentrations and greater hypocapnia at presentation of DKA are at increased risk for clinically-apparent CE.[3] Similar studies by other groups likewise found higher initial serum urea nitrogen concentrations and lower P_{CO_2} levels, as well as greater acidosis,[11,12] to be risk factors for CE.[12,13] These data further support the concept that dehydration, acidosis, and hypocapnia before DKA treatment are associated with CE.

Elevated osmolality at presentation of DKA has not been found to be a risk factor for CE in studies which employed appropriate multivariable statistical techniques to adjust for indicators of illness severity, possible confounding factors and other important variables. A lesser rise in serum sodium concentration during treatment for DKA, however, has previously been shown to be associated with increased risk of CE[3,8], and a lower initial serum sodium concentration has been associated with increased risk of CE in 1 study.[11] In the current study, there were no significant associations between serum sodium concentrations and ADC changes, although there was a trend toward lower initial serum sodium concentrations in children with greater ADC changes. The reason that a lesser rise in serum sodium concentration during treatment was not associated with CE in this study, despite the association in previous studies, is unclear but may be related to differences in severity of CE in the study populations (severe, clinically-apparent CE in previous studies vs mild, subclinical CE in the current study). It is possible that physiological alterations that may occur in children with overt, severe CE, and cerebral injury, such as changes in secretion of brain peptides or hormones influencing sodium and fluid balance, are not present in children with mild or subclinical CE.

The cause of CE during DKA treatment has been debated for decades and is still poorly understood. Many investigators have hypothesized that osmotic fluctuations during DKA therapy and aggressive fluid resuscitation might be involved, therefore proposing that slowing the rate of fluid resuscitation and rate of decline in serum osmolality might prevent CE. Although this hypothesis seems intuitively appealing, associations between fluid resuscitation rates or osmotic changes and risk for CE have been difficult to demonstrate. Rather, data from large epidemiologic studies suggest that the severity of dehydration before DKA treatment and the degree of hypocapnia in response to acidosis are linked to the development of CE.[3,12,13] These data suggest that cerebral hypoperfusion, caused by severe dehydration in association with hypocapnia, might play a role in causing cerebral injury and subsequent edema. Data from single photon emission tomography studies suggest that subclinical declines in baseline cerebral blood flow may also be present in children with diabetes.[26] This baseline hypoperfusion may possibly predispose children to ischemic injury when hypocapnia and dehydration are superimposed.

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Studies with an animal model of DKA suggest that untreated DKA is associated with reduced cerebral blood flow and decreased ADC values,[14,15] suggestive of cerebral ischemia. During DKA treatment in children, our data demonstrate that ADC values are elevated and that the greatest elevation occurs in children with higher initial serum urea nitrogen concentrations and higher respiratory rates. These data lend further support to the concept that cerebral hypoperfusion may be present in untreated DKA and that vasogenic edema may occur during DKA treatment as a result of reperfusion of previously ischemic brain tissue, regardless of the rate of reperfusion.

This study has some limitations. As previously noted, children in this study were symptom free or had only subtle mental status changes, and CE was mild, without clinically apparent increased intracranial pressure or overt cerebral injury. Whether the physiological and biochemical causes of this mild, frequently-occurring CE and the causes of rare, severe CE are equivalent is unclear. It is possible that additional factors might contribute to CE in severe cases but that these factors would not be evident when evaluating children with more subtle edema. In addition, the sample size for this study was relatively small, and not all biochemical values were measured on all patients at presentation because some children were referred to the study center from other hospitals. These factors limited our ability to detect associations of smaller magnitude, which might be apparent with a larger study sample. In particular, many initial P_{CO_2} measurements were missing. We used respiratory rate as a proxy for P_{CO_2}, but the correlation between these 2 variables, although significant, was less than ideal. Furthermore, the timing of MRI in relation to the initiation of DKA treatment differed among the patients. It is possible that greater uniformity in timing of the MR imaging may have increased our ability to detect some associations between biochemical variables and ADC changes. Analysis of the ADC changes in relation to the timing of MR imaging, however, did not suggest any relationship between scan timing and ADC change. Finally, because all patients in this study were treated according to a uniform protocol, we could not assess the relationship between treatment variations and ADC changes. Therefore the current data do not provide information to guide clinicians in choosing the optimal treatment for children with DKA.

In summary, this study confirms our previous findings that ADC values during DKA treatment in children are elevated, suggesting vasogenic edema. Furthermore, this study suggests that greater severity of dehydration and greater hyperventilation at presentation of DKA are associated with elevation of ADC values during DKA treatment. These data are consistent with the findings of previous epidemiological studies investigating risk factors for DKA-related CE in children and strengthen the hypothesis that cerebral hypoperfusion before treatment for DKA, followed by reperfusion, may be an important cause of CE and cerebral injury.

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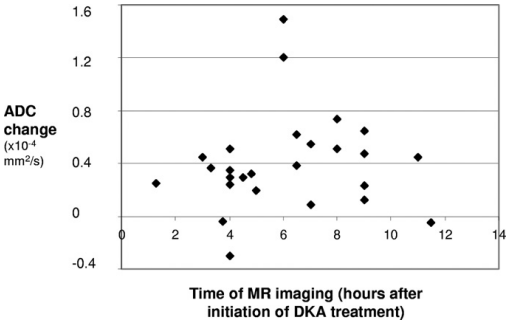

Figure 4. Correlation of ADC elevation during DKA treatment with the timing of MR imaging during treatment.

Table II. Biochemical factors associated with ADC change during DKA treatment (n = 26)

Variable	Coefficient*	*P* value	95% Confidence interval
Initial glucose	−2.76	.33	−8.62, 3.10
Initial sodium	−2.14	.13	−4.95, 0.66
Initial serum urea nitrogen	1.57	.04	0.07, 3.06
Initial pH	−3.35	.70	−21.27, 14.65
Initial respiratory rate	1.45	.05	0.02, 2.89

Variable	Coefficient*	*P* value	95% Confidence interval
Change in osmolality	1.51	.17	−0.72, 3.74
Initial osmolality	0.10	.89	−1.33, 1.53
Initial serum urea nitrogen	2.15	.01	0.55, 3.74
Initial pH	−2.14	.80	−19.51, 15.22
Initial respiratory rate	1.43	.04	0.04, 2.81

*Coefficients indicate the following incremental changes in the variable of interest: glucose: 100 mg/dL; sodium: 1 mEq/L; serum urea nitrogen: 1 mg/dL; pH: 0.1; respiratory rate: 1 breath/min; osmolality: 1 mOsm/L.

Table III. Association of biochemical variables with abnormal mental status during DKA treatment

Variable	Odds ratio	*P* value	95% Confidence interval
Initial glucose	0.97	.40	0.91, 1.04
Initial sodium	0.96	.73	0.73, 1.24
Initial serum urea nitrogen	1.05	.59	0.87, 1.27
Initial pH	5.08	.14	0.59, 43.45
Initial respiratory rate	1.26	.02	1.04, 1.53

Odds ratios indicate the following incremental changes in the variable of interest: glucose: 100 mg/dL; sodium: 1 mEq/L; serum urea nitrogen: 1 mg/dL; pH: 0.1; respiratory rate: 1 breath/min.

Part V

Appendices

Appendix A

Patient Study File Worksheets

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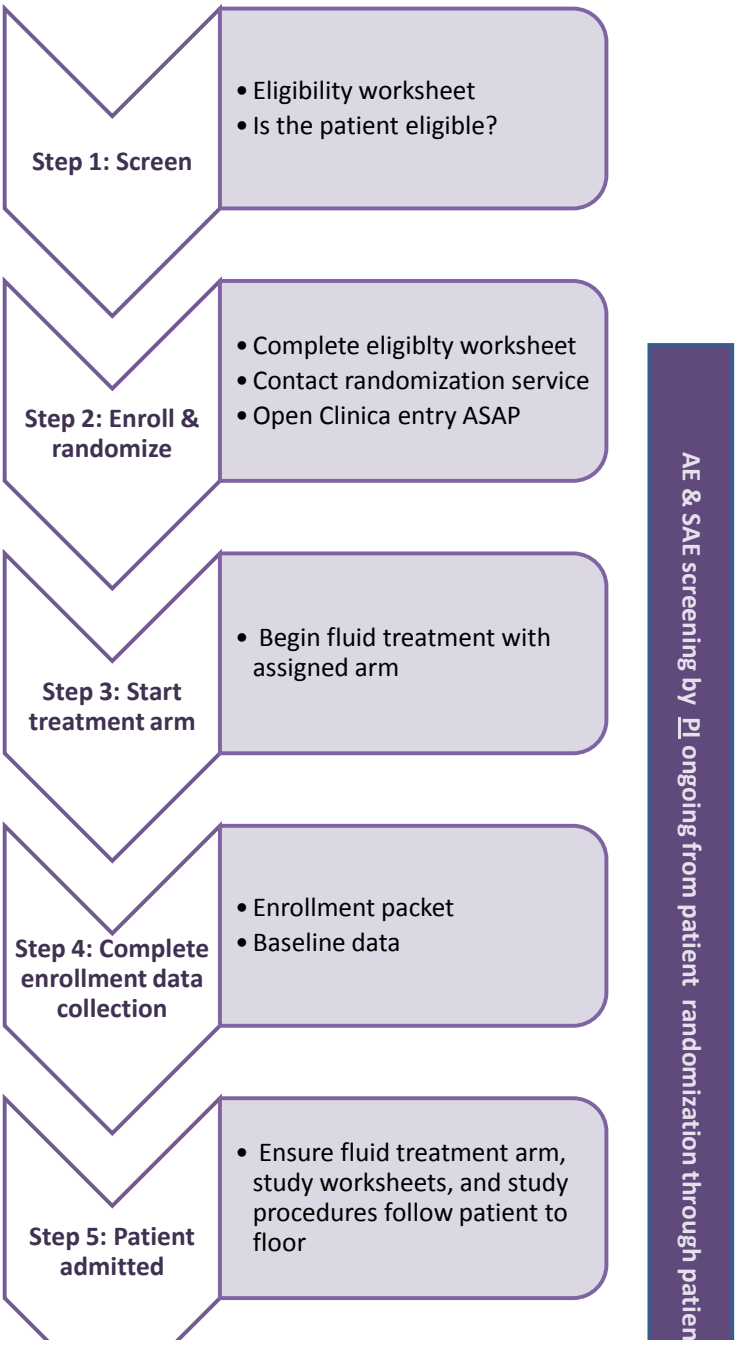
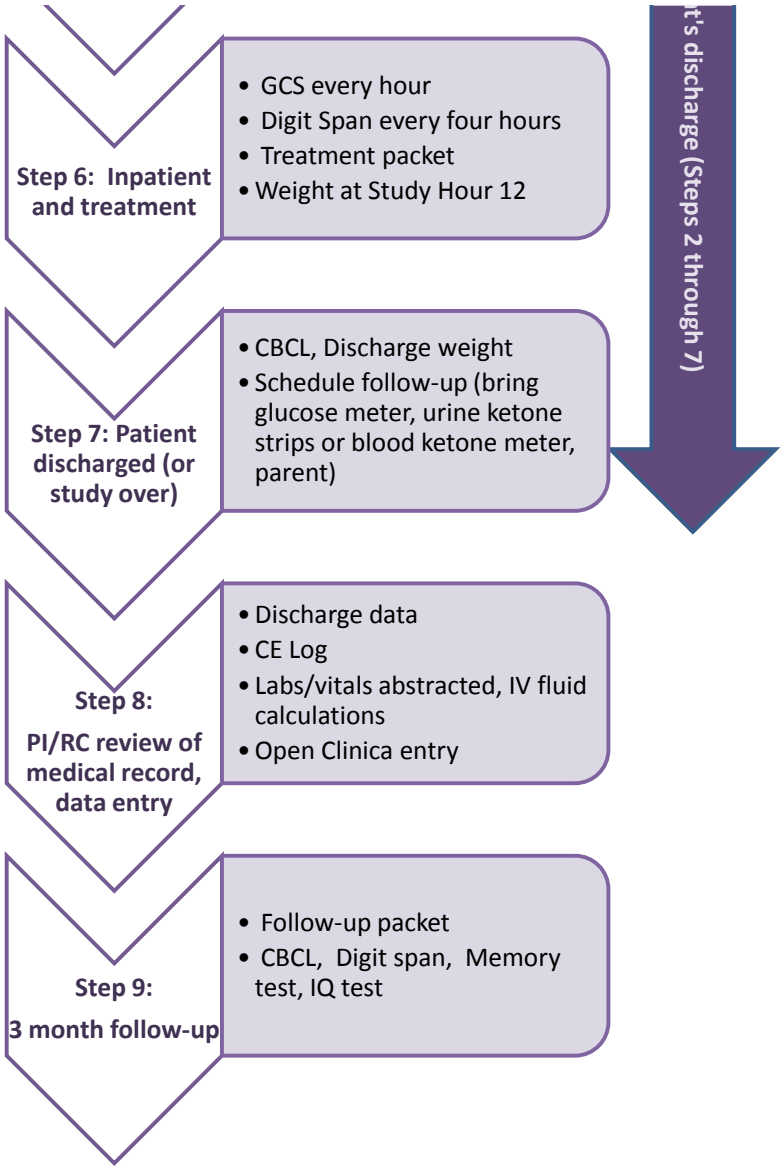
A.1 OpenClinica events and Patient Study File worksheet reference

OpenClinica Event	OpenClinica CRF	FLUID Study Worksheet	FLUID Study Worksheet Packet
Screening and Enrollment	Demographics	Demographics	Enrollment
Screening and Enrollment	Screening & Enrollment	Screening and Enrollment	Enrollment
Study Initiation	Diabetes History	Diabetes History	Treatment
Study Initiation	Physical Examination	Physical Examination	Enrollment
Study Initiation	Physician Treatment Initiation	Physician Treatment Initiation	Enrollment
Study Initiation	Review of Medical Conditions	Review of Medical Conditions	Enrollment
DKA Treatment	Cerebral Edema Treatment Log	Specific Treatment Log	Discharge
DKA Treatment	Discharge Data	Discharge Data	Discharge
DKA Treatment	Fluid Administration	Fluid Administration Log	Discharge
DKA Treatment	GCS & Digit Span Log	First Digit Span	Enrollment
DKA Treatment	GCS & Digit Span Log	GCS Log	Treatment
DKA Treatment	GCS & Digit Span Log	Digit Span packets	Treatment
DKA Treatment	Imaging Reports	Discharge Data: CTs & MRIs	Treatment
DKA Treatment	Laboratory Data & Vital Signs Log	Vitals and Lab Log	Discharge
Family Data	Caregiver Information	Caregiver Demographics	Treatment
Family Data	Caregiver Information	Inpatient CBCL	Treatment
Safety Data	Adverse Event Log	Adverse Event Log	Treatment
Safety Data	Adverse Event Log	Adverse Event Log	Discharge
Safety Data	Concomitant Medications Log	Concomitant Medications	Treatment
Safety Data	Concomitant Medications Log	Concomitant Medications Log	Discharge
Serious Adverse Event	Serious Adverse Event Report	Serious Adverse Event Reporting	Treatment
Serious Adverse Event	Serious Adverse Event Report	Serious Adverse Event Reporting	Discharge
3-Month Follow-up	3-Month Follow-up Status & History	Follow-up worksheet	Follow-up
3-Month Follow-up	3-Month Follow-up Visit	Follow-up CBCL	Follow-up
3-Month Follow-up	3-Month Follow-up Visit	Follow-up Digit Span	Follow-up
3-Month Follow-up	3-Month Follow-up Visit	IQ test	Follow-up
3-Month Follow-up	3-Month Follow-up Visit	Memory test	Follow-up
Unscheduled	Not Enrolled	Not Enrolled	Not Enrolled
Unscheduled	Outside of Protocol Specifications	OOPS Log	Miscellaneous
Unscheduled	Withdrawn Consent	Study Withdrawal	Miscellaneous
CDMCC Use Only	CBCL Scores	NA	CDMCC
CDMCC Use Only	Cognitive Testing Scores	NA	CDMCC

A.2 FLUID Study General Workflow


Step 1: Screen
• Eligibility worksheet
• Is the patient eligible?
Step 2: Enroll & randomize
• Complete eligiblty worksheet
• Contact randomization service
• Open Clinica entry ASAP
Step 3: Start treatment arm
• Begin fluid treatment with assigned arm
Step 4: Complete enrollment data collection
• Enrollment packet
• Baseline data
Step 5: Patient admitted
• Ensure fluid treatment arm, study worksheets, and study procedures follow patient to floor
AE & SAE screening by PI ongoing from patient randomization through patien


Step 6: Inpatient and treatment
• GCS every hour
• Digit Span every four hours
• Treatment packet
• Weight at Study Hour 12
Step 7: Patient discharged (or study over)
• CBCL, Discharge weight
• Schedule follow-up (bring glucose meter, urine ketone strips or blood ketone meter, parent)
Step 8: PI/RC review of medical record, data entry
• Discharge data
• CE Log
• Labs/vitals abstracted, IV fluid calculations
• Open Clinica entry
Step 9: 3 month follow-up
• Follow-up packet
• CBCL, Digit span, Memory test, IQ test
t's discharge (Steps 2 through 7)

A.3 Patient Study File: Enrollment worksheets

Enrollment

FLUID Study Worksheets: **Screening and Enrollment**

ENROLLING PHYSICIAN should complete this worksheet

Study Subject ID:__ __ __ __ __ __ __

Instructions: Completed by the enrolling physician to determine patient eligibility and begin the study. Completed based on the patient's condition at the time of ED presentation.

Inclusion Criteria

All inclusion criteria must be answered "yes" in order to meet study eligibility

1. Is the patient less than 18 years of age?	Yes	No
2. Does the patient have a diagnosis of DKA?	Yes	No
3. Is serum glucose or finger stick glucose concentration > 300 mg/dL? (_____)	Yes	No
4. Is venous pH < 7.25 or serum bicarbonate concentration < 15 mmol/L? (_____ or_____)	Yes	No

Exclusion Criteria

All exclusion criteria must be answered "no" in order to meet study eligibility

1. Does the patient have a pre-existing neurological disease that substantially impacts mental status or neurocognitive exam (e.g. cerebral palsy with developmental delay or autism)?	Yes	No
2. Does the patient present with concomitant alcohol or drug use, head trauma, meningitis or other conditions which might affect neurological function?	Yes	No
3. Has the patient been transferred after initiation of DKA treatment with anything other than one 10 cc/kg intravenous bolus of 0.9% saline? *(This exclusion criteria refers to boluses only; maintenance fluid & insulin treatment should not be considered. Please be sure to exclude patients who have received more than 10 cc/kg bolus at an outside hospital.)*	Yes	No
4. Is the patient known to be pregnant?	Yes	No
5. Has the patient been enrolled in this study twice previously? (per parent/patient recollection)	Yes	No
6. Has the patient been receiving IV fluids at a maintenance rate or greater for more than two hours? (maintenance per the 4-2-1 rule)	Yes	No
7. Has it been more than four hours since the start of DKA therapy (IV fluids, bolus, or insulin)?	Yes	No
8. Has the patient been given hyperosmolar therapy (i.e. mannitol or 3% normal saline) prior to or since arriving at your site?	Yes	No
9. Does the treating physician **intend** to *immediately* administer hyperosmolar therapy (i.e. mannitol or 3% normal saline) to the patient?	Yes	No
10. Is the patient's baseline GCS 11 or less?	Yes	No

Is this patient eligible to be approached for participation?	**Yes**	**No**

Physician's signature:_____

Screening Date (MM/DD/YYYY): _____ Screening Time (HH:MM): _____

Enrollment

FLUID Study Worksheets: **Screening and Enrollment**

ENROLLING PHYSICIAN should complete this worksheet

Study Subject ID:__ __ __ __ __ __ __

GCS

Patient's Total GCS at time of ED Evaluation: [ ]

NEXT STEPS TO ENROLLING ELIGIBLE PATIENTS:
1. Obtain parental permission
2. Randomize patient to study arm
Will need patient's GCS
3. Complete Enrollment Packet of patient information

Parental Permission

1. If eligible, was the parent/guardian approached for permission? Yes | No
   a. If not approached, please provide the reason:
   - ☐ Treating physician believes a specific fluid & electrolyte regimen is warranted
   - ☐ Site investigator or coordinator resources inadequate
   - ☐ Impossible to consent/randomize patient within study timeframe
   - ☐ Other, please describe:
2. If parent/guardian was approached, was permission given? Yes | No

   If yes, please complete the eligibility re-check & randomize as soon as possible!

   a. Parental permission signature date and time: MM/DD/YYYY | HH:MM

Final Eligibility Re-check

1. Was informed consent (parental permission) obtained within 2 hours of IV fluid initiation (of maintenance rate or greater)? Yes | No
2. Was informed consent (parental permission) obtained within 4 hours of DKA treatment initiation (IV bolus, IV insulin, IV fluids)? Yes | No

If the answer to either of these questions is NO, then please STOP.
This patient is no longer eligible for the study.

STOP | Patient still eligible | Patient ineligible

Randomization

HOW TO RANDOMIZE A PATIENT INTO THIS STUDY:
1. Call the randomization service (1-888-814-6525)
2. Enter study number: 026; Enter study password: 393; Follow automated prompts accordingly
3. Write down randomization number & study arm
NEVER EVER RE-Randomize! Once the patient is randomized they are in the study, on that assigned arm.
For help, call: (888) 814-6525. If the phone service is unavailable, try https://www.pecarn.org/fluid/randomization (NOTE: this is https; the "s" is important!)
If more than one GCS has been done since ED presentation, use the GCS done closest to but prior to the time of randomization

1. GCS used for randomization (*Use GCS closest to but prior to randomization) 3-13 | 14-15
2. Randomization number:
3. Treatment arm patient was assigned to:
   - ☐ A1: Additional bolus of 10 cc/kg; 0.45% NS rehydration fluid for assumed 10% body weight deficit
   - ☐ A2: Additional bolus of 10 cc/kg; 0.9% NS rehydration fluid for assumed 10% body weight deficit
   - ☐ B1: No additional bolus; 0.45% NS rehydration fluid for assumed 5% body weight deficit
   - ☐ B2: No additional bolus; 0.9% NS rehydration fluid for assumed 5% body weight deficit

Enrollment

FLUID Study Worksheets: **Screening and Enrollment**

ENROLLING PHYSICIAN should complete this worksheet

Study Subject ID:__ __ __ __ __ __ __

4. Randomization date & time:

MM/DD/YYYY	HH:MM

5. If randomization did not occur, though eligible and consent obtained, why was the patient not randomized?

HOW TO START THE STUDY:
1. Complete Physician Treatment Initiation worksheet; Use the calculation guides on the worksheet or the FLUID study calculator to determine and begin study bolus & maintenance fluid
2. Conduct the first Digit Span Recall Test (& ensure these are done every four hours)
3. Ensure GCS is done every hour

Enrollment

FLUID Study Worksheets: **Physician Treatment Initiation**

ENROLLING PHYSICIAN should complete this form

Study Subject ID:__ __ __ __ __ __

Instructions: The enrolling physician should complete this form after the consent process and as close to randomization as possible. ED Evaluation Clinical Data should reflect the patient's condition *before* any fluid was administered. This worksheet also includes study treatment arm fluid calculations.

ED Evaluation Date and Time

1. What was the date and time of the patient's initial ED Evaluation in your ED?

MM/DD/YYYY	HH:MM

ED Evaluation Clinical Data (before bolus or fluid initiation)

2. Did the patient complain of headache at ED presentation? Yes | No

2a. If yes, please indicate the headache severity:
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Unknown

3. Were the patient's peripheral pulses evaluated at ED presentation? Yes | No

3a. If yes, please indicate the results:
- ☐ Bounding
- ☐ Increased
- ☐ Normal
- ☐ Weak
- ☐ Absent or nonpalpable

4. Was the patient's capillary refill evaluated at ED presentation? Yes | No

4a. If yes, please indicate the results:
- ☐ <2 seconds
- ☐ 2-5 seconds
- ☐ >5 seconds

5. Has the patient been previously diagnosed with diabetes? Yes | No

Note: If yes, please complete the Diabetes History worksheet

IV Bolus Prior to Randomization

1. Did the patient receive any IV boluses before randomization? Yes | No
(≥ 10 cc/kg over one hour or less)

2. If the patient received any IV bolus, what was the total amount received? _____ cc/kg

3. What was the date and time of the initial IV bolus?

MM/DD/YYYY	HH:MM

Weight

Instructions: Please ensure that an **actual** weight (done in pjs or gown, no shoes) is used. No estimates.

1. What is the patient's actual weight? _____ kg

2. What was the date and time the actual weight was obtained?

MM/DD/YYYY	HH:MM

Note: The maximum weight used should be 100 kg. If a patient weighs more than 100 kg, please record the correct weight here but use 100 for study fluid calculations.

STUDY SOURCE DOCUMENT

Enrollment

FLUID Study Worksheets: **Physician Treatment Initiation**

ENROLLING PHYSICIAN should complete this form

Study Subject ID:__ __ __ __ __ __

Starting Study Treatment Arm: IV bolus

Instructions: If the patient received previous IV boluses totaling more than 10 cc/kg, **SUBTRACT** previous bolus amount over 10 cc/kg from the treatment arm. For arms A1 or A2, the goal is for the patient to receive boluses totaling 20 cc/kg. For example:
*If the patient received a previous IV bolus of 10 cc/kg and is assigned to either arm B1 or B2, no additional bolus should be given. If assigned to either A1 or A2, the additional 10 cc/kg bolus should be given.
*If the patient received a previous IV bolus of 15 cc/kg and is assigned to either arm B1 or B2, no additional bolus should be given. If assigned to either arm A1 or A2, the additional 5 cc/kg bolus should be given.
*If the patient received a previous IV bolus of 20 cc/kg (or more), regardless of the treatment arm, no additional bolus should be given.

1. Did the patient receive any additional IV bolus after randomization (including treatment arms A1 or A2)?	Yes	No
2. If the patient received any additional IV bolus, what was the additional amount received?	cc/kg	
3. What was the date and time of this additional IV bolus?	MM/DD/YYYY	HH:MM

Study IV Fluid Calculations: Replacement Deficit & Maintenance

For rate calculations, the total volume of ALL boluses given (prior to and after randomization) should be included and subtracted from maintenance and deficit rates.

ARM A1 OR A2

Deficit: Assume 10% dehydrated: weight (kg) x 100 =	(a)	ml
Remaining Deficit: subtract all boluses given: (a) – bolus IVF =	(b)	ml
Replace half of remaining deficit over 12 hours: (b) x 0.5 / 12 hours =	(c)	ml/hr
Maintenance IV fluid (calculate using 4-2-1 rule):	(d)	ml/hr
Replace remaining deficit over next 24 hours: (b) x 0.5 / 24 hours =	(e)	ml/hr
Total IV fluid (maintenance + remaining deficit) for first 12 hours:	(c) + (d)	ml/hr
Total IV fluid (maintenance + remaining deficit) for the following 24 hours:	(d) + (e)	ml/hr

Note: *Arm A1 uses maintenance & deficit fluid of 0.45% saline; Arm A2 uses maintenance & deficit fluid of 0.9% saline*

ARM B1 OR B2

Deficit: Assume 5% dehydrated: weight (kg) x 50 =	(a)	ml
Remaining Deficit: subtract all boluses given: (a) – bolus IVF =	(b)	ml
Replace remaining deficit over 48 hours: (b) / 48 hours =	(c)	ml/hr
Maintenance IV fluid (calculate using 4-2-1 rule):	(d)	ml/hr
Total IV fluid (maintenance + remaining deficit) for 48 hours:	(c) + (d)	ml/hr

Note: *Arm B1 uses maintenance & deficit fluid of 0.45% saline; Arm B2 uses maintenance & deficit fluid of 0.9% saline*

Perry Point Cooperative Studies
Interactive Touch-Tone Randomization System (ITTRS)
(888) 814-6525
(410) 642-1736

Randomizing a Subject

ITTRS: Welcome to Perry Point Cooperative Studies Randomization System.

ITTRS: Please enter your Study Number, followed by the pound sign.

Caller: Enter on telephone keypad 026#

ITTRS: Please enter the three-digit study password, followed by the pound sign.

Caller: Enter on telephone keypad 393 #

ITTRS: Please enter your two-digit site number, followed by the pound sign.

Caller: Enter on the telephone keypad _ _ #

ITTRS: Please enter your site password, followed by the pound sign.
.

Caller: Enter on the telephone keypad _ _ _ #

ITTRS: Please enter the randomization personnel's two-character initials.

Caller: Enter on the telephone keypad _ _

ITTRS: The initials you entered were _ _. If this correct press 1, if this is incorrect press 2, to hear your response again press 3. For assistance in entering letters using the keypad, press 4.

Caller: Enter on the telephone keypad 1 or 2 or 3 or 4

ITTRS: To randomize a subject, press 1. To request re-transmission of randomization information, press 2. To make a test call, press 3.To end this call, press 9.

Caller: Enter on the telephone keypad 1 or 2 or 3 or 9

ITTRS: If the subject has met all eligibility criteria, press 1. If the subject has not met all eligibility criteria, press 2.

Caller: Enter on the telephone keypad 1 or 2

ITTRS: Please enter this subject's 2-digit GCS score.

Caller: Enter on the telephone keypad _ _

ITTRS: The GCS score you entered was _ _ If this is correct press 1, if this is incorrect press 2, to hear your response again, press 3.

Caller: Enter on the telephone keypad 1 or 2 or 3

ITTRS: If the subject's parent or guardian has signed the informed consent, press 1; if not, press 2.

Caller: Enter on the telephone keypad 1 or 2

ITTRS: We will now review the randomization information. The subject you are randomizing (has a GCS score of _ _**.** If this information is correct, press 1. If the information is incorrect, press 2, and you will be able to correct the randomization information. To hear your response again, press 3.

Caller: Enter on the telephone keypad 1 or 2 or 3

ITTRS: subject has been randomized into study 026 The randomization date for this subject is **mm/dd/yyyy; hh:mm**. The protocol # assigned is _ _ **-**_ _ _ _.

ITTRS: For verification purposes, please enter the protocol number assigned. You do not need to enter the dash.

Caller: Enter on the telephone keypad _ _ **-**_ _ _ _

ITTRS: subject has been randomized into study treatment arm:
A1: Additional bolus of 10 cc/kg; 0.45% Normal Saline fluid for assumed 10% body weight deficit
A2: Additional bolus of 10 cc/kg; 0.90% Normal Saline fluid for assumed 10% body weight deficit
B1: No additional bolus; 0.45% Normal Saline fluid for assumed 5% body weight deficit
B2: No additional bolus; 0.90% Normal Saline fluid for assumed 5% body

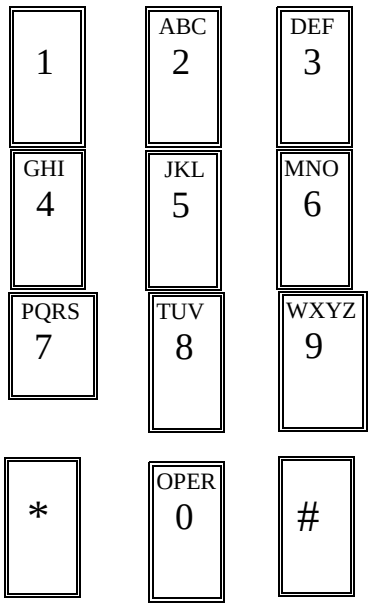
weight deficit

ITTRS: For verification purposes, please enter the study treatment arm assigned. For A1, press 1; for A2, press 2, for B1, press 3, for B2, press 4.

Caller: Enter on the telephone keypad 1 or 2 or 3 or 4

ITTRS: To repeat the randomization information, press 1, to randomize another patient, press 2, to end this call, press 9. If you need further assistance, please call 443-690-1102.

Letter Conversion for Reference Code



A	**21**	**P**	**71**
B	**22**	**Q**	**72**
C	**23**	**R**	**73**
		S	**74**
D	**31**	**T**	**81**
E	**32**	**U**	**82**
F	**33**	**V**	**83**
G	**41**	**W**	**91**
H	**42**	**X**	**92**
I	**43**	**Y**	**93**
		Z	**94**
J	**51**		
K	**52**		
L	**53**		
M	**61**		
N	**62**		
O	**63**		

To enter a letter using a telephone key pad it must be converted into two numbers.

First, press the key where the letter appears then press 1, 2, 3, or 4 to indicate whether the letter is the 1st, 2nd, 3rd or 4th letter on that key.

Example:

To enter a W, 1st press 9 because the letter appears on that key
Then press 1 because W is the 1st letter on the 9 key.

If your telephone does not have letters, or does not have the letters "Q" or "Z" , you must use the letter conversion chart or the telephone pad provided above.

Enrollment

FLUID Study Worksheets: **Review of Medical Conditions**

RC (with PI help), PI, OR ENROLLING PHYSICIAN

should complete this form

Study Subject ID:__ __ __ __ __ __ __

Review of Medical Conditions

Instructions: Please use this form to capture the patient's ***history of medical conditions*** prior to randomization. Please complete this form as close to randomization as possible. If "Abnormal" is selected for any system, a description must be provided. RC may abstract from the medical record; PI should answer all questions. This may be updated to include all hospitalization information, if needed. This data is for AE baseline reporting.

System	Normal	Abnormal	Unknown	Description
HEENT				
Cardiovascular				
Respiratory/Pulmonary				
Gastrointestinal				
Hepatic				
Genitourinary				
Renal				
Neurologic				
Psychiatric/Behavioral				
Endocrine				
Hematologic				
Musculoskeletal				
Dermatologic				
Allergies				
Immunology				
Alcohol/Drug Abuse				

Date of Review: _____ (MM/DD/YYYY)

Time of Review: _____ (HH:MM, military format)

Enrolling Physicians signature: _____

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Version 1.0

Enrollment

FLUID Study Worksheets: **Physical Examination**
RC (with PI help), PI, OR ENROLLING PHYSICIAN
should complete this form

Study Subject ID:__ __ __ __ __ __ __

Physical examination

Instructions: Please use this form to capture the patient's status ***physical condition*** just prior to the time of randomization. Please complete this form as close to randomization as possible. If "Abnormal" is selected for any system, a description must be provided. RC may abstract from the medical record; PI should answer all questions. This may be updated to include all hospitalization information, if needed. This data is for AE baseline reporting.

System	Normal	Abnormal	Not Assessed	Description
HEENT				
Cardiovascular				
Respiratory/Pulmonary				
Gastrointestinal				
Hepatic				
Genitourinary				
Renal				
Neurologic				
Psychiatric/Behavioral				
Endocrine				
Hematologic				
Musculoskeletal				
Dermatologic				
Allergies				
Immunology				
Alcohol/Drug Abuse				

Date of Physical Exam: _____ (MM/DD/YYYY)

Time of Physical Exam: _____ (HH:MM, military format)

Enrolling Physician's signature: _____

Page 1 of 1
Version 1.0

Enrollment

FLUID Study Worksheets: **Demographics**

Study Subject ID:__ __ __ __ __ __ __

RC OR PI OR ENROLLING PHYSICIAN WITH PARENT/GUARDIAN
should complete this form

Patient Demographics

1. Patient's Name: _____
2. Patient's Date of Birth: _____ (MM/DD/YYYY)
3. Patient's MRN: _____
4. Patient's Study ID: _____
5. Patient's Parent/Guardian's Name(s): _____
6. Home Phone: _____
7. Alternate Phone(s):

8. Other contacts:

9. Patient's Mailing Address:

10. Patient's sex:
- ☐ Male
- ☐ Female

11. Patient's Race (Check all that apply):
- ☐ American Indian or Alaska Native
- ☐ Asian
- ☐ Black or African American
- ☐ Native Hawaiian or Other Pacific Islander
- ☐ White
- ☐ Unknown

12. Patient's Ethnicity (check one):
- ☐ Hispanic or Latino
- ☐ Not Hispanic or Latino
- ☐ Unknown

Note: *Race and ethinicity should be as reported by the parent/guardian; not abstracted from the medical record. See instructions for definitions.*

13. Has this patient been enrolled in this study previously?

Yes	No

13a. If yes, what was the patient's previous study subject ID?

Note: *Patients can be enrolled in this study twice only.*
Second enrollment note: *If this is the patient's second enrollment in the study and they have not yet completed the follow-up for the first enrollment, no follow-up for the first enrollment is needed. Schedule only one follow-up visit for 3 months (+/- 4 weeks) from this second enrollment.*

Form Completed by: _____

Enrollment

FLUID Study Worksheets: **Demographics**

Study Subject ID:__ __ __ __ __ __ __

RC OR PI OR ENROLLING PHYSICIAN WITH PARENT/GUARDIAN

should complete this form

Demographics Instructions:

Pick all races that apply to the patient (multiple choices are ok). Subjects who ask should be told to mark all races that apply to them. Choices are defined by the NIH Policy on Reporting Race Data as follow:

American Indian or Alaska Native: A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

Black or African American: A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American".

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Only one choice should be made for the ethnicity. Subjects who ask should be told to mark the ethnicity that they most identify as. Choice are defined by the NIH Policy on Reporting Ethnicity Data as follow:

Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino".

A.4 Patient Study File: Treatment worksheets

Enrollment
Treatment

FLUID Study Worksheets: **Digit Span Recall**
RC, PI, or BEDSIDE CARE PROVIDER
should complete DIGIT SPAN packets

Study Subject ID:__ __ __ __ __ __ __

Digit Span Recall Test packets should be printed from eRoom!

This worksheet is a placeholder. **Sites will use the actual Digit Span Packet for each patient**. These packets will follow patient through the study, digit span will be scored directly on them, entered into Open Clinica as below, and completed packets will be uploaded to Open Clinica.

Digit Span Recall Logs

Instructions: Please assess a Digit Span Recall score for this patient every 4 hours during the 24-hour study period using the digit span packets. The first Digit Span Recall test should be administered as soon as possible after randomization. Please do NOT wake up a patient for the digit span recall test between the hours of 10 PM and 7 AM. If needed, the first Digit Span Recall of the day should be completed as close to 7 AM as possible.

Conducting a Digit Span Recall Test Instructions:
For each testing session, you will conduct two parts in each digit span, one forward and one backward, in this order. Read the instructions on the packet worksheets to the participant. Each session should have one completed set (i.e. 1 forward and 1 backward). Proceed to the next set in the packet at each new session. Score the tests as instructed on each sheet.

Open Clinica Data Entry

Date	*Time*	*Digit Span Total Score Forward*	*Digit Span Total Score Backward*

*****Upload completed Digit Span packets to Open Clinica*****
Digit Span Recall Test packets are STUDY SOURCE DOCUMENTS

Enrollment
Treatment

FLUID Study Worksheets: **GCS Log**

BEDSIDE CARE PROVIDER should complete this form

Study Subject ID:__ __ __ __ __ __ __

Hourly GCS Log

STUDY PERIOD ENDS: Date: _____ Time _____ : _____

Instructions: Please assess a GCS score for this patient every hour and record the scores on this log. The next GCS should be done as close to an hour after the previous as possible. Please circle each section's score and total the score.
For infants under 2 years of age, use the descriptions provided in parentheses ().

If a GCS is 13 or less, please verify the assessment with a repeat GCS in 15 minutes. If a GCS is 13 or less please report to the attending physician, per usual hospital protocol.

GCS

Date															
Time (military format)															
Eye Opening															
Spontaneously	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
To Speech (shout)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
To Pain	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
No Response	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Verbal Response															
Oriented (Coos, Babbles)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Confused (Irritable, Cries)	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Inappropriate Words (Cries to pain)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Incomprehensible Sounds (Moans to pain)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
No Responses	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Motor															
Obeys (Spontaneous)	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Localized Pain	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Withdrawal to Pain	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Flexion to Pain (Decorticate)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Extension to Pain (Decerebrate)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
No Response to Pain	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
TOTAL SCORE															
Is this GCS 13 or below?	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No
If yes, time redone (Please redo the GCS in a new column)															

Weight

Date:

Patient's actual weight at Study Hour 12 (____:____)
PJs or gown, no shoes — Time (HH:MM)

_____ kg

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Version 1.0

Enrollment
Treatment

FLUID Study Worksheets: **GCS Log**

BEDSIDE CARE PROVIDER should complete this form

Study Subject ID:__ __ __ __ __ __ __

Hourly GCS Log continued

STUDY PERIOD ENDS: Date: _____ Time _____ : _____

Instructions: Please assess a GCS score for this patient every hour and record the scores on this log. The next GCS should be done as close to an hour after the previous as possible. Please circle each section's score and total the score.
For infants under 2 years of age, use the descriptions provided in parentheses ().

If a GCS is 13 or less, please verify the assessment with a repeat GCS in 15 minutes. If a GCS is 13 or less please report to the attending physician, per usual hospital protocol.

GCS Date															
Time (military format)															
Eye Opening															
Spontaneously	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
To Speech (shout)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
To Pain	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
No Response	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Verbal Response															
Oriented (Coos, Babbles)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Confused (Irritable, Cries)	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Inappropriate Words (Cries to pain)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Incomprehensible Sounds (Moans to pain)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
No Responses	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Motor															
Obeys (Spontaneous)	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Localized Pain	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Withdrawal to Pain	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Flexion to Pain (Decorticate)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Extension to Pain (Decerebrate)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
No Response to Pain	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
TOTAL SCORE															
Is this GCS 13 or below?	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No
If yes, time redone (Please redo the GCS in a new column)															

If ANY GCS was not done, please explain why not:

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Treatment

FLUID Study Worksheets: **Diabetes History**

Study Subject ID:__ __ __ __ __ __ __

RC OR ENROLLING PHYSICIAN, WITH PARENT INTERVIEW

should complete this form

Instructions: The enrolling physician or RC should complete this form with parent interview after the consent process and after the patient has been randomized to a treatment arm. This form is only needed for patients who have been previously diagnosed with diabetes.

Diagnosis History

1. Please indicate the year of first diabetes diagnosis: _____ (YYYY)

2. Has the patient ever had an episode of severe hypoglycemic episodes with loss of consciousness or seizures:

Yes	No	Unable to determine

2a. If yes, how many times?
- ☐ One-two (1-2)
- ☐ More than two (>2)
- ☐ Unable to determine

3. Has the patient ever been previously diagnosed with diabetic ketoacidosis (DKA)?

Yes	No	Unable to determine

3a. If yes, how many times?
- ☐ One-two (1-2)
- ☐ More than two (>2)
- ☐ Unable to determine

To help parents answer these questions, use these prompting questions:

*When your child was diagnosed with diabetes, did he/she have DKA? Did your child need to be admitted to the ICU?

*Did your child start insulin shots right away or after a day or so of receiving IV treatments?

*Since diagnosis of diabetes, has your child ever needed to be in the hospital for diabetes? If so, was it because of DKA/ because he/she had ketones? How many times?

If the parent says the child was never in the hospital/ ED because of diabetes, the answer to previous DKA episodes should be "no." If the parent says "yes" the child was in the hospital/ED for diabetes, but are unsure as to why or whether the child had ketones at the time, please look back in your hospital's medical records.

- If you find a previous DKA episode, please answer "yes" to previous DKA episodes and answer "1-2" for the number of times.
- If you find more than two previous DKA episodes, please answer "yes" and "more than two".
- If you look in your hospital's medical records and find no documentation of a previous DKA episode, please answer "unable to detemine."

If the parent is unsure and has not been to your hospital, please request a medical release from the parent so that the Site PI can contact the doctor who manages the patient's diabetes to ask.

HbA1c

Please collect all HbA1c lab results done within the past 12 months.

4. Does the patient receive regular diabetes care at an endocrinology clinic associated with your hospital system?

Yes	No

4a. If no, where does the patient receive care?

Please request a medical release form to access HbA1C data from the past 12 months from the patient's regular endocrinologist (if not within your hospital system).

Treatment

FLUID Study Worksheets: **Diabetes History**

Study Subject ID:__ __ __ __ __ __ __

RC OR ENROLLING PHYSICIAN, WITH PARENT INTERVIEW

should complete this form

HbA1c continued

Medical Release Requested:	Yes	No
Medical Release Signed:	Yes	No
Medical Release sent to primary physician:	Yes	No
Lab results received from primary physician:	Yes	No

HbA1C history	Date	HbA1c%
1st HbA1c level		
2nd HbA1c level		
3rd HbA1c level		
4th HbA1c level		
5th HbA1c level		
**DO NOT collect beyond the past 12 months.*		

Treatment

FLUID Study Worksheets: **Caregiver Demographics**

PATIENT'S PARENT/GUARDIAN should complete this form

Study Subject ID:__ __ __ __ __ __ __

Instructions: This form is to be completed with information from the patient's caregiver(s). This should be collected prior to the patient's discharge. This can be done in conjunction with the CBCL administration. Caregiver A should be the same caregiver who completes the CBCL survey.

Caregiver's information:

Caregiver A: CBCL Respondent

1. Caregiver's initials: _____

2. Caregiver's sex:
   - ☐ Male
   - ☐ Female

3. Caregiver's relationship to the patient:
   - ☐ Biological parent
   - ☐ Adoptive parent
   - ☐ Step parent
   - ☐ Foster parent
   - ☐ Grandparent
   - ☐ Other legal guardian
   - ☐ Other (specify): _____

4. Caregiver's highest education received:
   - ☐ No education
   - ☐ Some high school or less
   - ☐ High school graduate or GED
   - ☐ Vocational school or some college
   - ☐ College degree
   - ☐ Master's or doctoral degree

Caregiver B: Additional caregiver (if available)

5. Caregiver's initials: _____

6. Caregiver's sex:
   - ☐ Male
   - ☐ Female

7. Caregiver's relationship to the patient:
   - ☐ Biological parent
   - ☐ Adoptive parent
   - ☐ Step parent
   - ☐ Foster parent
   - ☐ Grandparent
   - ☐ Other legal guardian
   - ☐ Other (specify): _____

8. Caregiver's highest education received:
   - ☐ No education
   - ☐ Some high school or less
   - ☐ High school graduate or GED
   - ☐ Vocational school or some college
   - ☐ College degree
   - ☐ Master's or doctoral degree

Household information:

5. What is the patient's family annual household income?
   - ☐ Less than $20,000
   - ☐ $20,000 to $39,999
   - ☐ $40,000 to $59,999
   - ☐ $60,000 to $79,999
   - ☐ $80,000 to $99,999
   - ☐ $100,000 to $119,999
   - ☐ $120,000 to $149,999
   - ☐ $150,000 to $199,999
   - ☐ $200,000 or more

Note: Income should include all the resources available to the patient, so this should include the income of both parents, even in the case of shared custody or a foster family situation.

CBCL

Did Caregiver A complete the CBCL survey? ☐ Yes ☐ No

FLUID Study Worksheets: **AE and SAE Instructions**

Study Subject ID:__ __ __ __ __ __ __

Adverse Event

An **Adverse Event (AE)** is an untoward medical occurrence experienced by a subject. An event constitutes a disease, a set of related signs or symptoms, or a single sign or symptom. On each study day, the site PI will evaluate for adverse events.

• Report AEs if they occurred after randomization and before hospital discharge

• Report only new AEs (not previously reported) unless the symptom got worse

• Do not report pre-existing conditions that were described on the Review of Medical Conditions or the Physical Exam form unless the symptom got worse. E.g: Patient presents with a headache and on day 1 pt still has a headache and it has not worsened. This is not an AE. If the headache was a pre-existing condition but is now worse, report it.

• Abnormal lab results already collected for the study (Glucose, Sodium (NA), Potassium, (K), Chloride (Cl), Bicarbonate (HC03), BUN, Creatinine (Cr), Venous pH, PC02, Serum Ca, Phosphate, Calcium (CA), magnesium (Mg), and HbA1C) should not be included as an adverse event unless they are considered to be a Serious Adverse Event by the site PI.

• Abnormal lab results not already collected for the study should be recorded as AEs if the severity is a grade 2 or higher on the CTCAE.

Serious Adverse Event (SAE)

A **Serious Adverse Event (SAE)** is an adverse event that meets one or more of the following criteria:

- Results in death; OR
- Is life threatening (the patient was, in the view of the Principal Investigator, in immediate danger of death from the event as it occurred); OR
- Requires inpatient hospitalization or prolongs an existing hospitalization; OR
- Results in persistent or significant disability/incapacity; OR
- Results in congenital anomaly/birth defect; OR
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

If an adverse event is determined to be a SAE, report it to the CDMCC within 24 hours & complete the SAE form within 72 hours.

Relationship to the study intervention

The determination of the association between the adverse event and the study intervention **MUST be made by the Principal Investigator for the study.** The Research Coordinator should never determine the association of an adverse event to the study intervention.

Expectedness:

An adverse event is considered expected if it is known to be associated with diabetic ketoacidosis, the underlying medical condition of the subject, is directly related to study outcome (e.g. cerebral edema, somnolence), or is otherwise mentioned in the protocol, informed consent, or other study documents.

For this protocol, **expected events include**:

- Death
- Thromboses
- Renal failure
- Cerebral Edema
- Cerebral infarction
- Cerebral thrombosis
- Seizure
- Gastrointestinal necrosis
- Pancreatitis
- Hemolytic anemia
- Cardiac arrhythmias
- Rhabdomyolysis
- Pulmonary edema
- Hyperchloremic acidosis
- Somnolence

Unanticipated Problem

Unanticipated problems (UP) are defined as incidents, experiences, or outcomes that are unexpected, related to participation in the FLUID study, and suggest that the research places subjects at a greater risk of harm than was previously known or recognized. The Site PI will report unanticipated problems to the CDMCC within 24 hours. A detailed completed report will be required to be sent to the CDMCC within 3 working days of the event.

***Sites must report any SAE to the CDMCC within 24 hours of becoming aware of the SAE.**
***Completed SAE Forms must be faxed to CDMCC at 801-585-3243 within 72 hours.**

Through Discharge

FLUID Study Worksheets: **Adverse Event Log**

RC AND PI should complete this form

Study Subject ID:__ __ __ __ __ __ __

Instructions: Adverse events (AE) that occur between the time of randomization and hospital discharge should be recorded on this log. Abnormal lab results already collected for the study (glucose, Na, K, Cl, HCO3, BUN, Cr, pH, pCO2, Serum Ca, Mg, Phos, HbA1c) should not be included as an adverse event unless they are considered to be a Serious Adverse Event by the site PI. Abnormal lab results not already collected for the study should be recorded as AEs if the severity a grade 2 or higher on the CTCAE.

Name of Adverse Event	AE Start Date (MM/DD/YYYY)	AE End Date (MM/DD/YYYY)	**Relationship to the Study Intervention**	Action Taken	Outcome	Was the AE Expected or Unexpected?	Intensity	Is this a serious adverse event?	Investigator (PI or Sub-I) Signature and Date
			1) Not Related 2) Possibly Related 3) Probably Related	1) None 2) Intervention: Surgery or Procedure 3) Med initiation, change, or discontinue 4) Other (please describe)	1) Recovered (returned to baseline) 2) Recovered with sequelae 3) Symptom persists 4) Death	1) Expected 2) Unexpected	1) Mild 2) Moderate 3) Severe	1) Yes **(this is an SAE; please complete the SAE Report form)** 2) No	

****A DELEGATED STUDY INVESTIGATOR MUST ASSESS RELATEDNESS****

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Through Discharge

FLUID Study Worksheets: **Serious Adverse Event Reporting**

PI should complete this form

Study Subject ID:__ __ __ __ __ __ __

Reporter Name and Title: _____

PLEASE ENTER THE FOLLOWING INFORMATION INTO OPEN CLINICA:

Date Form Completed: (MM/DD/YYYY)	**Date & Time Site Became Aware of SAE:** (MM/DD/YYYY; HH:MM)	**Date & Time SAE Report Faxed to CDMCC:** (MM/DD/YYYY; HH:MM)

Primary Serious Adverse Event:	**Date & Time SAE Started:** (MM/DD/YYYY; HH:MM)	**Date & Time SAE Resolved:** (MM/DD/YYYY or blank if ongoing)	☐ **or ongoing**

Criteria for Serious Adverse Event Check (✓) All That Apply	**Serious Adverse Event Status at this Time** (✓)
☐ Death Date of Death(MM/DD/YYYY): _____ ☐ Life Threatening ☐ Inpatient hospitalization ☐ Prolongation of existing hospitalization ☐ Persistent or significant disability/incapacity ☐ Congenital abnormality/birth defect ☐ Other (specify) _____	☐ Death ☐ Recovered (returned to baseline) ☐ Recovered with sequelae ☐ Symptoms persist

****Relationship to Study Intervention**** (✓)	**Intensity of Event** (✓)	**Action Taken in Response to the Event** (✓)
☐ Not Related	☐ Mild	☐ None
☐ Possibly Related	☐ Moderate	☐ Study treatment discontinued
☐ Probably Related	☐ Severe	☐ Study treatment interrupted/restarted

**** PI MUST ASSESS RELATEDNESS****

Was the Serious Adverse Event Expected or Unexpected? (✓)	**For this study, the following are Expected Adverse Events:**	
☐ Expected	➢ Death	➢ Hemolytic anemia
☐ Unexpected	➢ Thromboses	➢ Cardiac arrhythmias
	➢ Renal failure	➢ Rhabdomyolysis
	➢ Cerebral Edema	➢ Pulmonary edema
	➢ Cerebral infarction	➢ Hyperchloremic acidosis
	➢ Cerebral thrombosis	➢ Somnolence
	➢ Seizure	➢ Pancreatitis
	➢ Gastrointestinal necrosis	

*****Fax completed SAE Form to the CDMCC at 801-585-3243 within 72 hours of site becoming aware of SAE*****

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Through Discharge

FLUID Study Worksheets: **Serious Adverse Event Reporting**

PI should complete this form

Study Subject ID:__ __ __ __ __ __ __

Relevant Test/Laboratory Data or attach laboratory reports (check box if lab reports are attached) ☐				
Test name	Normal Range	Value/Date	Value/Date	Value/Date

Relevant Background Information (Include pre-existing medical conditions)

Narrative for Serious Adverse Event (Please include any other important information that is not included on this form)

Investigator Signature: _____ **Date:**_____

STUDY SOURCE DOCUMENT

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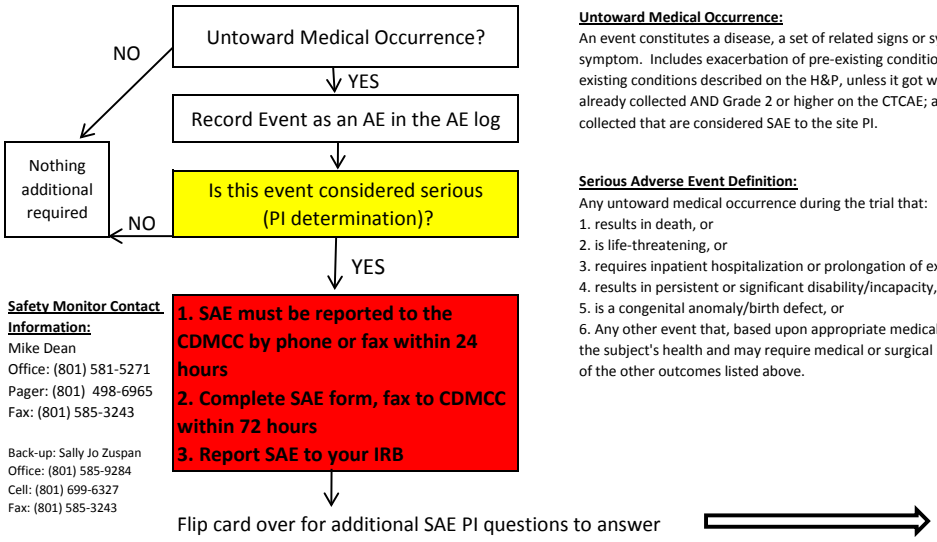
PECARN AE & SAE Reporting

Review medical record daily from randomization through hospital discharge



Safety Monitor Contact Information:
Mike Dean
Office: (801) 581-5271
Pager: (801) 498-6965
Fax: (801) 585-3243

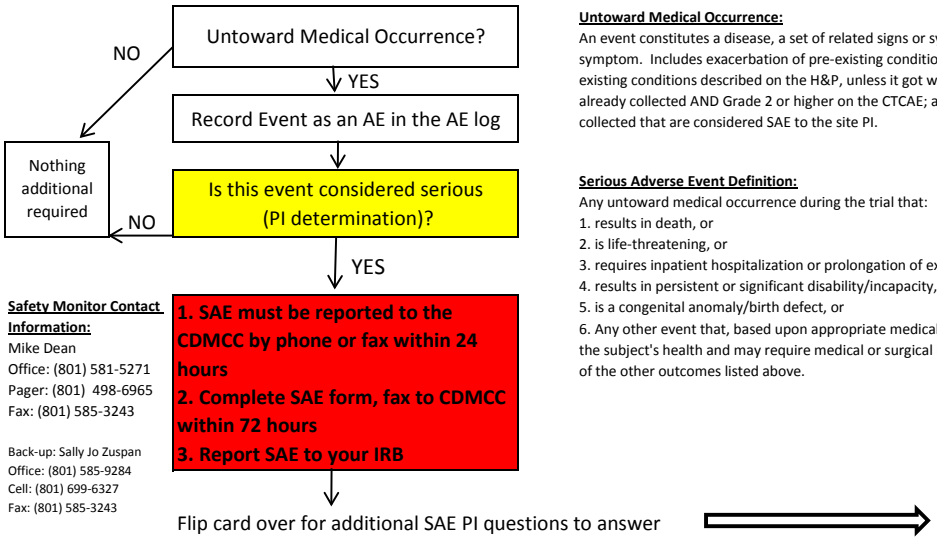
Back-up: Sally Jo Zuspan
Office: (801) 585-9284
Cell: (801) 699-6327
Fax: (801) 585-3243

Untoward Medical Occurrence:
An event constitutes a disease, a set of related signs or symptoms, or a single sign or symptom. Includes exacerbation of pre-existing condition or events (though not pre-existing conditions described on the H&P, unless it got worse); abnormal labs NOT already collected AND Grade 2 or higher on the CTCAE; abnormal labs already collected that are considered SAE to the site PI.

Serious Adverse Event Definition:
Any untoward medical occurrence during the trial that:
1. results in death, or
2. is life-threatening, or
3. requires inpatient hospitalization or prolongation of existing hospitalization, or
4. results in persistent or significant disability/incapacity, or
5. is a congenital anomaly/birth defect, or
6. Any other event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above.

PECARN AE & SAE Reporting

Review medical record daily from randomization through hospital discharge



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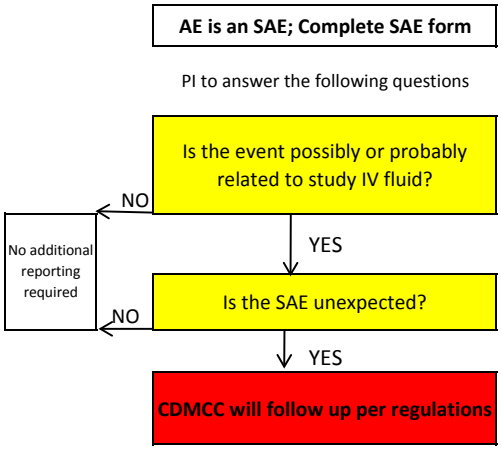
Serious Adverse Event Definition:
Any untoward medical occurrence during the trial that:
1. results in death, or
2. is life-threatening, or
3. requires inpatient hospitalization or prolongation of existing hospitalization, or
4. results in persistent or significant disability/incapacity, or
5. is a congenital anomaly/birth defect, or
6. Any other event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above.

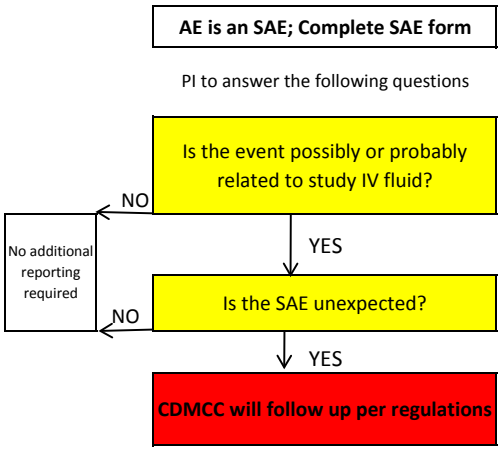
PECARN AE & SAE Reporting Continued
SAE Questions



Assessment of Causality:
Not Related: The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.
Possibly Related (reasonable possibility): The event follows compatible temporal sequence from the time of beginning the assigned study intervention, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.
Probably Related: The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention, and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Expectedness
For this protocol, expected events include:
* Death * Cerebral thrombosis * Cardiac arrhythmias * Thromboses
* Seizure * Rhabdomyolysis * Renal failure * Pulmonary edema
* Gastrointestinal necrosis * Cerebral Edema * Pancreatitis
* Hyperchloremic acidosis * Cerebral infarction * Hemolytic anemia
* Somnolence

PECARN AE & SAE Reporting Continued
SAE Questions



Assessment of Causality:
Not Related: The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.
Possibly Related (reasonable possibility): The event follows compatible temporal sequence from the time of beginning the assigned study intervention, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.
Probably Related: The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention, and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Expectedness
For this protocol, expected events include:
* Death * Cerebral thrombosis * Cardiac arrhythmias * Thromboses
* Seizure * Rhabdomyolysis * Renal failure * Pulmonary edema
* Gastrointestinal necrosis * Cerebral Edema * Pancreatitis
* Hyperchloremic acidosis * Cerebral infarction * Hemolytic anemia
* Somnolence

Through Discharge

FLUID Study Worksheets: **Concomitant Medications**

PI should complete this form

Study Subject ID:__ __ __ __ __ __ __

INSTRUCTIONS: Record concomitant medications administered from the time of randomization through patient's discharge from the hospital.

All pharmacological agents should be recorded on the Con Med Log. DO NOT collect INSULIN or IV fluids as a con med.

Medication Name	Start Date (MM-DD-YYYY)	Start Time (HH:MM)	Continuing? (Yes or No)	Stop Date (MM-DD-YYYY)	Stop Time (HH:MM)	Was the medication given in relation to an adverse event? (Yes or No)	If yes, provide reason

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A.5 Patient Study File: Discharge worksheets

Discharge

FLUID Study Worksheets: **Discharge Data**

RC AND PI should complete this form

Study Subject ID:__ __ __ __ __ __ __

Instructions: Data to be collected upon discharge (no matter when discharge occurs). This is also a reminder checklist of what should be completed prior to discharge.

Discharge Tasks

For patients/parents

- ☐ Discharge weight done
- ☐ Three Month Follow-up appointment made (patients age 3 years and up)
  - ☐ Contact information confirmed for reminder
  - ☐ To bring: parent, glucose meter, ketone strips
- ☐ Study contact info given to parents
- ☐ CBCL completed by parent
- ☐ Future Studies Form completed

For research team

- ☐ All AEs & SAEs reviewed by PI, forwarded to CDMCC as needed
- ☐ Specific Treatment Log completed by PI (if applicable)
- ☐ GCS log, glucose/digit span log, and CBCL uploaded to OpenClinica
- ☐ Space for follow-up visit reserved
- ☐ Reminder to remind patient/parent of follow-up visit placed
- ☐ All worksheets completed, data entered into OpenClinica

Discharge Data

1. What was the patient's measured (actual) weight at hospital discharge? (gown or pjs, no shoes) [ ] kg

2. Hospital Discharge Date: [ ] MM/DD/YYYY Time: [ ] HH:MM

3. Date of scheduled 3-month follow-up visit: [ ] MM/DD/YYYY

4. Did the parent/guardian consent to contact for possible future studies? Yes | No

PI Questions

5. Did the patient have clinically-overt cerebral edema? **Yes** | **No**

Note: Please see MOO for definition; not based on GCS, but on receipt of any one of these treatments: mannitol, endotrachael intubation, or hypertonic saline. If yes, please complete a "Specific Treatment Log" for patient. Also, for FLUID, cerebral edema is an SAE; complete the AE Log and SAE Reporting Form & notify the CDMCC within 24 hours..

6. Did the patient die during hospitalization? Yes | No

Note: *Death is an SAE; complete the AE Log and SAE Reporting Form; notify the CDMCC within 24 hours*

7. Did the patient have any head CTs or MRIs done? Yes | No

If yes, please upload all head CT and MRI reports to OpenClinica (DKA Treatment Event, Imaging Reports tab)

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Version 1.1

Discharge

FLUID Study Worksheets: **Fluid Administration Log**

RC AND PI should complete this form

Study Subject ID:__ __ __ __ __ __ __

Instructions: Please calculate the following IV fluid totals from the medical record. Half normal saline (1/2 NS), normal saline (NS), any other fluid and a total IV fluid volume should be calculated for all three time periods. The time periods are: 1) from IV start to DKA resolution, 2) from IV start to Study Hour 12, 3) from IV start to Study Hour 24. Study Hours are calculated from the time since randomization; Study Hour 12 = 12 hours after randomization, Study Hour 24 = 24 hours after randomization. Fluid calculations should start at IV start (even at an outside hosptial) and include ALL fluid (bolus & maintenance) the patient received.

Date and Times

1. IV Start date (MM/DD/YYYY) _____ IV Start time (HH:MM) _____

2. Study Treatment Start date (MM/DD/YYYY) _____ Study Treatment time (HH:MM) _____

NOTE: *This is the time the study calculated IV fluid rate was started for the assigned randomized treatment arm*

3. DKA Resolution date (MM/DD/YYYY) _____ DKA Resolution time (HH:MM) _____

NOTE: *"DKA resolution" is defined as the date & time the IV insulin drip is stopped.*

4. Study Hour 12 _____ HH:MM 5. Study Hour 24 _____ HH:MM

Fluid Calculations

From IV start	1/2 NS	NS	Other fluid	Total IV fluid
to DKA Resolution	mL	mL	mL	mL
to Study Hour 12	mL	mL	mL	mL
to Study Hour 24	mL	mL	mL	mL

Notes: *Please include all fluid given. In each row, 1/2 NS + NS + Other fluid should = Total IV fluid volume. Fluid volumes should be calculated regardless of dextrose or other additives. (1/2 NS includes "D5 .45" or "D10 .45")*

Please include fluids from all three time periods, even if DKA resolved before Study Hour 12 or 24. It's possible that all three time periods are the same (e.g. DKA resolved in Study Hour 10 & IV was stopped). However, once DKA is resolved, the IV fluid may continue, so please review and calculate all three time points (e.g. DKA resolved in Study Hour 10, IV stopped at Study Hour 13). If the patient was discharged before Study Hour 24, please indicate the fluid totals the patient received through discharge (so up to Study Hour 24).

<u>If you need assistance calculating these totals, please contact the CDMCC.</u>

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Version 1.1

Discharge

FLUID Study Worksheets: **Specific Treatment Log**

PI should complete this form

Study Subject ID:__ __ __ __ __ __ __

Clinically-overt Cerebral Edema Log

INSTRUCTIONS: Once the patient has been discharged, the PI should review the medical record for any indication of clinically-overt cerebral edema. For study purposes, this is identified as "Neurological impairment in association with administration of (1) mannitol or (2) hypertonic saline, or (3) endotracheal intubation." Please record any of these specific procedures listed here. This form should be completed only for patients listed as having clinically-overt cerebral edema on the Discharge Data Worksheet.

Indicate the following treatment(s) that the patient received.	**Treatment Start Date (MM/DD/YYYY)**	**Treatment Start Time (HH:MM)**	**Treatment Stop Date (MM/DD/YYYY)**	**Treatment Stop Time (HH:MM)**
1) Mannitol 2) Hypertonic saline 3) Endotracheal intubation				

Treatment

FLUID Study Worksheets: **Vitals and Lab Log**

RC (from the medical record) should complete this form

Study Subject ID:__ __ __ __ __ __ __

Instructions: Please enter ALL lab results from the medical record through hospital discharge (even if this is after the 24-hour study period). The timelines given are estimates based on the standard of care & site protocols for DKA treatment. If a particular part of a row of data was not done at that time, leave it blank (this does not need OOPS documentation).

Lab and Vitals to be recorded are:

1. Ketones (initial only)
2. Hourly glucose
3. Hourly vitals: blood pressure, respirations, heart rate (only needed for the first 24-hours)
4. Serum electrolytes (typically every 2-4 hours): Sodium, Potassium, Chloride, Bicarb, BUN and Creatinine
5. Serum Calcium, Serum Magnesium, Serum Phosphate (typically every 4-8 hours)
6. Blood gases (typically every 2-4 hours): pH & pCO_2

Ketones

Was the patient positive for ketones (by any test, blood or urine)? (only the first ketone test done)	Yes	No	Test not done
If yes, ketone test date: (MM/DD/YYYY)		Ketone time: (HH:MM)	

Glucose (typically recorded every hour)

Note: If both serum and i-STAT or other point-of-care glucose values are available from the same date and time, please enter the lab serum result as the study-preferred result. If the only result at that date and time is from an i-STAT or point-of-care test, it should be included.

Date	*Time*	*Glucose (mg/dL)*		*Date*	*Time*	*Glucose (mg/dL)*

Treatment

FLUID Study Worksheets: **Vitals and Lab Log**

RC (from the medical record) should complete this form

Study Subject ID:__ __ __ __ __ __ __

Vital Signs (typically recorded every hour)

Note: Vital signs are only needed for the first 24 hours.

Date	***Time***	***Systolic BP*** *(mm Hg)*	***Diastolic BP*** *(mm Hg)*	***Respiratory Rate*** *(per minute)*	***Heart Rate*** *(per minute)*

Treatment

FLUID Study Worksheets: **Vitals and Lab Log**

RC (from the medical record) should complete this form

Study Subject ID:__ __ __ __ __ __ __

Serum Electrolytes (typically recorded every 2-4 hours)

Date	*Time*	*Sodium*	*Potassium*	*Chloride*	*Bicarb*	*BUN*	*Creatinine*
		mEq/L	mEq/L	mEq/L	mEq/L	mg/dL	mg/dL
		mEq/L	mEq/L	mEq/L	mEq/L	mg/dL	mg/dL
		mEq/L	mEq/L	mEq/L	mEq/L	mg/dL	mg/dL
		mEq/L	mEq/L	mEq/L	mEq/L	mg/dL	mg/dL
		mEq/L	mEq/L	mEq/L	mEq/L	mg/dL	mg/dL
		mEq/L	mEq/L	mEq/L	mEq/L	mg/dL	mg/dL
		mEq/L	mEq/L	mEq/L	mEq/L	mg/dL	mg/dL
		mEq/L	mEq/L	mEq/L	mEq/L	mg/dL	mg/dL
		mEq/L	mEq/L	mEq/L	mEq/L	mg/dL	mg/dL
		mEq/L	mEq/L	mEq/L	mEq/L	mg/dL	mg/dL
		mEq/L	mEq/L	mEq/L	mEq/L	mg/dL	mg/dL

Notes: mEq/L and mmol/L are the same unit of measurement
Sodium can be Na; Potassium can be K; Chloride can be Cl; Serum bicarbonate can be HCO_3, Total CO_2, TCO_2, or bicarb;
BUN can be Urea nitrogen, Urea, Blood Urea Nitrogen; Creatinine can be Creat, Cre, Blood creatinine

Serum Ca, Mg, P (typically recorded every 4-8 hours)

Date	*Time*	*Serum Calcium*	*Serum Magnesium*	*Serum Phosphate*
		mg/dL	mEq/L	mg/dL
		mg/dL	mEq/L	mg/dL
		mg/dL	mEq/L	mg/dL
		mg/dL	mEq/L	mg/dL
		mg/dL	mEq/L	mg/dL
		mg/dL	mEq/L	mg/dL

Notes:
Serum Calcium should be total calcium, not ionized; may be called Ca
Serum Magnesium may be called Mg or Mag
Serum Phosphate may also be called phosphorous, P, or PO_4

Treatment

FLUID Study Worksheets: **Vitals and Lab Log**

RC (from the medical record) should complete this form

Study Subject ID:__ __ __ __ __ __ __

Blood Gases (typically every 2-4 hours)

	Date	Time	pH	pCO_2	Route
Notes: *For both tests, venous is preferred, but arterial are acceptable. Please indicate the route.* *pCO 2 : is NOT pO 2 (partial pressure O 2) and is NOT Total CO 2 and is NOT Oxygen Saturation (O 2 Sat)*				mm HG	☐ Venous ☐ Arterial
				mm HG	☐ Venous ☐ Arterial
				mm HG	☐ Venous ☐ Arterial
				mm HG	☐ Venous ☐ Arterial
				mm HG	☐ Venous ☐ Arterial
				mm HG	☐ Venous ☐ Arterial
				mm HG	☐ Venous ☐ Arterial
				mm HG	☐ Venous ☐ Arterial
				mm HG	☐ Venous ☐ Arterial
				mm HG	☐ Venous ☐ Arterial
				mm HG	☐ Venous ☐ Arterial
				mm HG	☐ Venous ☐ Arterial

A.6 Patient Study File: Follow up worksheets

Follow-up

FLUID Study Worksheets: **3 Month Follow-up**

RC should complete this form

Study Subject ID:__ __ __ __ __ __ __

Instructions: Complete the History & Status section for all patients, regardless of follow-up visit. Follow up testing should be completed only for patients ages 3-18 (at the time of the follow up visit). Complete the Follow Up Visit History and Follow Up Visit Screening sections only for patients who have returned for their follow-up visit. Once completed, give the CBCL to the parent for completion while patient does the cognitive tests.

History & Status This section completed for ALL study patients.

1. Did the patient die before the follow-up visit? *(If yes, complete this section, then stop)*	Yes	No
A. If yes, please indicate the cause of death, if known:		

2. Has the patient seen a medical care provider for anything other than usual diabetes care since the study DKA episode? *(If the patient did not receive additional medical care, then thrombosis, severe hypoglycemia, and additional DKA episodes can be assumed as "no". Skip to Follow Up Visit Screening)*	Yes	No
If yes, complete table below for all additional medical care visits: (use extra paper, if needed)		

What was the medical care for?	What was the date of the additional medical care?	Was the patient rehospitalized?	
		Yes	No
		Yes	No
Was the care provided at your hospital? *(if no, request medical records for PI verification)*		Yes	No

3. Since the hospital discharge from the DKA episode, has the patient experienced thrombosis? (blot clot in some part of the body like leg, arm, or lung. ***Note:*** *PI will need to verify this by reviewing the medical record.*)	Yes	No
A. If yes, date of thrombosis:		

Follow Up Visit History This section to be completed only if the follow-up visit is done.

1. Since the hospital discharge from the DKA episode, has the patient experienced any severe hypoglycemia (*low* blood sugar with loss of consciousness or substantial mental status changes)?	Yes	No
A. If yes, how many severe hypoglycemic episodes since discharge? (1, 2, or >2)		

2. Since the hospital discharge from the DKA episode, has the patient experienced any additional DKA episodes?	Yes	No
A. If yes, how many additional DKA episodes since discharge? (1, 2, or >2)		

Follow Up Visit Screening This section to be completed only if the follow-up visit is done.

1. Follow up visit date: (MM-DD-YYYY)	

2. How old was the patient on the day of the follow-up visit?

☐ 0 through 2 years of age *(No follow up visit needed)*
☐ 3 through 5 years of age *(Age appropriate testing: WPSSI, CBCL)*
☐ 6 through 17 years of age *(Age appropriate testing: WASI, CBCL)*
☐ 18 years of age *(Informed consent needed, perform WASI, CBCL)*

3. Glucose screening (via patient's meter) _____ mg/dL

A. If this glucose is less than 70 mg/dL patient should be treated for hypoglycemia and follow up visit rescheduled.

B. If this is more than 350 mg/dL, evaluate for ketones:

☐ Positive for ketones → *Refer to endocrinologist, reschedule follow up*
☐ Negative for ketones → *Complete the follow up visit*

Follow-up

FLUID Study Worksheets: **3 Month Follow-up**

RC should complete this form

Study Subject ID:__ __ __ __ __ __ __

Cognitive Testing scores This section to be completed only if the follow-up visit is done.

Digit Span Recall Test

Digit Span Recall Total Forward	
Digit Span Recall Total Backward	

Memory Tests

Memory-Color Position Task completed?	Yes	No
If not, why not?		
Memory-Spatial Position Task completed?	Yes	No
If not, why not?		
upload of csv output from the test		
upload of memory test notes		

WASI or WPSSI Tests

Test completed?	Yes	No
If not, why not?		
Which test was completed?	WPSSI	WASI
Upload of testing form		

Child Behavior Checklist

Completed by parent:	Yes	No
If not, why not?		
If yes, which CBCL was completed?	3 - 5	6 - 18
Upload of CBCL		

FLUID Study
Follow-up data diagram

Patient comes to follow-up visit & is asked about medical care outside of usual diabetes care since discharge

- If the patient/parent says "yes" they have received medical care, the RC will request the medical records. The PI will review, looking for thrombosis.
- If the patient/parent says "no" additional medical care, no additional action will take place.
- *Follow up worksheet sections: Status & History, Follow Up Visit History*

Patient is unable to come for follow-up visit. If able, the RC will attempt to ask about additional medical care since discharge via phone.

- If the patient/parent says "yes" they have received medical care, the RC will request the medical records. The PI will review, looking for thrombosis only.
- If the patient/parent says "no" additional medical care, no additional action will take place.
- *Follow up worksheet sections: Status & History, Follow Up Visit History*

Patient no-shows the visit & is unable to be rescheduled, or the patient is unreachable

- The PI will review the medical record for any return visits to their HEDA during the 3 months since discharge, looking for thrombosis only.
- *Follow up worksheet section: Status & History only*

Follow-up visit is not required (patient is under 3 at the time of follow-up, had a repeat enrollment, or is a non-English speaker/reader)

- The PI will review the medical record for any return visits to their HEDA during the 3 months since discharge, looking for thrombosis or death.
- *Follow up worksheet section: Status & History only*

Fluid Therapy and Cerebral Injury in Pediatric Diabetic Ketoacidosis

Telephone Reminder of 3-month Neurocognitive Follow-up Appointment

Follow-up Log: Record contact attempts. **If you leave a reminder message for the parent/guardian, please provide them with your call-back number in case they would like to reschedule their appointment.

Date	Time	Result:	Comments:

If Parent/Guardian is Present:

Hello Mr/Ms._____, this is _____(name of CRC)

calling from _____ medical center. I am calling to remind you about

_____'s (name of child) follow-up appointment on _____ at _____

am/pm (circle one) for the diabetic ketoacidosis research study.

1. Does that date and time still work for you?

☐ **No**: OK, let's find an alternate date [set a different date].

- **Alternate Date/Time:** _____

** *If this date is more than 1 week after the original date:* Thanks very much, I'll be calling you in a few days to remind you of the date and the items we need you to bring to the visit. ***[end call]***

☐ **Yes**: Great. The appointment will be in _____ (name of building or clinic/address/ floor, etc) at this address: _____.

2. Do you know how to get to this location?

☐ **No:** Give directions

☐ **Yes:** OK, great. It's very important that you bring _____'s (name of child) home glucose meter to the visit because we are going to ask him/her to test his/her glucose level before doing the testing at the visit. If we don't know his/her glucose level on the day of the follow-up visit, we will have to reschedule the visit.

3. Also, do you have urine ketone test strips at home or a blood ketone meter?

☐ **No:** OK. You should talk with _____'s (name of child) endocrinologist about getting some ketone test strips for home. Most children with diabetes should have a way to test ketones at home when they are sick. However for the visit, I'll make sure we have some urine ketone strips available.

☐ **Yes:** OK, great. Please bring those/that to the visit as well. We may not need them, but in case _____'s (name of child) glucose level is very high, we would need him/her to test for ketones too.

Thanks again for helping with the study. We'll see you on _____ at _____o'clock.

Note: If the parent/guardian asks additional questions regarding the care of the patient, please inform them that this is a reminder call only and that you are unable to provide them with information about medical care. If the guardian has questions about his/her child's diabetes care, please refer him/her to the Pediatric Endocrinology Clinic at 916-734-8223. If the parent/guardian requests additional information about the study, please direct them to call the study PIs, Dr. Nathan Kuppermann, MD, MPH at 916-734-1535 or Dr. Nicole Glaser, MD at 916-734-0406.

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UC DAVIS MEDICAL CENTER

Fluid Therapy and Cerebral Injury in Pediatric Diabetic Ketoacidosis

[Date]

Dear [Parent Name]:

Thank you for your/your child's participation in the Pediatric Diabetic Ketoacidosis (DKA) study at [institution name]. You are being contacted because of the results of your child's recent memory and IQ testing, part of the standard study procedures. When you consented for your child to be part of this study, we stated that we would contact you if the results of our testing indicated possible learning problems.

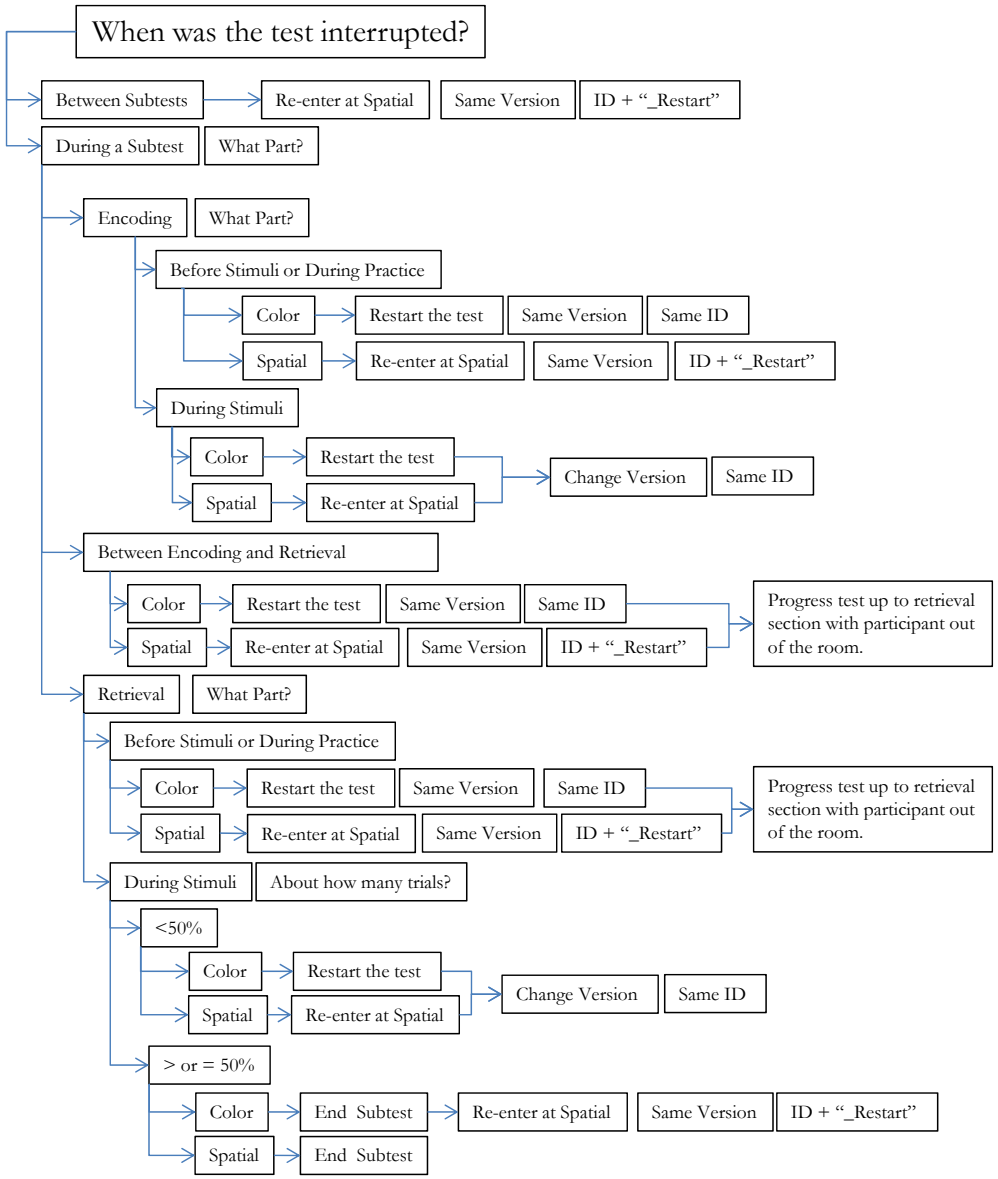
The results of _____[child's name]'s testing, completed on _____ [insert date of IQ testing], may indicate possible learning problems. This test result is not definitive. While our research staff are trained carefully on the performance of memory and IQ testing, they are not licensed psychologists. In addition, there are other explanations for low scores, including your child not feeling well on the day of testing or not feeling motivated to try his/her hardest to answer the questions. Thus, we would recommend that you follow up with your child's school and/or a psychologist for definitive testing.

We really appreciate your participation in this study. If you have questions about the study, please do not hesitate to contact us.

Kind Regards,

DKA study investigators
[phone numbers]

VERSION DATE: (April 23, 2012)



Remember, that when you are restarting the memory task, the condition will <u>always</u> remain unchanged.

A.7 Patient Study File: Miscellaneous worksheets and tools

FLUID Study Worksheets: **OOPS Log**

RC should complete this form

Study Subject ID:__ __ __ __ __ __ __

Instructions: This Outside Of Protocol Specifications log should be used the RC to record any event that happens to a patient that falls outside the protocol specifications. This may include protocol deviations, but is not limited to those. Site IRBs may want you to report a protocol deviation to them as well; check with your IRB to see if you need to report.

Date event was first identified (MM-DD-YYYY)	Date event occurred (MM-DD-YYYY)	Which phase of the study was this event associated with?	Describe event
		1) Screening 2) Enrollment 3) Randomization 4) Treatment/ Fluid administration 5) After 24 hour/ Pre-discharge 6) 3-month follow-up	

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Not Enrolled

FLUID Study Worksheets: **Not Enrolled patients**
RC (with medical record) should complete this form

Study Subject ID:__ __ __ __ __ __ __

Instructions: This form should be completed for all patients considered for the study, but not enrolled. This includes patients who were eligible but not approached for whatever reason, patients who were eligible but declined to participate, & patients who were consented but not randomized. Please also complete the "Screening and Enrollment" & "Demographics" worksheets.

Diabetes History

1. Is this patient new onset (first diagnosis of diabetes at this ED visit)? | Yes | No |

Lab Data

2. Did the patient have a serum glucose test done while in the ED? | Yes | No |

   2a. If yes, the result was: _____ mg/dL

3. Did the patient have a serum BUN test done while in the ED? | Yes | No |

   3a. If yes, the result was: _____ mg/dL

4. Did the patient have a pH test done while in the ED? | Yes | No |

   4a. If yes, the result was: _____
   4b. Route of pH? ☐ Venous ☐ Arterial

Completed by: _____
Date completed: _____

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Version 1.1

FLUID Study Worksheets: **Study Withdrawal**

RC should complete this form

Study Subject ID:__ __ __ __ __ __ __

Study Withdrawal

1. During which phase of the study was parental permission withdrawn?

   ☐ Intervention Phase (includes time from randomization through the end of intervention)

   ☐ Post-intervention but pre-discharge (after the 24 hour study period but before the patient leaves the hospital)

   ☐ Prior to the three month follow-up and after hospital discharge (prior to neurocognitive assessment follow-up phase)

2. Why was the patient withdrawn?

   ☐ Parental preference

   ☐ Child's preference

3. Please describe withdrawal (for any reason):

Date consent was withdrawn: (MM/DD/YYYY)	
Time consent was withdrawn: (HH:MM)	

Note: Please notify the CDMCC immediately upon a patient withdrawal; please keep study records.

FLUID Study Overview Grid

	During hospitalization								3-month follow-up visit
	At Enrollment	Every Hour	Every 2-4 Hours	Every 4 hours	Every 4-8 Hours	Study Hour 12	Study Hour 24	Before discharge	
Actual Weight	x					x		x	
AEs & SAEs	*Record all AEs from randomization through hospital discharge*								
Blood Gases (pH, PCO2)	x		x						
CBCL								x	x
CE Therapy ***(Mannitol, intubation, hypertonic saline)***	*Record all therapies from randomization through hospital discharge*								
Concomitant meds *(not insulin)*	*Record all con meds from randomization through hospital discharge*								
Diabetes History *(only for previously diagnosed)*								x	
Digit Span	x			x					x
Electrolyte labs (Sodium, Potassium, Chloride, Bicarb, BUN, Creatinine)	x		x						
GCS	x	x							
Glucose	x	x							x
IQ Test									x
Memory Tests									x
Physical Exam, Review of Medical Conditions								x	
Physician Treatment Initiation	x								
Schedule 3 month follow-up visit								x	
Serum Magnesium, Calcium, Phosphate	x				x				
Total fluid calculations						x	x	x	
Vital Signs (Blood pressure, pulse, respirations)	x	x							

Enrollment Packet:
- Screening and Enrollment
- Physician Treatment Initiation
- Demographics
- Review of Medical Conditions
- Physical Exam
- First Digit Span

Treatment Packet:
- Digit Span worksheets
- GCS log worksheet
- AE/SAE/con med logs
- Diabetes History (if applicable)
- Caregiver Demographics
- CBCL

Discharge Packet:
- Discharge Data
- Fluid Administration log
- Specific Treatment Log
- AE/SAE/con med logs
- Labs & Vitals log

Follow-up Packet:
- Follow-up worksheet
- CBCL
- Digit Span
- Memory Test
- IQ Test

Key
- ***Study specific tasks***
- Standard of care events
- Enrolling physician must complete

Additional Study tools:
- Overview Grid
- Study Withdrawal
- Hour conversion chart
- OOPS log
- Informed consent checklist

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Version 1.0

FLUID Study Worksheets: **Informed Consent checklist**

RC OR ENROLLING PHYSICIAN should complete this form

Study Subject ID:__ __ __ __ __ __ __

Instructions: This checklist is intended to help enrolling staff document the informed consent process. As each item is reviewed during the informed consent process, check them off. Sign & date the bottom. Include any notes or questions that pertain to the patient's informed consent process.

- ☐ The parental permission process was completed prior to the initiation of any study related procedures.
- ☐ The subject's rights were reviewed and I provided a thorough explanation of this study and the protocol requirements.
- ☐ The Subject/Parent(s) were given a thorough explanation of the risks/benefits associated with participation as outlined in the Informed Consent Form. Alternative treatment options were explained to the Subject/Parent(s).
- ☐ The Subject/Parent(s) were given ample time to read the consent form and consider participation.
- ☐ The Subject/Parent(s) were given the opportunity to voice questions/concerns regarding their participation. The following questions/concerns were asked and addressed:

_____

_____

_____

- ☐ The Subject/Parent(s) appeared to comprehend the study information by verbalizing their understanding of the study and the study-related procedures.
- ☐ The Subject/Parent(s) understand that he/she can withdraw from the study at any time.
- ☐ The Subject/Parent(s) were informed that he/she will be provided with updated information regarding the study if applicable. Consent/permission/assent for continuation of their participation in the study will be repeated if indicated.
- ☐ The Subject/Parent(s) voluntarily agreed to participate In this study. The following forms have been signed and signed copies have been given to the Subject/Parent(s):
  - •Parental Permission Form (signed by the parent or guardian of the subject)
  - •Informed Consent (signed by subjects ≥ 18 years of age) ***Only applicable during 3 months follow up**
  - •Assent (signed by subject; only if applicable at your site)
- ☐ A copy of the signed parental permission/informed consent/assent was placed in the subject's medical record.
- ☐ I observed the above referenced components of the informed consent process and certify that each of the steps were followed.

Signature of person obtaining consent:

_____

Date

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FLUID Study Worksheets: **Hour Conversion**

For Study team use

Study Subject ID:__ __ __ __ __ __ __

Study Hour	Real Time (HHMM: Military format)	What's Happening:
0	_____	Randomization, first GCS (every hour), first Digit Span (every 4 hours)
1	_____	GCS
2	_____	GCS
3	_____	GCS
4	_____	GCS, Digit Span
5	_____	GCS
6	_____	GCS
7	_____	GCS
8	_____	GCS, Digit Span
9	_____	GCS
10	_____	GCS
11	_____	GCS
12	_____	GCS, Digit Span, 12 Hour weight & fluid total needed
13	_____	GCS
14	_____	GCS
15	_____	GCS
16	_____	GCS, Digit Span
17	_____	GCS
18	_____	GCS
19	_____	GCS
20	_____	GCS, Digit Span
21	_____	GCS
22	_____	GCS
23	_____	GCS
24	_____	GCS, Digit Span 24 Hour Fluid total needed

Discharge	_____	GCS, discharge weight, fluid total needed, discharge checklist
3 Months:	_____	Schedule follow-up visit within 4 weeks of this date

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Version 1.0

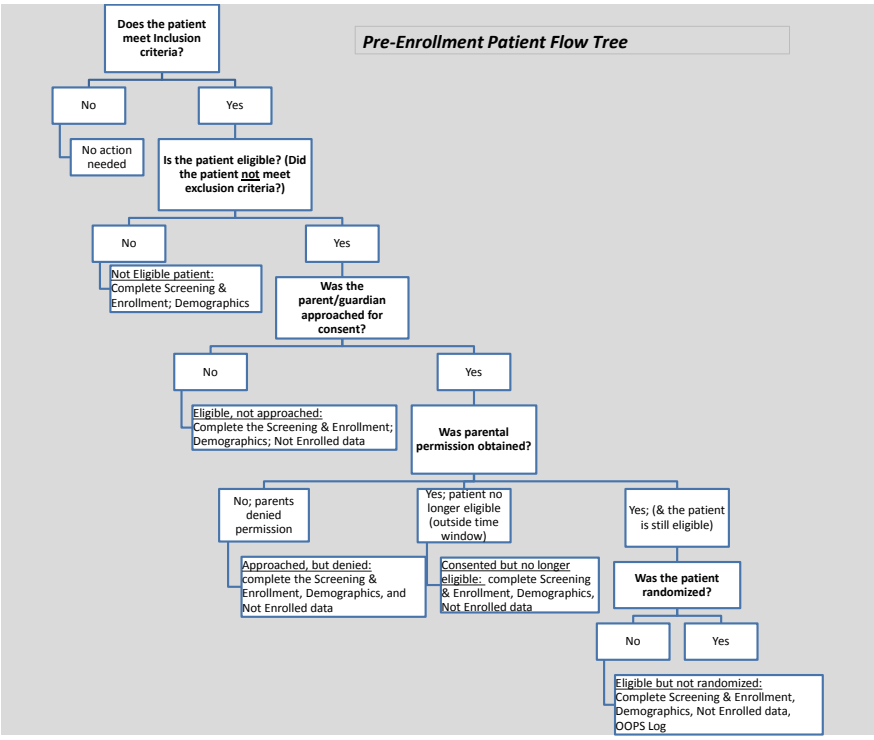
MILITARY TIME CONVERSION CHEAT SHEET

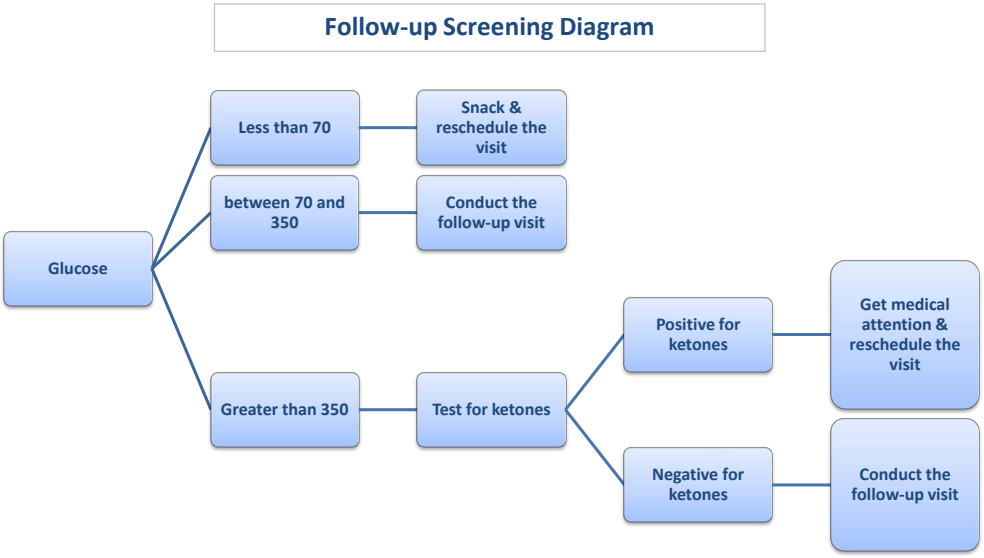
AM/PM Time	Military time
1:00 AM	0100
2:00 AM	0200
3:00 AM	0300
4:00 AM	0400
5:00 AM	0500
6:00 AM	0600
7:00 AM	0700
8:00 AM	0800
9:00 AM	0900
10:00 AM	1000
11:00 AM	1100
12:00 PM (noon)	1200
1:00 PM	1300
2:00 PM	1400
3:00 PM	1500
4:00 PM	1600
5:00 PM	1700
6:00 PM	1800
7:00 PM	1900
8:00 PM	2000
9:00 PM	2100
10:00 PM	2200
11:00 PM	2300
12:00 AM (midnight)	0000

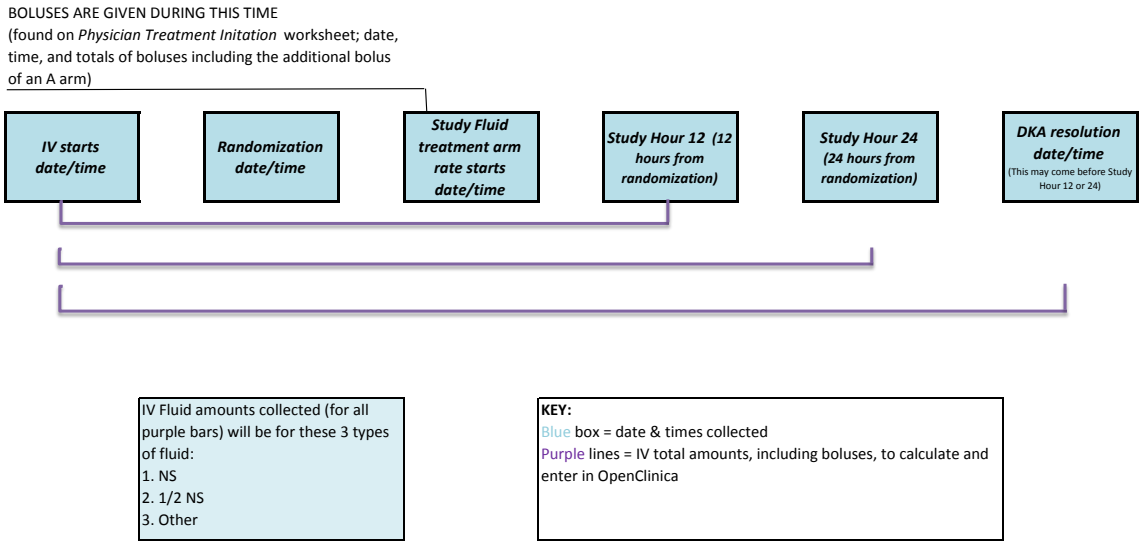
FLUID Screening Log

Instructions: Enter all patients that are eligible and approached on to the screening log. If the patient met all inclusion/exclusion criteria but refused consent, you must still enter them into OpenClinca. All patients documented on the screening log should obtain an OpenClinica #. How to enter patients that refused consent into OpenClinica can be found in section XX.XX on page XX of the MOO.

Screening Log #____	Date Enrolled	**Parental Permission** (Document if parental permission was obtained by checking Yes or No below)			
Site Unique Identifier #		**Yes**	**No**	Add the Study ID # (OpenClinica #) in the space provided	If the patient consented but you were unable to obtain Study ID # from OpenClinica add MRN # or other patient identifier in the space provided
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	
	- -	☐	☐	Study Subject ID _ _ _ _ _ _	


Pre-Enrollment Patient Flow Tree
Does the patient meet Inclusion criteria?
No
No action needed
Yes
Is the patient eligible? (Did the patient not meet exclusion criteria?)
No
Not Eligible patient: Complete Screening & Enrollment; Demographics
Yes
Was the parent/guardian approached for consent?
No
Eligible, not approached: Complete the Screening & Enrollment; Demographics; Not Enrolled data
Yes
Was parental permission obtained?
No; parents denied permission
Approached, but denied: complete the Screening & Enrollment, Demographics, and Not Enrolled data
Yes; patient no longer eligible (outside time window)
Consented but no longer eligible: complete Screening & Enrollment, Demographics, Not Enrolled data
Yes; (& the patient is still eligible)
Was the patient randomized?
No
Eligible but not randomized: Complete Screening & Enrollment, Demographics, Not Enrolled data, OOPS Log
Yes


Follow-up Screening Diagram
Glucose
Less than 70
Snack & reschedule the visit
between 70 and 350
Conduct the follow-up visit
Greater than 350
Test for ketones
Positive for ketones
Get medical attention & reschedule the visit
Negative for ketones
Conduct the follow-up visit


BOLUSES ARE GIVEN DURING THIS TIME
(found on *Physician Treatment Initation* worksheet; date, time, and totals of boluses including the additional bolus of an A arm)
IV starts date/time
Randomization date/time
Study Fluid treatment arm rate starts date/time
Study Hour 12 (12 hours from randomization)
Study Hour 24 (24 hours from randomization)
DKA resolution date/time
(This may come before Study Hour 12 or 24)
IV Fluid amounts collected (for all purple bars) will be for these 3 types of fluid:
1. NS
2. 1/2 NS
3. Other
KEY:
Blue box = date & times collected
Purple lines = IV total amounts, including boluses, to calculate and enter in OpenClinica

FLUID Admin Log optional template - Microsoft Excel

1	**Patient ID**													
2	Study Arm								IV start date		IV start time			
3	Study Arm Calculated Rate(s)								Randomization Date		Randomization Time			
4	Study Arm Type								Study Start Date		Study Start Time			
5	Study Arm Bolus Amount								DKA Resolution Date		DKA Resolution Time			
6	Patient's weight (kg)								Study Hour 12		Study Hour 24			
7				**A arm changeover**					Initial Bolus		cc/kg			
8				Should have been at			(12 hours after start)		Additional Bolus		cc/kg			
9				Rate was changed at			(from MR)		Total CC of bolus					
10														
11	**Rate**	**Start**	**Stop**	**Type**	**Hours**	**Minutes** (min /60)	**Total CCs**	**Before DKA res. =** 0		**Before SH 12 =** 0		**Before SH 24 =** 0		
12							0.0							
13							0.0							
14							0.0							
15							0.0							
16							0.0							
17							0.0							
18							0.0							
19							0.0							
20							0.0							
21							0.0							
22							0.0							
23							0.0							
24							0.0							
25							0.0							
26							0.0							
27							0.0							
28	**Totals**						0.0	0.0		0.0		0.0		
29														
30														
31		**Into OpenClinica:**												
32		From IV Start	**1/2 NS**	**NS**	**Other**	**Total fluid**			**OOPS, NTF or comments?**					
33		**to DKA Resolution**				0			Did this patient get the study rate through DKA resolution?					
34		**to Study Hour 12**				0			Did this patient get the study type through DKA resolution?					
35		**to Study Hour 24**				0			Did this patient get the bolus amount indicated on their arm?					
36									If this patient was an A arm & DKA lasted longer than 12 hours, was th					
37														
38														
39														

Template / A1 Example / A2 Example / B1 Example / B2 Example / Categories

Ready

Appendix B

Use of OpenClinica 3.1 Electronic Data Capture Software

Contents

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B.1 What is OpenClinica?

OpenClinica is an open source electronic data capture (EDC) system developed by OpenClinica, LLC. OpenClinica is backed by an open source community comprising over 18,000 registered individuals from hundreds of leading industry, academic, and government research institutions in over 100 countries around the world. The University of Utah Data Coordinating Center (CDMCC) is using this application to support clinical research studies that are conducted within the Pediatric Emergency Care Applied Research Network (PECARN).

B.2 Accessing OpenClinica Studies

OpenClinica is a web-based software system, and is accessed from either Internet Explorer 5.5+ or Mozilla Firefox 1.0+ on Windows or Macintosh based computers. When the user types in the URL for OpenClinica, it will start with 'https: //' rather than 'http: //' because it uses secure socket layer (SSL) encryption. User accounts are administered through a single sign-on system called Active Directory. This system allows a single account to access multiple systems utilized by the DCC. Password changes or resets are managed via Active Directory. The actual URL for OpenClinica, as well as account names and passwords, are provided separately from this Manual when individual user accounts are configured.

The log-on page has a place to enter the username and password (See Figure B.1 on the facing page). Once a username and password are entered, click the "Login" button or "Enter" key to access the system.

Logging in will lead to the homepage navigation screen (See Figure B.2 on page 352). The homepage displays the study currently logged into and the user's role within that study. By default, the last study a user was logged into will be the study that opens upon re-entry in to the system. If users are participating in more than one study, there is an option to "Change Study/Site" at the top middle of the screen. Selecting the "Change Study/Site" option will navigate the system to another screen where users can click a radio button to switch to a different site and/or study.

The homepage screen contains an information column down the left side of the page. This information column is displayed on all pages in which there is no data entry. The information column displays the study a user is logged in to, the site for which a user is viewing/entering data, the start and end date of the study, the clinical site principal investigator, and the

Figure B.1: Logging into OpenClinica

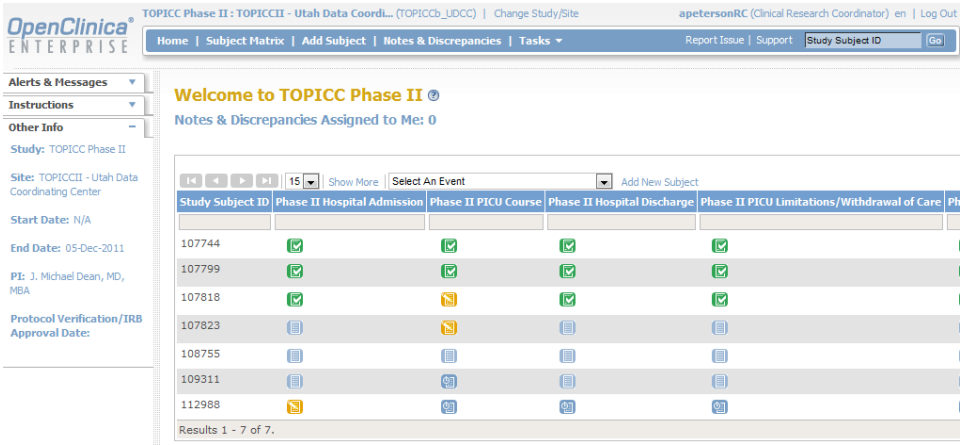

Figure B.2: Homepage navigation screen

protocol verification / IRB approval date for the study.

B.3 Subjects and Events

Also displayed on the homepage navigation screen is the "Subject Matrix." This table provides an event completion status summary of subjects enrolled at a clinical site and listed by study subject ID (automatically generated by OpenClinica). Users only see subjects who have been enrolled at their own site. The option to view 15, 25 or 50 subjects within a screen is available from the drop down menu located above the "Study Subject ID" field.

The column(s) in the subject matrix are the events defined for the study. The number of columns displayed depends on the number of events in the study. The icon just below the event name displays the status of the event for each patient listed in the table. There are also a number of available filtering options: by Study Event, by Study Subject ID and by status of a given Study Event.

An icon key is provided on the left margin of all pages that use the icons within OpenClinica.

B.4 Adding a New Subject

OpenClinica offers a few options to create a study subject ID. The following options do the same thing but vary slightly with the number of fields to

enter within the screens:

1. Two "Add Subject" links are available at the navigation bar. The first, located on the bar, allows users to save and assign one study event or add multiple study subject IDs at one time. The fields included in this view are Study Subject ID, Secondary ID, Date of Enrollment and Sex. The second link is located under the "Tasks" menu. The fields in this view are identical to the "Add Subject" link.

2. An "Add New Subject" link is also located at the top of the Subject Matrix table, to the right of the "Select An Event" drop-down menu. There are additional questions in this view: Study Event, Location and Start Date. Users do not have the option to schedule multiple study events or create additional study subject IDs from this screen.

Refer to Figure B.3 on the following page for the "Add Subject" link that is located on the top navigation bar. The fields on the "Add Subject" screen are defined by the specific requirements of the study. Please refer to each study's specific data entry guidelines for instructions on how to complete the "Add Subject" screen.

B.5 Scheduling an Event

In order to enter data into the electronic case report form (eCRF) for the study, the event that contains the eCRF a user wishes to enter must be scheduled. There are several ways to schedule an event. The most direct is from the "Add Subject" screen (see Figure B.3 on the next page), where users may click the "Save and Assign Study Event" box to navigate to the "Schedule Study Event" screen. Another option from the Subject Matrix is to click on the notepad icon ( ) directly below the name of the event for the subject data entry needs to be completed for. Either navigation will bring users to the "Schedule Study Event for (*Study Subject ID*)" screen (See Figure B.4 on page 355).

From this screen, select the "Study Event Definition" from the dropdown box to the right of the field. All the events available in the study will be listed in the selection options. Unless otherwise noted for a particular study, all of the remaining necessary information to schedule the event will be pre-populated. The only action users must complete is clicking the "Proceed to Enter Data" button, in the middle left of the screen. *Please note: some study specific requirements may require users to change the "Start Date / Time" field.*

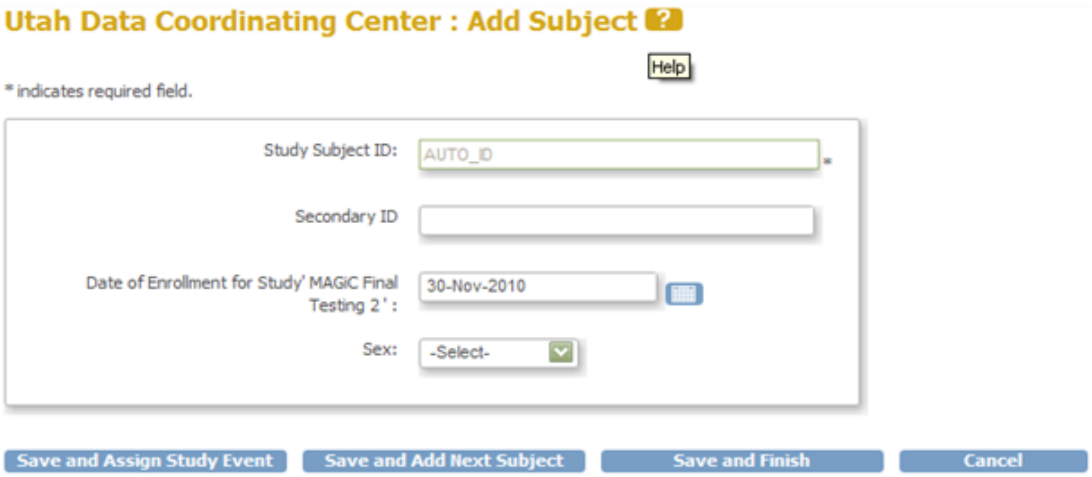

Figure B.3: "Add Subject" screen

Schedule Study Event for 1048

* indicates required field.

Study Subject ID: **1048**

Study Event Definition: Patient Demographics & History (non-repeatin *

Location: Salt Lake City *

Start Date/Time: 17-Mar-2010 : (DD-MMM-YYYY HH:MM) *

End Date/Time: : (DD-MMM-YYYY HH:MM)

Leave this field blank if the end date/time is not applicable.

Schedule Another Event: (optional)
Schedule Another Event: (optional)

Schedule Another Event: (optional)

Schedule Another Event: (optional)

Proceed to Enter Data | Cancel

Figure B.4: "Schedule Study Event for (Study Subject ID)" screen

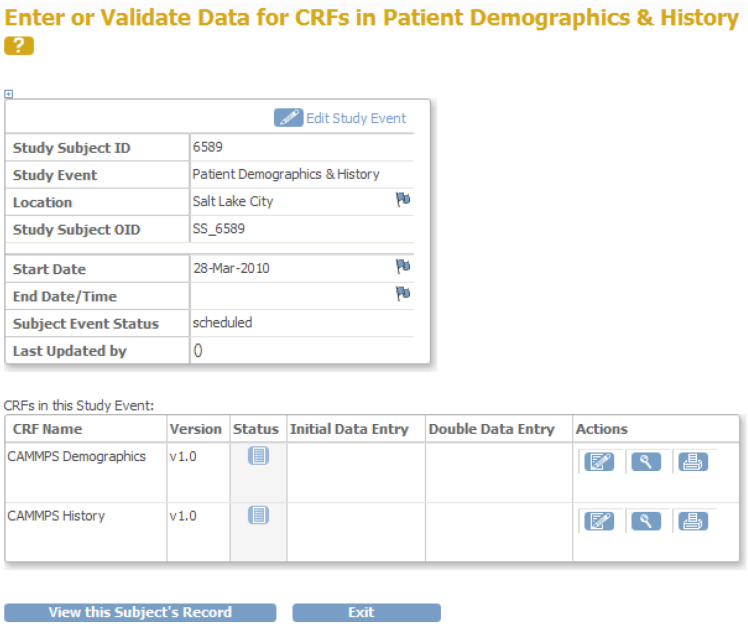

Figure B.5: "Enter or Validate Data for eCRFs in (Event Name)"

B.6 Selecting and Entering Specific eCRFs

After the "Proceed to Enter Data" button has been selected, users will be navigated to the "Enter or Validate Data for eCRFs In (*Event Name*)" (See Figure B.5). This page displays the event data in the top box and an Edit Study Event icon ( ) can be clicked to edit the event status, if necessary. The bottom box displays the eCRFs available for data entry for the event that has been scheduled. To the right of the box an "Actions" column with 3 options for each eCRF is displayed. To start entering data into the eCRF, click the icon that looks like a notepad with a pencil ( ) and proceed to enter data. *Please be sure to save data as each section is completed or the data entered will be lost.*

B.7 Viewing or Printing eCRFs

From the "Enter or Validate Data for CRFs In (*Event Name*)" screen (See Figure B.5 on the facing page), users may also view or print an eCRF by clicking on the appropriate icon in the "Actions" column. Select the magnifying glass icon ( ), the middle option in the "Actions" column, next to the eCRF users wish to view the data for. Select the print icon ( ), the last option in the "Actions" column, next to the eCRF users wish to print data for.

B.8 Entering Data in eCRFs

OpenClinica has a relatively consistent interface for the eCRFs. At the top of each eCRF is a box containing header information. Below this box is the main body of the eCRF, which can consist of one or many sections (See Figure B.6 on the next page) each section of the form is represented by a tab.

B.8.1 eCRF Header

At the top of every eCRF, the header displays the current eCRF being worked on, a discrepancy notes (query) section which will show users the number of new, updated, resolved, proposed, closed, and not applicable queries for this eCRF. Discrepancy notes are managed differently for each study; please refer to study specific guidelines for specifications. The study subject ID, study/site, and event are also displayed in the eCRF header. If the study requires the name of the person doing the data entry and the date for which the event was created, the Interviewer Name and Interviewer Date columns will be displayed. All of the information in the eCRF header has been populated from either the study subject or event information previously entered on other screens. The eCRF header is not editable on the data entry screens. This information is always seen in the header section so that the person entering data can be certain they are entering data for the right patient.

B.8.2 Main Body of the eCRF

The main body of the eCRF contains questions broken out by each defined section. eCRFs may have one or more sections. Each section is displayed in there defined order by tabs from left to right. If an eCRF has more than

TOPICC Phase II Hospital Admission Information v1.0 **107823**

CRF Header Info

Event:	Phase II Hospital Admission (09-May-2013)	**Sex:**	
		Age At Enrollment:	
Study:	TOPICC Phase II		
Site:	TOPICCII - Utah Data Coordinating Center		
Interviewer Name: *	apetersonRC	Interview Date: *	09-May-2013

Discrepancy Notes on this CRF:

New	Updated	Resolution Proposed	Closed	Not Applicable
0	0	0	0	0

Demog (0/8) | History (0/10) | Baselin...(0/10) | -- Select to Jump --

Title: Patient Demographics

Page: Save Exit

Was this patient already enrolled in the TOPICC study during a previous hospitalization?

(select one) If yes, enter the EDC Subject ID for the first enrollment:

Date of birth: * (DD-MMM-YYYY)

Sex: Male Female *

Ethnicity: Hispanic or Latino * Not Hispanic or Latino Unknown or Not Reported

Race: (select all that apply) American Indian or Alaska Native * Asian Black or African American Native Hawaiian or Other Pacific Islander White Unknown or Not Reported

Residential Zip Code:

Please select the most appropriate primary payer type:

(select one)

Return to top Save Exit

Figure B.6: Anatomy of OpenClinica

three sections, only three tabs will be displayed across the top at a time. Each section has a label which is shown on the tab and a title which is shown at the top of the page for each section. In Figure B.6 on the facing page, notice that there are three tabs displayed followed by a "Select to Jump" drop down box. This box allows navigation from one section to any other section on the form without first needing it displayed as a tab on top.

The forms display one section (tab) at a time and NOT a complete eCRF. Displaying the forms in this manner allows users to save data entered one section at a time. To continue to the next section of an eCRF, select "Save". If a user happens to select exit prior to completing data entry, a pop-up warning will display stating "You have unsaved data. Are you sure you want to exit without saving?"

As noted previously, only three tabs are displayed at once on an eCRF, but an eCRF can have more than three sections. Please take note of the small blue arrow between the last tab and the "Select to Jump" box which also allows navigation between different sections.

As data are entered in each section and "Save" is clicked, the tabs will automatically advance. Once the last tab is reached on the eCRF, a "Mark CRF Complete" checkbox will be displayed next to the "Save" button at both the top and bottom of the screen. Users will also know they have reached the end of the eCRF because upon hitting "save," the screen will not advance. The "Mark CRF Complete" checkbox should be selected when data entry on the form has been completed for all sections.

OpenClinica employs different options for answering the data collection questions such as: single-select radio buttons or drop down lists, multi-select drop down lists or checkboxes, and open text fields. The open text fields can be programmed to accept only the type of data the question is asking for. For example, if the question is asking to provide a time value in the 24-hour clock, only data entered in the 24-hour clock format will be accepted. Otherwise users will receive a discrepancy alert (pop-up warning box) describing the type of data that are acceptable to enter in the open text field.

Skip logic, also known as conditional branching, is used in OpenClinica to display different questions based on answers given to previous questions. For example, the question asks "Was this patient enrolled in the study during a previous hospitalization?" If the reply is "yes," the question "Enter the OpenClinica Subject ID from the first enrollment" will display. If the reply is "no," the question to provide the OpenClinica Subject ID will not display. In the view mode of OpenClinica, all questions will be displayed regardless of the conditional branching. However, in data entry mode only the questions

that require data entry will be available for data entry.

B.9 Discrepancy Alerts

Fields that are required are noted by an asterisk (*) next to the item name in OpenClinica. If a required field has not been answered, upon clicking save, users will be prompted with a discrepancy alert. Users must answer the missing question. If data for a required field has not been provided, the system will not allow the eCRF to be saved.

Dates must be entered in DD-MMM-YYYY format, with MMM being the 3 letter English month abbreviation with only the first letter capitalized, i.e., Jan, Feb, Mar, Apr, May, etc. Dates not entered in this format cannot be saved. Using the pop-up calendar function will ensure dates are correctly formatted.

Times must be entered in HHMM format using the 24 hour clock. The valid range for times is 0000 through 2359, with 0000 referring to midnight.

Another type of discrepancy alert is a warning when a value is out of range. A discrepancy alert will appear as with the required, date, and time fields; however, if the data entered are correct, hitting the Save button again will advance users to the next tab of the eCRF. This type of discrepancy alert does not have to be corrected in order to save data.

B.10 Adding Rows to a Repeating Question Group

eCRFs containing repeating question groups (RQG) are a common feature. They are often seen in instances of multiple laboratory collections and in logs such as Adverse Events and Concomitant Medications. To add a row within the repeating group, click on the "ADD" button. Users are not allowed to delete a row from a RQG once the form has been saved. In cases when a row of data must be removed, manually delete each response. If one of the questions contains a choice set, de-select the response by selecting the default value, which is typically named "Select one."

B.11 Uploads

Some studies will require reports to be uploaded within an eCRF. Before uploading any report, ensure that all subject identifiers are removed and the Study Subject ID is clearly written on at least the first page of the report. In addition, if the file is required to be converted to a specific format,

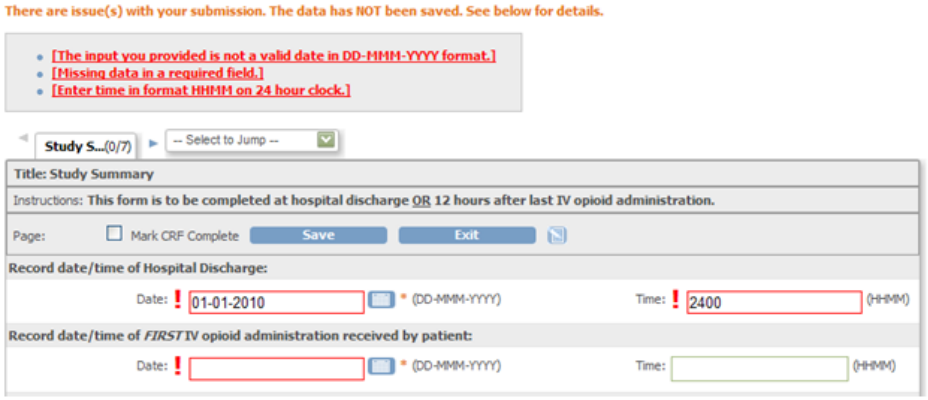

Figure B.7: Discrepancy Alerts

instructions for how to do this can be located in the data management chapter of this MOO. To upload a report, click on the "Click to upload file" button. A pop-up window will appear, containing a browse field to select the file to be uploaded. Once the file is selected, click the "Upload File" button and then close the window. Note that only one upload can be saved at a time.

After the report has been uploaded and the eCRF has been saved, two new buttons will appear giving the option to "Replace" or "Remove" the upload.

B.12 Deletion of Study Subject IDs, Study Events and eCRFs

If an eCRF is mistakenly created, contact the Lead Clinical Data Manager and make a request to delete the eCRF from the database. The same also applies to Study Subject IDs and Study Events, contact the Lead Clinical Data Manager to remove these from the database. A reason for each removal must be provided. Users do not have the capability to delete eCRFs or remove Study Events or Subject IDs.

B.13 Getting Help

For study related questions regarding data entry for an eCRF, please contact the study Lead Clinical Data Manager at the CDMCC.

B.14 How to Log Out

It is important to log out of the system when finished by selecting the "Log Out" button from the top right hand corner of any non-data entry screen. If a user forgets to log out, or if there is no activity on the system for 30 minutes, the session will automatically disconnect. If the session is disconnected the system will direct users back to the main log in screen.

B.15 What If the Internet Is Down?

OpenClinica requires an Internet connection. If the clinical site or the Utah DCC loses connectivity, OpenClinica will not be available. While this is rare, it does occur occasionally. In the event that OpenClinica is not accessible, clinical site staff should use paper forms until connectivity is re-established.

Appendix C

Use of eRoom^{TM} in PECARN

Contents

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C.3 Common Items **366**
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C.3.3 Polls 369
C.3.4 Databases 370
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C.5 eRoom^{TM} Backup **372**

The CDMCC uses a commercial software product produced by Documentum called eRoom^{TM} to support collaboration among users across the United States, and we currently have approximately 500 users. The system is designed as an electronic, virtual office facility, and can be reached from anywhere in the world via the Internet, using a simple Internet browser. The purpose of this appendix is to refresh PECARN investigators with the use of the system.

C.1 How to Connect

The eRoom^{TM} facility is maintained on an SSL (secure socket layer) server at the University of Utah. All this means to you is that instead of typing

Figure C.1: Logging in to eRoom^{TM}

http:// at the beginning of the address that your browser will try to contact, you must type https:// (note the s). All communications between your browser and the SSL server are securely encrypted.

The URL or Internet address of our eRoom^{TM} system is https://www.nedarcssl.org/eroom and you may access this with Microsoft Internet Explorer, Netscape, Mozilla, Safari, Firefox, or almost any browser available to you. You will see something similar to Figure C.1.

Your user name has been provided to you, but in case you forgot it, it is your first name initial and last name, typed all in lowercase, typed as one word. In the example figure, Mike Dean's user name is mdean. If you have never logged into the eRoom^{TM} facility before, your initial password is pediatrics.

On a Windows machine, you will be asked if you wish to install a plug-in to help you work with eRoom^{TM}. This plug-in is not relevant to Macintosh users. If you are offered this option, we recommend that you accept the plug-in. The most important added functionality is that you can drag and drop files between your Windows desktop and the eRoom^{TM} pages. If you prefer not to install the plug-in, or if you are located at a computer on which you are not allowed to install software, then indicate that you do not wish to use the plug-in.

If you have never logged in previously or if your password has been reset, you will be asked to change your password. The dialog for doing this

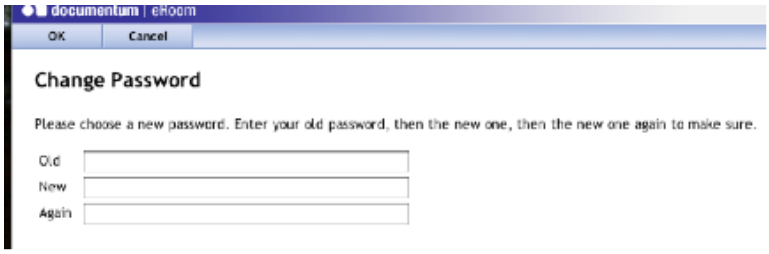

Figure C.2: Changing your password.

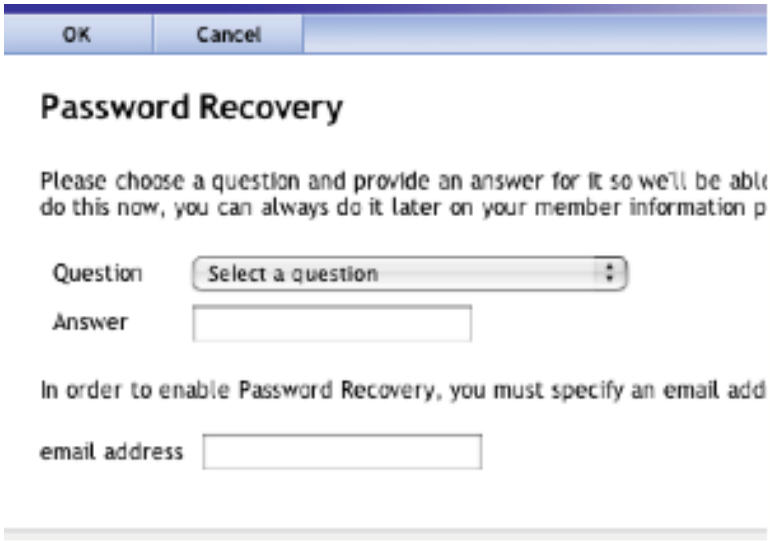

Figure C.3: Recovering your password after you forgot it.

is shown in Figure C.2.

You will have an opportunity to enter a password recovery question, which is a personal question so you can verify your identity to the system and reset your own password (see Figure C.3).

After you type your name and password, press the return or enter key, and you will go to a page called "My eRooms", resembling Figure C.4 on the following page. Only the eRooms for which you are a member will be listed on the page.

You can check any eRooms that are listed and then these will be added to your "Active eRooms" section toward the top of the screen. If you prefer, you can just click on the name of the eRoom (for example, "PECARN Steering Committee and Staff") and you will be taken directly to the eRoom. When

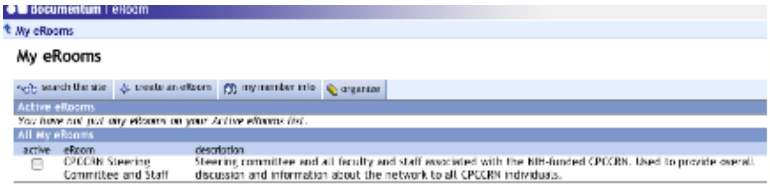

Figure C.4: Listing of your active eRooms.

you are a member of many eRooms, it is convenient to set up your "Active eRooms" to simplify finding the eRoom you wish to use. For example, an administrator might have more than 200 eRooms listed. The top of his page might look like the screen shown in Figure C.5 on the next page.

C.2 PECARN Steering Committee eRoom

The top section of a network Steering Committee eRoom looked something like Figure C.6 on page 368 in the late spring, 2005. The section on the left side is an outline-like navigation view, the bulky section is the icon view of the eRoom, and the red text is material that you have not previously seen.

Red arrows or red text, as shown in Figure C.6 on page 368, indicate that you personally have not opened or seen the material. This is convenient because if you visit a busy eRoom, you would like to know what is new for you. If you click on the red arrow on the top right of the screen, this will take you to the first unread item.

If you want to indicate that you have seen everything without reading it, you may click on the "mark read" button that is below all the icons. This is convenient if you are starting out fresh but want to keep up with all new items henceforth.

C.3 Common Items

Your use of eRoom^{TM} will increase with time and experience, but several items are worthy of description.

C.3.1 Folders and Files

There are a number of folders, which contain other things. The meeting folder will contain information about Steering Committee meetings. There

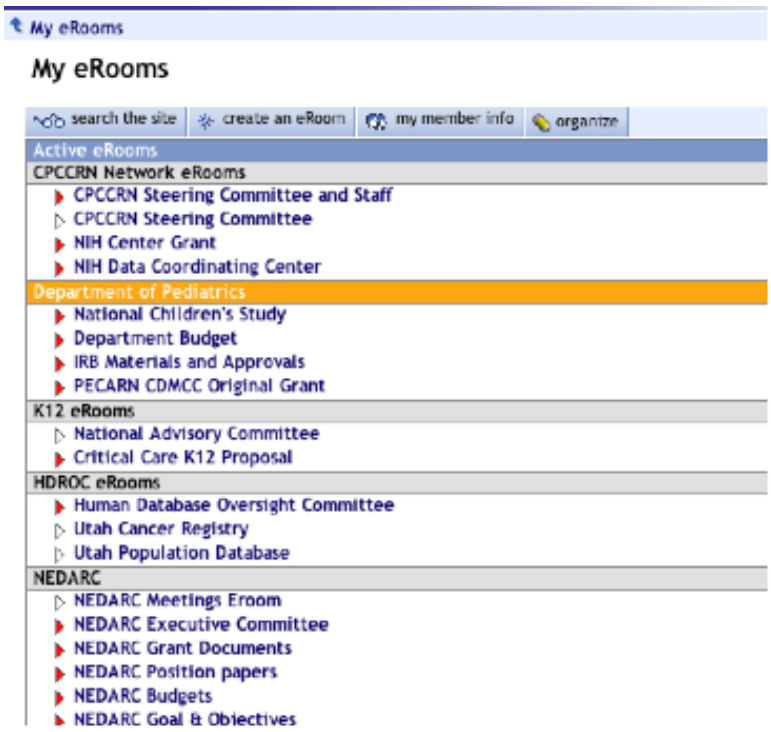

Figure C.5: Listing of active eRooms for busy user.

Figure C.6: Sample Network Steering Committee eRoom, circa July 2007.

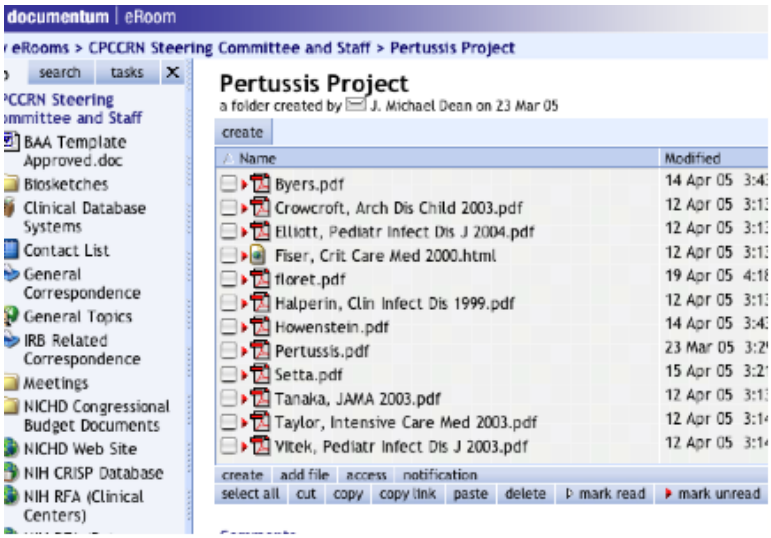

Figure C.7: Old pertussis folder in Steering Committee eRoom, May 2005.

was a folder about the pertussis project, and it contained additional documents, as shown in Figure C.7. Note that this folder does not exist today, because the project has been moved to its own eRoom.

You see the pertussis proposal (Pertussis.pdf) in the middle of the documents shown in Figure C.7, as well as references that were included as background to the project. If you click on such PDF documents and have Adobe Acrobat or Reader on your computer, then the PDF documents will automatically open.

C.3.2 Web Links

Anything that looks like a green globe is a Web link. In Figure C.6 on the facing page, you will see several links to the MCHB main page, NEDARC, and the GCP training website.

C.3.3 Polls

These icons look like voting boxes and are used to get opinions or answers from members of the eRoom. This is very convenient for avoiding large numbers of phone calls and email traffic. The two polls that are visible in Figure C.6 on the preceding page concerned the future dates of steering committee meetings and some brief questions about your computer systems.

Figure C.8: Showing contact information by name.

C.3.4 Example Database - the Contact List

There is a blue grid-like icon called Contact List (in the upper right of Figure C.6 on page 368). The CDMCC entered data about your contact information in this database, and PECARN investigators and research coordinators have maintained their own information. You may edit your entries into this database. Data coordinating center staff will try to keep this up to date, but we stress that you should make an effort to keep your own information up to date.

The contact list can be rearranged in a variety of ways. You might look at the database by name (Figure C.8), by your organization (Figure C.9 on the facing page), or by role in the PECARN (Figure C.10 on the next page).

C.4 How to Use Versioning

Finally, a few words about how documents can be produced in a collaborative environment. First, you may place a new document into the eRoom by dragging it directly into the eRoom. You may create folders or other items by clicking on the create button inside the eRoom, and you may organize documents, etc.

When you place a document in the eRoom, you are the owner. You can set several important things by right-clicking on the item. This will result in a drop down menu. The drop down has an item called "track versions" which is checked in Figure C.11 on page 372. This means that eRoom^{TM} will save all versions of the document. You should ALWAYS set this on, because then eRoom^{TM} will take care of saving every version. You may also

Figure C.9: Showing contact information by organization.

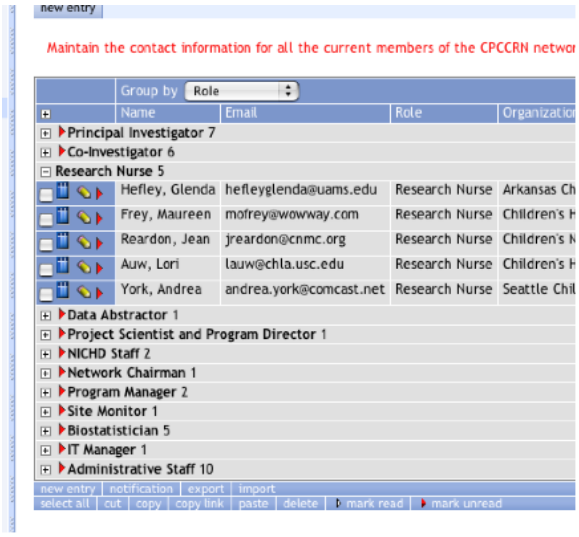

Figure C.10: Showing contact information by role in network.

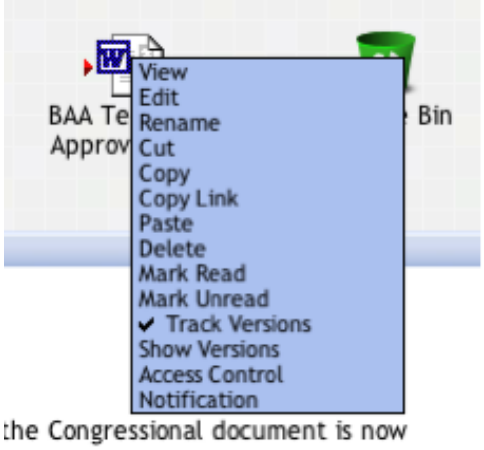

Figure C.11: Right clicking the mouse to turn on version tracking.

set the "access control" which determines who can open, edit, or see your document. Finally, if you wish to edit a document in eRoom^{TM}, you need to use this right-click method and select "edit". When you simply left-click on an item in eRoom^{TM}, which is the normal mouse click, then the default is that you can view the document but your are not in an editing mode.

Consider the workflow that might ensue with a research manuscript. A draft document would be placed in the eRoom by the original author, who could set it to be visible to everyone in our eRoom, but only editable by one or two people. When the editors want to work on the paper, they select the edit drop down, and the paper will open on their computer automatically. After working on the paper, they save it and it will be placed back in eRoom. They will be asked to provide some version information. While a document is being edited, it is locked and no other people can simultaneously edit it. However, other people CAN read the version on the eRoom.

The real working version should always be stored on eRoom^{TM}. This eliminates any confusion about who has the most recent version on which computer. By doing this, you can reach any of your work from any computer in the world. In addition you take advantage of our back up facilities.

C.5 eRoom^{TM} Backup

The eRoom^{TM} is backed up at the University of Utah every hour during the week, and on a weekly basis, a complete backup is stored deep in a

mountain that is capable presumably of sustaining a nuclear blast. For this reason, we urge all network participants to store their network-related work on eRoom^{TM} at all times. There is no reason for you to keep private versions on your own computers, but this is a work habit that takes some time to develop.

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