Informed Consent Form

Protocol FLUID

Study: FLUID

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Table of Contents

1. Study Summary 3

2. Background and Purpose 4

3. Number of Participants 5

4. Study Procedures 6

5. Alternative Procedures 7

6. Risks and Discomforts 8

7. Benefits 9

1. Study Summary

Informed Consent Summary

The purpose of this study is to find out whether different types and rates of intravenous fluids given to children with diabetic ketoacidosis (DKA) affect their risk of developing brain problems, like swelling or memory issues, during and after treatment.

If your child takes part in this study, they will receive one of four commonly used fluid treatment plans for DKA. All of these fluid plans are standard in hospitals and involve different salt (sodium) levels and rates of giving fluids through an IV. Your child's mental status (how alert they are) will be checked often during DKA treatment, and they will also have some simple memory and IQ tests in the hospital and about three months later. The study staff may collect extra blood samples as part of the usual care for DKA, but no extra blood draws are planned just for the study.

The time in the study will last for the duration of the hospital stay for DKA (usually about 1-2 days), with one follow-up visit or phone call about three months after discharge. Most participants will have 1-2 study visits (in the hospital plus one follow-up). Participation is voluntary, and all information will be kept private as required by law. If you have any questions, please ask the study team.

Status: Approved | Word Count: 217 | Section: summary

2. Background and Purpose

Certainly! Below is a comprehensive **Background** section for the Fluid Therapy in DKA study informed consent form (ICF), written in clear, non-technical language consistent with FDA 21 CFR 50 guidelines. This section addresses: the medical condition, the need for the study, a summary of existing research, and how the study will advance medical knowledge.

Background

What is Diabetic Ketoacidosis (DKA) and Why Is It Important?

Diabetic ketoacidosis, sometimes called DKA, is a serious and potentially life-threatening complication of diabetes that is most common in children and teenagers with type 1 diabetes. DKA happens when the body does not have enough insulin. When this occurs, sugar cannot enter the cells to provide energy, so the body starts breaking down fat for fuel. This process leads to a build-up of acids in the blood called “ketones,” causing symptoms like rapid breathing, dehydration (dryness and low body fluids), stomach pain, vomiting, confusion, and in severe cases, loss of consciousness.

One of the most serious problems that can happen during DKA is swelling of the brain (known as “cerebral edema”). Cerebral edema is rare, but when it does occur, it can cause permanent brain injury or even death. Even when visible swelling does not happen, some children experience subtle or temporary changes in thinking or behavior during DKA treatment, and some may have memory or learning problems that last beyond their recovery.

Why Is This Study Needed?

Doctors know that DKA must be treated quickly and safely. Treatment typically involves giving fluids through a vein (intravenous or IV fluids) to replace lost fluids and correct imbalances, along with insulin to help return blood sugar to a safe range. There are several different approaches to how fast fluids are given and what type of fluid (for example, fluids with different amounts of salt, or sodium) is used. The best combination of fluid speed and type to protect the brain and prevent complications like cerebral edema is not known.

Current medical guidelines are often based on expert opinion rather than solid research evidence. Some experts worry that giving fluids too quickly might increase the risk of brain swelling, while others are concerned that giving fluids too slowly may not reverse dehydration fast enough, possibly causing more harm. Because of this uncertainty, children with DKA may currently receive different treatments depending on where they are cared for.

What Does Earlier Research Show?

Some earlier studies suggested a possible link between faster IV fluid treatment and brain swelling, leading to recommendations for slower fluid administration, especially in children. However, newer research, including animal studies and studies using advanced brain imaging, suggests that the situation is more complex. Recent evidence shows that children with DKA often experience reduced blood flow to the brain (called “cerebral hypoperfusion”) before receiving treatment, which may contribute to brain injury.

Research using MRI scans has shown that some brain swelling happens even in children who do not have obvious symptoms, and minor changes in mental status are common during DKA treatment. Children who experience DKA may also have more challenges with memory or thinking skills months after recovering, compared to children with diabetes who have never had DKA.

Despite this knowledge, there is no clear answer as to how the rate and type of IV fluids given during DKA treatment affects brain health and recovery in children.

How Will This Study Advance Knowledge?

This study is designed to help answer these important questions. It will compare different commonly used fluid treatment strategies (varying rate and sodium concentration) in a large group of children with DKA. By carefully tracking how children's thinking abilities, memory, and brain health are affected during and after treatment, this research aims to find out which fluid treatment works best to:

- Lower the risk of worsening mental status or brain swelling during DKA
- Reduce long-term changes in memory or learning
- Provide the most effective and safest care for children with DKA

The information from this study will help doctors make evidence-based decisions about fluid treatment in DKA, with the goal of improving short-term safety and long-term quality of life for children with diabetes.

References available upon request. If you have any questions about this study or DKA, please ask your study doctor or nurse.

Status: Approved | Word Count: 709 | Section: background

3. Number of Participants

Participants

How many participants will be in this study?

We expect about **1,510 children and teenagers** to take part in this study.

Who can be in the study?

Children and teens may be eligible to participate if they meet **all** of the following:

- Are **less than 18 years old**
- Come to, or are transferred to, a participating Pediatric Emergency Care Applied Research Network (PECARN) emergency department (ED)
- Are diagnosed with diabetic ketoacidosis (DKA), which requires:
- A blood sugar (glucose) higher than **300 mg/dL**
- AND either: a blood pH less than 7.25 **or** a blood bicarbonate level less than 15 mmol/L

Who cannot be in the study?

Children and teens will **not** be able to participate if any of these apply:

- Have a pre-existing (already diagnosed) neurological disease that affects mental status or thinking (such as cerebral palsy with developmental delay or autism)
- Are currently intoxicated with alcohol or other drugs, or have recent head injury, meningitis, or another condition that could affect the brain
- Were already given more than one IV fluid bolus (more than 10 mL per kg) at another hospital before transfer to the study hospital
- Are currently **pregnant**
- Have already been enrolled in this study two or more times
- Need a specific fluid or electrolyte treatment as determined by their doctor (for example, if the doctor thinks a special protocol is needed)
- Have already been receiving IV fluids at maintenance rate or higher (by the 4-2-1 rule) for more than two hours before coming to the study hospital
- Began DKA treatment (either IV fluids, IV bolus, or IV insulin) more than four hours before arriving at the study hospital
- Received certain treatments for brain swelling (such as mannitol or 3% saline) before arrival or since arriving at the study hospital, or need them right away as determined by the doctor
- Have a low Glasgow Coma Scale (GCS) score of 11 or less at the start

Where is the study offered?

The study is being conducted at several **major pediatric hospitals** that are part of the Pediatric Emergency Care Applied Research Network (PECARN) across the United States. If your child is being cared for in a participating hospital's emergency department, you may be asked to consider participating.

Do you have questions?

If you have any questions about whether your child can participate, please speak with the research team at the hospital.

This section meets the requirements outlined in FDA 21 CFR 50 regarding informed consent and clarity, and is written in language suitable for the general public.

Status: Approved | Word Count: 441 | Section: participants

4. Study Procedures

Certainly! Below is a **detailed Study Procedures section** written for the informed consent form (ICF) for the Fluid Therapy in DKA Trial (Kuppermann and Glaser), following FDA 21 CFR 50 guidelines. The content is organized step-by-step, presented chronologically, and describes all key procedures, time commitments, tests, interventions, and follow-up.

Study Procedures

If you decide to participate, your/your child's participation in this research study will involve several steps during your hospital stay and one follow-up visit after recovery. The procedures are described below in order, so you know what to expect at each stage.

1. **Screening and Enrollment (Initial Assessment in Emergency Department)**

- **When:** Upon arrival for DKA evaluation (usually in the Emergency Department).
- **What will happen:**
- Study staff will review medical history and current symptoms to determine eligibility.
- Basic information will be collected, including age, sex, race/ethnicity, diabetes history, and other chronic conditions.
- Medical assessment includes measurement of vital signs, assessment of peripheral perfusion (e.g., pulse, capillary refill), and neurological function (mental status using the Glasgow Coma Scale, or GCS).
- Blood and urine samples will be collected to measure glucose, electrolytes, blood gases, kidney function, and other labs.
- Parents of eligible children will be asked to sign the consent document; children old enough may be asked for their assent.
- **Time commitment:** Approximately 30-60 minutes.

2. **Randomization and Start of Study Treatment**

- **When:** Right after consent and eligibility confirmation.
- **What will happen:**
- Your/your child's DKA treatment will begin with a study-assigned fluid regimen (different sodium content and rate of intravenous rehydration).
- The assigned treatment protocol will determine:
- The concentration and type of intravenous fluids used.
- The rate at which fluids are administered.
- Physicians may adjust fluid or insulin therapy in case of medical necessity, for safety.
- **Time commitment:** No extra time beyond normal DKA treatment.

3. **Hospital Stay for DKA Management**

a. **Initial and Ongoing Monitoring**

• **When:** Throughout the hospital stay (typically 1–2 days).

• **What will happen:**

• **Blood glucose**: Measured at presentation and hourly.

• **Blood chemistry (electrolytes, BUN, creatinine, etc.), blood pH, and pCO,**: Measured at presentation and every 2–4 hours for the first 24 hours, or until DKA resolves.

• **Serum calcium, magnesium, phosphate**: Measured at presentation and every 4–8 hours as needed.

• **Vital signs**: Monitored hourly.

• **Neurological assessment (GCS):** Performed at enrollment and then every hour. If the score drops below 14, it will be rechecked in 15 minutes. Persistent scores below 14 will be reported and managed per hospital protocol.

• **Memory/working memory (Digit Span Recall Test):**

• For children **older than 3 years**, this test is given at enrollment and every 4 hours during normal waking hours (7am–10pm).

• For children **younger than 3 years**, this test will not be performed.

• Each digit span test takes approximately 5–10 minutes.

• **Fluid intake and urine output:** Recorded as per standard care.

• **Time commitment:** Neurocognitive testing (digit span) adds about 5–10 minutes per session (about every 4 waking hours); other monitoring is standard care.

b. **Behavioral Assessment**

• **When:** Prior to hospital discharge (while still admitted).

• **What will happen:**

• Parents of children aged 3–17 will complete the **Child Behavior Checklist (CBCL)**. This asks parents about their child's behavior before this illness.

• Completion time: About 10–15 minutes.

4. **Discharge from Hospital**

• **When:** When DKA is resolved and the medical team decides discharge is safe.

• **What will happen:** No special procedures, but you will be reminded about follow-up requirements.

5. **Follow-up Neurocognitive Testing (Outpatient Visit)**

• **When:** **About 3 months (+/- 4 weeks) after hospital discharge** (for children aged 3–17 at follow-up).

• **What will happen:**

• You/your child will be scheduled for an outpatient visit lasting approximately 1.5–2 hours.

• **Blood glucose** will be measured by fingerstick before testing. If it is too low (<70 mg/dL) or too high with ketones (>350 mg/dL with urine ketones), testing may be rescheduled.

• **Neurocognitive tests** will be administered by trained study staff:

• **For children 6–18 years:** Wechsler Abbreviated Scale of Intelligence (WASI) for IQ (~30 minutes), and memory tasks (color task, spatial location; ~50 minutes, with a rest break). Digit span recall will also be repeated (5–10 minutes).

• **For children 3–5 years:** Abbreviated WPPSI-III for IQ (10–30 minutes), shortened memory tests, digit span (5–10 minutes). Testing is designed to be shorter and age-appropriate.

• **For children younger than 3:** No follow-up neurocognitive testing.

• **Behavioral Assessment (CBCL):** Parents will complete the CBCL again.

• **Time commitment:** Entire visit will take about 1.5–2 hours. Testing may be shorter for very young children.

6. **Follow-up of Serious Adverse Events**

• **When:** If you/your child experiences a serious, study-related, and unexpected medical problem that is not resolved prior to hospital discharge.

• **What will happen:** Study staff will contact you regularly by phone or during clinic visits to monitor the event's resolution, for up to 3 months after enrollment, unless recovery or a clear explanation occurs sooner. Events beginning after discharge are not reported or followed as study-related adverse events.

• **Time commitment:** Varies if needed; follow-up is only for unresolved significant events.

Summary Table

Study Step	Main Activities	Estimated Time
Screening/Enrollment	Consent, baseline data and labs, eligibility check	30–60 minutes
Acute DKA Treatment	Fluid & insulin per study arm, frequent monitoring, digit span memory (e3yo)	DKA duration
Hospitalization	Routine care, parent CBCL (3–17yo), digit span (e3yo, every 4 hours waking hours)	Per standard care (plus ~10 min every 4h)
Discharge	No additional study procedures	
3-mo Outpatient F/U	Neurocognitive testing (3–17yo), CBCL, glucose check, digit span recall	1.5–2 hours
Adverse event F/U	If needed, phone/clinic follow-up of unresolved serious adverse events	If needed

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Additional Notes

• Participation in this study includes all procedures above. Your/your child's clinical care team may provide additional tests or treatments as medically necessary.

• You have the right to withdraw from the study at any time.

• Study staff will review any problems or abnormal test results with you as needed. If the neurocognitive test suggests “possible learning problems,” you will be notified, but specific scores will not be shared.

• Data collected will be kept confidential as described, and no identifiable results will be shared without your permission.

If you have any questions about these procedures, please ask the research team any time.

Status: Approved | Word Count: 1098 | Section: procedures

5. Alternative Procedures

ALTERNATIVE PROCEDURES AND TREATMENTS

Participation in this study is entirely voluntary. Before you decide whether to enroll your child in this research study, it is important for you to understand the other options available. The following section describes the alternatives to participation in the DKA Fluid Protocol clinical trial, including available treatments outside the study, standard care options, and important considerations.

1. Standard Care for Diabetic Ketoacidosis (DKA):

If you do not wish for your child to participate in this research study, your child will still receive high-quality medical care for DKA. The standard of care for treating children with DKA is well established and involves:

- Careful monitoring of vital signs, blood glucose, electrolytes, and neurological status.
- Administration of intravenous fluids to correct dehydration and electrolyte imbalances.
- Administration of insulin to reduce blood glucose and ketone levels.
- Correction of other metabolic disturbances as needed (such as potassium, phosphate, or sodium abnormalities).
- Ongoing assessment for potential complications, including cerebral edema and other organ involvement.

Each hospital, including those participating in this study, follows current national and institutional guidelines for DKA management. The protocols compared in this research study represent variations within accepted ranges of standard care presently used at many hospitals throughout the United States.

2. Treatment Outside the Study:

Your child can receive DKA care at this hospital or another medical center without being part of this clinical trial. The main difference is that, outside the study, treating physicians will select the specific fluid therapy regimen based on their own professional judgment and your child's clinical needs, rather than following one of the randomly assigned research protocols. The decision about the type and rate of fluids will be made according to the local standard protocols or the physician's recommendations, which are also considered safe and effective.

3. Other Treatment Options:

There are currently no other investigational or experimental therapies proven to be superior to standard DKA care in children. The available alternatives are the existing variations in fluid and insulin management used by healthcare professionals to successfully treat DKA.

4. Declining Participation:

It is important to emphasize that not taking part in this study is always an alternative. If you decide not to enroll your child, your decision will not affect the care your child receives. Your child will be treated with the best standard protocols available, and all appropriate measures will be taken to ensure their safety and recovery.

5. Comparison of Alternatives and Research Participation:

Aspect	Studies Protocol (Participation)	Usual Care (Non-Participation)
Fluid management	Randomly assigned to one of four acceptable protocols	Chosen by the treating physician
Monitoring	Standard monitoring; possible additional study visits	Standard monitoring-
Risks	Comparable to usual care; subject to protocols	Comparable to research protocols
Benefits	Possible benefit to future patients; possible added monitoring	Proven, effective standard care
Flexibility in treatment	Protocol assignment (with safety overrides by physician)	Physician discretion for all decisions
Impact on future knowledge	May help improve future care for DKA patients	No contribution to research knowledge

6. Pros and Cons

- **Potential Benefits of Participation:**
- Your child's care will be closely monitored according to the study protocol.
- The results may help guide future optimal care of children with DKA.
- The assigned treatment protocol is within currently accepted ranges for standard care.
- **Potential Risks/Disadvantages:**
- Participation involves being randomly assigned to a fluid regimen rather than your physician's standard preference.
- Additional assessments or follow-up may be required as part of the study.
- There may be unknown risks, but no study treatment is outside the limits of usual care.
- **Potential Benefits of Usual Care Without Participation:**
- Treatment is determined entirely by your child's clinical presentation and the treating physician's judgment.
- No additional study procedures or follow-up are required.
- **Potential Risks/Disadvantages of Usual Care:**
- No direct contribution to improving knowledge about the best management approach for DKA.

Summary:

You may choose for your child:

- To participate in this study,
- To receive standard treatment for DKA without joining the study, or
- To seek care at another hospital if you wish.

You are encouraged to discuss these alternatives with your child’s healthcare team or ask for clarification of any options before deciding. Your child’s well-being is our highest priority, and your decision regarding participation will not affect the quality of care they receive.

If you have any questions about these alternatives, please ask the study team or your healthcare provider.

(This section is written in accordance with FDA 21 CFR 50, which requires a disclosure of appropriate alternative procedures or courses of treatment that may be advantageous to the subject.)

Status: Approved | Word Count: 801 | Section: alternatives

6. Risks and Discomforts

Certainly. Below is a model Risks section for the Informed Consent Form for the DKA Fluid Protocol Study. This text follows FDA 21 CFR 50 guidelines and reflects the protocol content provided, including grouping risks by severity and likelihood, objective risk descriptions, monitoring, mitigation strategies, and acknowledgment of unknown risks.

RISKS OF PARTICIPATION

Your child is being asked to participate in a research study to compare different protocols for fluid treatment of diabetic ketoacidosis (DKA) in children. As with any research study, participation involves certain risks. These risks are explained below to help you make an informed decision.

Risks and Discomforts

During treatment of DKA with intravenous fluids, certain side effects or complications may occur. Some risks are common and expected in the treatment of DKA; others are less common but more serious. Because this study involves treatments already in common use, the risks are similar to the standard care for DKA. However, some risks may be more or less likely depending on the treatment group assigned.

1. Common and Anticipated Risks

a. Fluid and Electrolyte Imbalances

- **Hyperchloremic Acidosis**
- *Description*: Excess chloride in the blood (hyperchloremic acidosis) may develop, especially with use of 0.9% saline (one of the fluids studied).
- *Likelihood*: This is a known and relatively frequent complication during DKA treatment.
- *Severity*: Typically mild and self-limited; rarely causes symptoms or long-term problems. May delay some aspects of therapy until resolved.
- *Monitoring/Management*: Blood chemistry will be monitored regularly, and physicians may change the fluid used or end study participation if significant acidosis develops.
- **Rapid Changes in Blood Sodium (Hyponatremia or Hypernatremia)**
- *Description*: In rare cases, the level of sodium in the blood may fall or rise too quickly, especially in children with unusual sodium levels at the start of treatment.
- *Likelihood*: Uncommon, due to careful patient selection; however, still possible.
- *Severity*: Can be serious if it occurs (see below).
- *Monitoring/Management*: Sodium levels will be regularly checked, and the treating physician may adjust fluids or discontinue the protocol for safety.
- **Inadequate Fluid Resuscitation**
- *Description*: Receiving fluids too slowly may result in insufficient blood flow to vital organs (under-perfusion).
- *Likelihood*: Uncommon due to protocol safeguards and physician discretion.

• *Severity*: If unaddressed, could lead to organ injury (see below).

• *Monitoring/Management*: Protocol allows additional fluid boluses and monitoring of blood pressure and perfusion; treating physicians can make changes as needed to ensure safety.

2. Less Common but Serious Risks

a. Cerebral Edema (Swelling of the Brain)

• *Description*: DKA treatment can lead to swelling of the brain (cerebral edema), a known but rare and serious complication.

• *Likelihood*: Cerebral edema occurs in 0.5–1% of children during DKA treatment, regardless of protocol; the effect of fluid rates or concentrations on this risk is not fully known and is the subject of the study.

• *Severity*: Can be life-threatening and may result in temporary or permanent brain injury or death.

• *Monitoring/Management*: Patients in the study will have detailed and frequent assessments of mental status (hourly or more if concerns arise). If signs or symptoms of cerebral edema are detected, immediate treatment will be provided according to standard medical procedures.

b. Thrombosis (Blood Clots)

• *Description*: Insufficient or overly slow fluid administration can increase the risk of blood clots forming in veins (thrombosis).

• *Likelihood*: Rare, but possible.

• *Severity*: Can lead to serious complications, such as strokes or damage to organs.

• *Monitoring/Management*: Physicians monitor signs of poor circulation. Additional fluids or treatments may be given if needed.

c. Renal Failure, Gastrointestinal Necrosis, Cardiac Arrhythmias, Other Organ Injuries

• *Description*: Rare and severe complications that may occur due to the severity of DKA itself or due to fluid therapy.

• *Likelihood*: Very rare; most often related to severe DKA rather than treatment itself.

• *Severity*: Can be life-threatening or cause permanent harm.

• *Monitoring/Management*: Hospitalized patients are closely monitored for these complications; appropriate medical interventions will be taken if they arise.

d. Pulmonary Edema (Fluid in the Lungs)

• *Description*: Rapid or excessive fluid administration can cause fluid accumulation in the lungs.

• *Likelihood*: Very rare when monitored and treated appropriately.

• *Severity*: Potentially serious; can impair breathing.

• *Monitoring/Management*: Fluid administration is carefully regulated; respiratory status will be closely observed.

3. Risks Related to Study Procedures

a. Neurocognitive Testing

• *Description*: Children will undergo assessments of memory and cognitive function. These are non-invasive (do not involve needles, radiation, or drugs).

• *Likelihood/Severity*: There are no known physical or psychological risks from these tests, though some children may feel bored or slightly frustrated.

4. Unknown or Unforeseeable Risks

While the treatments studied are already commonly used for DKA, and the study is designed to minimize risks, research may uncover side effects or complications that are currently unknown or unanticipated. There may be risks that are currently unforeseeable.

Monitoring and Risk Management

- All participants will be cared for in hospitals with experienced pediatric teams.
- Neurological (mental status) checks will occur at least every hour while in DKA.
- Blood tests for electrolytes, glucose, and kidney function will be performed as part of routine monitoring.
- Treating physicians have the authority to discontinue or modify study treatments at any time if safety concerns arise.
- A Data and Safety Monitoring Board (DSMB) will review safety data throughout the study.
- Serious unexpected study-related complications will be reported rapidly to study leadership, national oversight boards, and ethics committees, and may result in stopping the study if necessary to protect participants.

Unknown Risks

There is a possibility that risks or side effects may occur that we do not currently know about. You will be informed of any new information that may affect your willingness to have your child continue in the study.

Risks Associated With Standard DKA Care

It is important to understand that most of the risks described above are inherent in the condition being treated (DKA) and are not unique to this study. Your child would face similar risks if treated for DKA outside of the study. The study is designed so that all treatments are within established standards of care.

If you have any questions about the risks described, please ask the study team. Your child's safety is our highest priority.

Status: Approved | Word Count: 1053 | Section: risks

7. Benefits

Certainly! Here is a balanced and regulatory-compliant Benefits section for the ICF, tailored to your study and following FDA 21 CFR 50 requirements:

9.3.2 Potential Benefits

Potential Direct Benefits to Participants

- The fluid therapy protocols being studied are all within the current standard of care for treating diabetic ketoacidosis (DKA) in children. Participation in the study provides careful and frequent monitoring of your child’s health status by experienced clinical staff.
- If your child experiences any complications during the study, the healthcare team will be able to respond quickly, and your child’s treatment can be adjusted as needed for safety.
- It is possible, but not certain, that your child may benefit from being assigned to a treatment protocol that, as a result of this study, is found to be more effective or safer than others. However, there is no guarantee that participation will result in any direct improvement in your child's health or outcome compared to standard treatment outside of the study.

Potential Benefits to Society and Future Patients

- The information gained from this study may help doctors in the future to determine the safest and most effective ways to provide fluid therapy for children with DKA.
- By participating, you are helping advance medical knowledge that may reduce complications (such as changes in mental status or cerebral edema) for future patients treated for DKA.
- The study results may influence national or international guidelines, potentially improving care for large numbers of children worldwide.

Limits and Uncertainty of Benefits

- It is important to understand that benefits are not guaranteed. The study treatment your child receives may not be better than, or may be similar to, the care they would otherwise have received.
- While the study closely follows existing best practices, the specific advantages or disadvantages of any individual protocol are not yet known—that is why this research is being conducted.
- Participation in research is voluntary, and you should only take part with the understanding that the main purpose of this study is to gather information that may benefit children with DKA in the future, rather than to provide a direct benefit to individual participants.

If you have any questions about the potential for benefit or would like more information, please ask the study team.

Status: Approved | Word Count: 382 | Section: benefits