

**Fluid Therapy and Cerebral Injury in Pediatric
Diabetic Ketoacidosis
(Fluid Therapy in DKA)**

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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.

1 Study Summary

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.

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).

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.

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.

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.

1.6 Patient Eligibility

1.6.1 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.)

1.6.2 Exclusion Criteria

The following patients will be excluded from the study:

- patients with pre-existing neurological disease that substantially impacts mental status or neurocognitive 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

1.6.3 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.

1.7 Anticipated Recruitment and Study Duration

The total number that we plan to enroll in the study is 1510. The participating sites see ≈ 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 Background and Preliminary Studies

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 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.

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.

4 Study Outcomes

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.

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.

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.

5 Patient Eligibility

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.)

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 neurocognitive 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

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.

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.

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.

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.

6.1.1 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 1 on the following 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 1 on the next page](#) outlines the fluid treatment protocols.

Table 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.

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 7.3 on page 25) for methods pertaining to Aim 3 neurocognitive assessments.

7 Data Collection

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 pCO₂, 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.

7.2 Data Collection during DKA Treatment

Data collection during management of DKA is summarized in Table 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 will be collected through hospital discharge - the frequencies of sampling indicated in Table 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: 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.

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 \pm 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 11.3 on page 49).

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 3 summarizes the neurocognitive assessment to be conducted.

Table 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.

7.3.1 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.

7.3.2 Cognitive testing children ≥ 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 1 shows a schematic summary of these testing procedures.

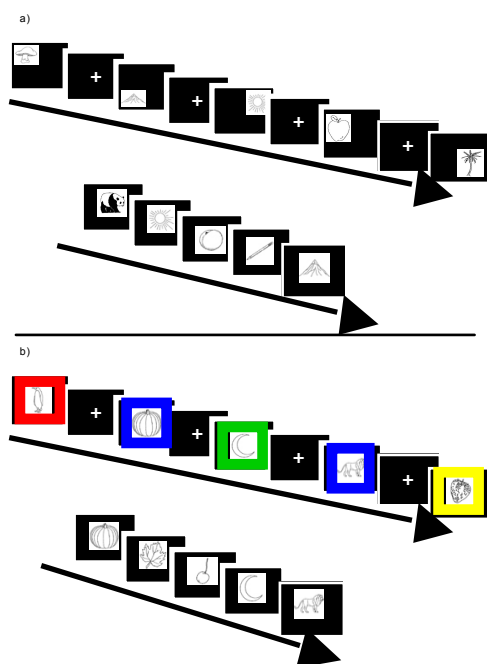


Figure 1: Memory task schematic

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.

7.3.3 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-III³⁰) 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 7.3.2 on the preceding 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.

8 Data Analysis

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.

8.2 Secondary Endpoints

8.2.1 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.

8.2.2 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.

8.2.3 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.

8.2.4 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.

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.

8.4 Child Behavior Checklist (CBCL)

The CBCL¹ 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.

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 Centers see ≈ 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.

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 8.5 on page 33).

9 Human Subjects Protection

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.

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.

9.2.1 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.

9.2.2 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.

9.2.3 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.

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 10.1 on page 42](#)).

9.3.1 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.

9.3.2 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.

9.3.3 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.

9.3.4 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.

9.3.5 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.

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 eRoomTM is used for communications about the study. The EDC, eRoomTM 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.

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.

10 Data and Safety Monitoring Plan

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 8.6 on page 34.

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 8.6 on page 34). 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.

10.2 Adverse Event Reporting

10.2.1 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

10.2.2 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.

10.2.3 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 on page 23 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 on page 23 because all values for these parameters will be collected. If an abnormality of a laboratory parameter in Table 2 on page 23 is considered to be serious by the Clinical Center investigator (see Section 10.2.1 on page 43), 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 10.2.5 on the following page.

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

10.2.4 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 eRoomTM 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.

10.2.5 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 10.2.1. 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.

10.2.6 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.

11 Data Quality Assurance

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.

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.

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.

11.3.1 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.

11.3.2 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.

11.3.3 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.

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.

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)].