RDCRN

Rare Diseases Clinical Research Network

Comparative Effectiveness of Therapy in Rare Diseases: Liver Transplantation vs. Conservative Management of Urea Cycle Disorders

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Table of Contents

1. Protocol Synopsis

Observational Synopsis

Protocol Number:	UCDC 5117
Protocol Title:	Comparative Effectiveness of Treatment in Rare Diseases: Liver Transplantation vs. Conservative Management of Urea Cycle Disorders
Study Chair:	Nicholas Ah Mew, MD
Statistician:	Robert McCarter, ScD
Consortium:	Urea Cycle Disorders Consortium
Participating Sites:	Children's National Health System The George Washington University National Urea Cycle Disorders Foundation
Activation Date:	March 4, 2016
Sample Size:	**Aim 1:**185 (92 with liver transplant, 93 without liver transplant) **Aim 2:** 32-48 primary caretakers, 25-40 providers **Aim 3:** 64-48 primary caretakers
Target Enrollment Period:	3 years
Study Design:	Mixed method concurrent study design. Quantitative research methods to address primary outcomes. Qualitative research methods to obtain information on the UCD patient/family experience when making critical treatment decisions
Primary Study Objective:	To study two urea cycle disorder (UCD) patient cohorts, one managed conservatively and the other treated by liver transplantation; comparing survival rate, neurocognitive function and patient-reported quality of life. (**Aim 1**)
Secondary Study Objective:	To examine, through a representative sample of pediatric patient's primary caretakers (typically a parent) and medical providers, including the treating physician and other clinicians on the team, how UCD treatment decisions are made, describing the factors that influence the patient/family's decision to continue conservative management or elect liver transplantation. (**Aim 2**) To develop a dissemination strategy for study findings of **Aim 1** that aligns with the decision-making considerations and process illustrated through **Aim 2** and which is responsive to the expressed needs of UCD patients and their primary caretakers. (**Aim 3**)
Study Population and Main Eligibility/ Exclusion Criteria:	**Aim 1** - Age 18 and under - Diagnosed with the following neonatal-type

	urea cycle disorders: CPSD, OTCD, ASD or ALD, as defined as follows: • Diagnosis of CPS1 deficiency, defined as decreased (less than 20 % of control) CPS1 enzyme activity in liver, and/or an identified pathogenic mutation, and/or hyperammonemia and first-degree relative meets at least one of the criteria for CPS1 deficiency • Diagnosis of OTC deficiency, defined as the identification of a pathogenic mutation, and/or less than 20% of control of OTC activity in the liver, and/or elevated urinary orotate (greater than 20 µM/mM) in a random urine sample or after allopurinol challenge test, and/or hyperammonemia and first-degree relative meets at least one of the criteria for OTC deficiency • Diagnosis of AS deficiency (Citrullinemia), defined as a greater than or equal to 10-fold elevation of citrulline in plasma, and/or decreased (less than 20% of control) AS enzyme activity in cultured skin fibroblasts or other appropriate tissue, and/or identification of a pathogenic mutation in the AS gene, and/or hyperammonemia and first-degree relative meets at least one of the criteria for AS Deficiency • Diagnosis of AL deficiency (Argininosuccinic Aciduria, ASA), defined as the presence of argininosuccinic acid in the blood or urine, and/or decreased (less than 20% of control) AL enzyme activity in cultured skin fibroblasts or other appropriate tissue, and/or identification of a pathogenic mutation in the AL gene, and/or hyperammonemia and first-degree relative meets at least one of the criteria for AL Deficiency - **Willing to participate in at least 1 neurocognitive assessment and at least 1 quality of life assessment** - **Permit access to medical records and medical providers** **Aims 2 & 3:** - Primary caretaker(s) of a patient age 25 and

	under who has been diagnosed with either CPSD, OTCD, ASD or ALD (typically a parent, but broadly defined as those individuals who are responsible for making the child's treatment decisions and who also provide the majority of the child's physical and emotional care) - Considered, are currently considering, or opted for, liver transplantation as a treatment for UCD. - Willing to participate in a 60-minute semi-structured interview and/or a 60-90 minute focus group discussion OR - Health care provider (e.g. metabolic disease physician, liver transplant surgeon, gastroenterologist, genetic counselor, or nurse) that participates in treating patients diagnosed with either CPSD, OTCD, ASD or ALD, - Willing to participate in a 60-minute semi-structured interview and/or a 60-90 minute focus group discussion
Statistical Considerations	**Aim 1:** Covariate-balancing propensity scoring based on the CBPS package in R to create comparable (balanced) groups based on their risk factor (covariate) profile in subjects according to their propensity (probability) to move from conservative management to liver transplantation **Aim 2:** Thematic content analysis of interview data (collected and coded using QSR International NVivo 10) will form the basis of our interpretation, which will move beyond a typology of participant accounts to look at the relationship between the identified themes **Aim 3:** Focus group data will also be analyzed using thematic content analysis
Sponsors:	National Institutes of Health (NICHD/NCATS)
Funder:	Patient-Centered Outcomes Research Institute (PCORI)

1.1. Overview

Urea cycle disorders (UCD) are genetic disorders caused by the liver's inability to break down ammonia from proteins; ammonia then accumulates and is toxic to the brain. UCD cause brain damage, intellectual, developmental disabilities, and even death. Medical treatment involves special diet low in protein, drugs that help metabolize ammonia and amino acid supplements (conservative management). However, many patients and families choose liver transplantation rather than conservative treatment; both alternatives are effective in reducing or normalizing blood ammonia. While liver transplantation eliminates the ammonia problem, conservative management does so only temporarily and in many patients, blood ammonia can rise during an infection or other stress. The long-term objective of this study is to help patients make decisions about management alternatives (medical vs. liver transplantation) by providing them with scientific information that is currently lacking.

The questions that will be addressed are:

1. What is the disease's risk of mortality and illness in each treatment approach?
2. What can parents expect in terms of the neurocognitive development of their child and his/her school performance?
3. What are the expected effects of each treatment on short-term and long-term quality of life?
4. What factors do primary caretakers (typically parents) consider when making the decision to pursue liver transplantation or continue conservative management for their child with UCD?

This research will have two components. In one, we will use statistical methods to compare survival, illness, psychological testing for IQ, executive function, memory, behaviors, and quality of life among patients that choose conservative management and those who have chosen liver transplantation. Some of this information is already being collected by the Urea Cycle Disorders Consortium (UCDC) in 14 metabolic clinics (11 of them in the US) as part of its longitudinal natural history study. To ensure that the information we analyze is representative of the UCD patient population in the US, we will also obtain data from the Studies of Pediatric Liver Transplantation (SPLIT) registry, which collects information about children who undergo liver transplantation for many different diseases (including UCD), and from the National Urea Cycle Disorders Foundation (NUCDF) a patient advocacy group for patients with UCD.

The qualitative component of this project will consist of individual interviews and focus groups with UCD pediatric patient families and caretakers and medical providers, including treating physicians and other medical staff on the team, to identify the important issues caretakers consider when deciding whether to opt for liver transplantation or continue conservative management.

The NUCDF and its Patient-Powered Research Team (PPRT) collaborated with the clinical investigators to design this research and to ensure that it that it covers the questions that are most important to patients and their families. The results of this study

will be disseminated to patients and families, doctors and clinical staff so that they receive current, validated information before making a decision about the best treatment choice for the individual patients.

2. Specific Aims (Hypothesis and Objectives)

This study will compare the outcomes of liver transplantation vs. medical treatment in patients with UCD for survival, neurocognitive status, and quality of life. The specific aims are:

Aim 1: To study two urea cycle disorder (UCD) patient cohorts, one managed conservatively and the other treated by liver transplantation, comparing survival rate, neurocognitive function and patient-reported quality of life.
Aim 2: To examine, through a representative sample of pediatric patient primary caretakers and medical providers, including the treating physician and other clinicians on the team, how UCD treatment decisions are made, describing the factors that influence a primary caretaker's decision to continue conservative management or proceed to a liver transplant.
Aim 3: To develop a dissemination strategy for study findings of **Aim** 1 that aligns with the decision-making process illustrated through **Aim 2** and which is responsive to the expressed needs of UCD patients and their primary caretakers.

This study's goal is to fill a critical needs gap by providing objective evidence of risk and benefit that will serve as a solid foundation for the decision-making process. The current decision-making process relies largely on subjective judgment. The study results and dissemination will provide patients and families with evidence-based information that is currently lacking on the treatment alternatives (conservative management vs. liver transplantation), including answers to the following questions: 1.What is the disease-specific risk of mortality and morbidity in the two approaches? 2. What outcomes can patients expect in terms of cognitive development and/or other developmental milestones? 3. What are the pros and cons in terms of quality of life considerations? The study will provide qualitative information on the decision-making process that caretakers undertake when choosing between these treatment alternatives so that dissemination efforts around study results can be designed to align with this process and better address caretakers' expressed needs and concerns.

3. Background

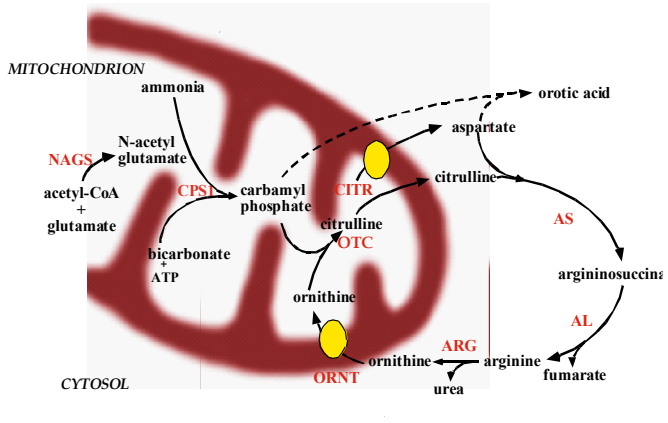
3.1. Overview of Urea Cycle Disorders

Urea cycle disorders (UCD) are a group of rare inherited disorders of metabolism caused by deficiencies of any one of eight proteins required for ammonia detoxification and urea synthesis (**Figure 1**) [1]. Collectively, they result in hyperammonemia, which in

its severe or prolonged form may have devastating effects on development and function of the central nervous system [2]. This can manifest soon after birth (neonatal onset) or later in childhood or even adulthood [3]. The variations of severity are most evident in ornithine transcarbamylase deficiency (OTCD) [4], the most common of UCD and the only X-linked disease among them, the rest of which are inherited as autosomal recessive traits. Thus, males with severe OTC deficiency may not survive infancy without vigorous medical intervention and/or liver transplantation [4]. Even with current medical treatment, some evidence suggests that less than 40% of the most severe neonatal cases survive [5]. Males with milder deficiencies may present much later, and females express a range of severity from neonatal onset to being asymptomatic throughout life [4]. Such asymptomatic or mildly affected females represent the largest group within the UCD population, while the more severely affected males and females require the most demanding, intensive, and expensive medical intervention. The classification, abbreviations and estimated prevalence of the various UCD are shown below; as a group, the combined prevalence is approximately 1:35,000 [6].

aFigure 1. The Urea Cycle and Enzymes

The Urea Cycle



- N-acetylglutamate synthase (NAGS) deficiency (<1:2,000,000)
- Carbamyl phosphate synthetase I deficiency (CPSD) (1:1,300,000)
- Ornithine transcarbamylase deficiency (OTCD) (1:56,100)
- Argininosuccinate synthase deficiency (ASD, Citrullinemia) (1:250,000)
- Argininosuccinate lyase deficiency (ALD, argininosuccinic aciduria) (1:218,750)
- Arginase (ARG) deficiency (argininemia) (1:950,000)
- Hyperornithinemia, hyperammonemia, homocitrullinuria (HHH) syndrome (or mitochondrial ornithine carrier deficiency-ORNT) (<1:2,000,000)
  Citrullinemia type II (mitochondrial aspartate/glutamate carrier deficiency-CITR) (<1:2,000,000, 1:21,000 in Japanese origin)

3.2. Impact of Hyperammonemia on the Health of Patients with UCD

Despite significant improvements in medical management following the wider availability of specialized diets, hemodialysis and alternate pathway therapy, infants and children and even adults with urea cycle disorders (UCD) are at high risk of early and recurrent brain damage from hyperammonemia [7, 8]. The insult that the brain suffers from high blood ammonia levels can manifest as cytotoxic brain edema and vascular compromise which frequently leads to intellectual and developmental disabilities [2, 9-11]. Moreover, clinical hyperammonemia recurs at variable intervals increasing the cumulative damage to the brain and the chance of irreversible coma and death during a hyperammonemia episode due to vascular compromise and/or brain herniation. This can, unfortunately, be

the outcome even in those patients whose condition appears to be amenable to conservative management (CM) since the ammonia can “get out of hand” during an intercurrent infection or another stress and cause the demise of the patient [12]. Because hyperammonemia in patients with UCD can occur at any time as a result of catabolic conditions (such as otherwise trivial infections), an increasing number of patients with recurrent hyperammonemia have been undergoing orthotopic liver transplantation as a procedure that “cures” the hyperammonemia [13-15], removing what the patients describe as a “ticking time bomb”. However, liver transplantation is a complicated surgical procedure which carries a significant risk of both mortality and morbidity. Patients, families and their providers are therefore facing a difficult dilemma. Should the patient be managed conservatively with diet, medications, and amino acid supplements or should he/she consider undergoing a liver transplant?

3.3. Gap of Evidence with Respect to Best Treatment for Patients with UCD

There are two major options in the management of severe UCD. One is conventional conservative management and the second is liver transplantation. The goal of conservative management is to prevent or reverse the accumulation of toxic ammonia in the body. This can be accomplished by a combination of the following interventions: 1) reducing protein catabolism by providing a high caloric intake [16]; 2) reducing dietary protein intake, except for required essential amino acids [16]; and 3) providing substrates for alternate pathways of nitrogen excretion (citrulline, arginine, sodium benzoate, phenylacetate, and phenylbutyrate) [17]. In milder cases, the first two nutritional interventions may be sufficient. In severe cases, all these approaches may need to be employed plus the use of hemodialysis to remove nitrogen during life-threatening hyperammonemic crises [18]. Liver transplantation represents a curative approach for the hyperammonemia by replacing the liver with the defective gene with a normal liver [13-15]. This approach, however, carries considerable risks.

3.3.1. Conservative Management and Outcome

The most effective medical advances in the acute and chronic treatment of UCD are the employment of substrates to promote alternative pathways of waste nitrogen excretion [7, 17]. Sodium benzoate combines with glycine to form hippurate, which can be readily excreted, removing one atom of nitrogen for each molecule of benzoate provided. Sodium phenylacetate combines with glutamine to form phenylacetylglutamine, also readily excreted in the urine and removing two atoms of nitrogen for each molecule of phenylacetate. The same phenylacetate pathway occurs with administration of sodium phenylbutyrate (Buphenyl®) or its prodrug glycerol phenylbutyrate (Ravicti®), which have a much less pungent odor and repugnant taste than phenylacetate itself. Combined therapy with intravenous infusion of glucose, lipid, arginine, and sodium benzoate/sodium phenylacetate (Ammunol®) is now used routinely for treatment of acute hyperammonemia, whereas sodium phenylbutyrate or glycerol phenylbutyrate are commonly used for chronic, long-term oral administration [19, 20]. All of these treatments carry risks of serious side effects. Among patients treated conservatively, many have been reported to succumb to hyperammonemic crises. Most survivors show significant

neurodevelopmental disabilities, the severity of which seems to correlate with the severity of the enzyme deficiency. In a longitudinal study performed by our NIH-funded Rare Diseases Clinical Research Center for Urea Cycle Disorders (UCDC) [21], the proportion of patients with a poor cognitive outcome (IQ/Developmental Quotient <70) was high, ranging from 47-68% in the various UCD. This was observed in patients below and above 4 years of age. Poor cognitive outcome was not fully explained by age of onset (<4 vs. >4 years), peak ammonia level or duration of the initial admission. Thus, we currently do not know what variables are associated with a poorer cognitive outcome in patients with UCD on conservative management, making it difficult to make progress in improving this approach.

3.3.2. Liver Transplantation and Outcome

Liver transplantation for UCD patients was initiated in the early 1990's, before alternate pathway medical therapy was widely available. There were anecdotal case reports of liver transplantation in four of the urea cycle disorders (CPSD, OTCD, ASD, and ALD) [13, 15, 22]. A larger survey of 16 US patients who had received liver transplants from four major transplant centers found that 14 of these cases had survived at least 1-6 years [14]. Their neurological status post-transplantation was in most cases moderately to severely impaired and correlated closely with their condition prior to transplantation. However, the quality of their lives seemed to have improved. Subsequently, to determine if aggressive medical therapy could improve the outcome of severe infantile onset UCD, 5 such cases were monitored at Baylor College of Medicine before and after liver transplantation, including 2 males with OTCD, 2 with CPSD, and one female with OTCD deficiency and intractable hyperammonemia [23]. Three of these infants had serial developmental testing (Griffiths scale) before and after transplantation. It was found that their pre-transplantation overall developmental scales (51, 86, 56) were stabilized after transplantation (70-83, 80-76, 51-47, respectively). Therefore, the authors recommended that early transplantation be considered as the treatment of choice in these severely affected infants.

Most recently, a retrospective analysis of 186 patients with UCD who underwent liver transplantation, [24] showed an increased frequency of liver transplantation for UCD and organic acidemia over the last decade, with 5-year survival rates of 88-99% depending on age. In summary, liver transplantation is now performed frequently to treat UCD and survival seems to have improved over time. However, the outcome of neurocognitive function following liver transplantation is unclear, and it is unknown how it compares to conventional conservative management.

3.3.3. The Process of Making UCD Treatment Decisions

Despite the importance of and complexity surrounding the decision to continue conservative management or consider liver transplant in UCD, no research has been conducted to date on how primary caretakers of pediatric UCD patients make these treatment choices and the issues that influence their decision to pursue one option over another. Some existing research investigating parent decision making in

pediatric treatments has been published in other disease areas such as end-of-life care, cardiac transplantation, lung transplant in patients with cystic fibrosis, and cancer treatment. A 2012 narrative review of the current research on parent decision making about pediatric treatment found that in addition to consulting their provider, most parents consider their child's health status, the perspectives of other members of their community, their prior knowledge, and other personal factors such as emotions and faith when making treatment decisions for their child [25]. Although the findings from these studies can help inform our understanding of the treatment decision-making process among the caretakers of pediatric patients with UCD, the characteristics of this disease group and the risks associated with its treatment options vary in several important ways from other disease areas, effectively limiting the applicability of these previous studies in this population. One of the most critical differences concerns the acuteness and unpredictable nature of severe hyperammonemia episodes, which carry the risk of death or increased neurocognitive dysfunction. Even if a patient's condition appears to be amenable to conservative management, he or she is still susceptible to acute hyperammonemia during incurrent infections or while experiencing other stressors. This "ticking bomb" phenomenon is factored in the treatment decision of patients on whether pursuing liver transplant, thus increasing the need for better research that focuses specifically on the experience of making treatment decisions by the UCD population.

3.3.4. Gaps in Knowledge to be Addressed by this Project

In spite of a number of reports (mostly case reports) on UCD, the mortality rate from these disorders remains uncertain. A mortality rate of up to 50% has been quoted in the literature for patients with neonatal onset UCD [22]. However, we have seen much lower mortality rates among the UCDC longitudinal study cohort (23%-34%) but it is unclear whether this discrepancy reflects a real improvement in the management of UCD during the last two decades or whether there exists an ascertainment bias; an effort is underway in the UCDC to remove survivorship bias and reassess the risk of mortality. Conservative management and liver transplantation are associated with mortality and morbidity, due to hyperammonemia in the former, and peri- and post-surgical complications in the latter. It is, therefore, important that we have information to compare survival as well as other outcomes of the two approaches, taking appropriate account of specific disorders (a type of UCD) and severity (neonatal or late onset). The second major gap in knowledge is with respect to neurocognitive outcome in patients with UCD. While we have both cross-sectional and longitudinal information about patients with UCD managed conservatively [8, 26], we need more information about patients with UCD who underwent liver transplantation. Our collaboration with SPLIT (Studies of Pediatric Liver Transplantation) will enable us to capture all or most patients with UCD who undergo liver transplantation and thus provide a nonbiased evaluation of their outcomes. The third gap in knowledge is regarding the quality of life in patients with UCD, both those managed conservatively and by liver transplantation. Although being on a restrictive diet contributes to a compliance issue, and has been shown to have a detrimental effect on children's quality of life [27], no comparisons with other treatments have been reported. Last but not least, there is a paucity of evidence

about how patients with UCD, their families, and their providers reach a shared decision on which management strategy to choose, how frequently and by what mechanisms these decisions are revisited, and what clinical, social, and/or system level factors influence this decision process. To date, there have been no published studies that examine the experience of providers or patients with UCD and their families in making this critical and difficult treatment decision.

4. Study Design and Methods

Overview: We will employ a mixed method concurrent study design utilizing quantitative research methods to address our primary outcomes, while simultaneously employing qualitative research methods to obtain information on the UCD patient/family experience when making critical treatment decisions **(Figure 2).**

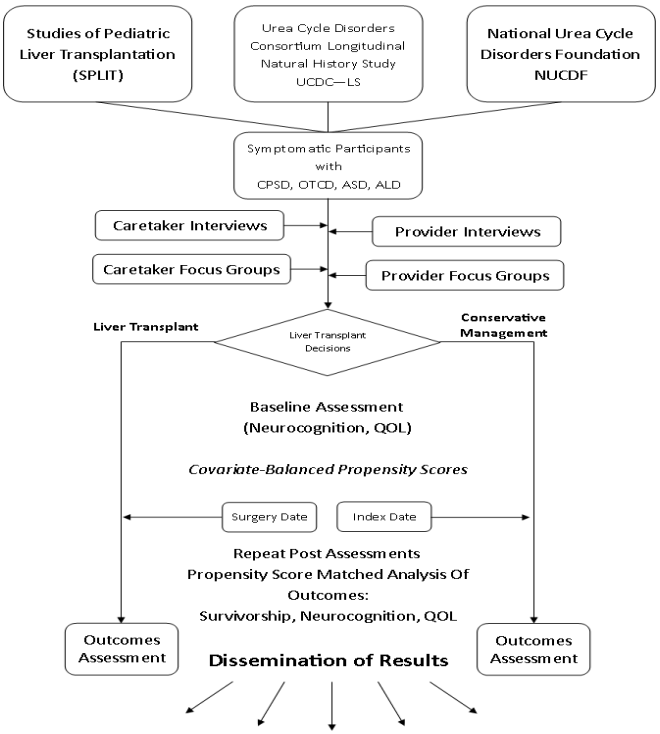


Figure 2. Overall Design of the Study

A randomized controlled trial (RCT) in UCDs is not a feasible option to fill an information gap because of the nature of the alternatives and dearth of affected patients. In the quantitative component of this study (**Aim 1**), we, therefore, propose to implement a natural history observational trial, relying on existing historical and concurrently collected registry data to identify our population of interest. This population consists of patients age 18 and under. Many such patients are already enrolled in a Longitudinal (natural history) Study of Urea Cycle Disorders conducted by the Urea Cycle Disorders Consortium (UCDC). This UCDC study captures data regarding survival, neurocognitive status and quality of life. In order to achieve our target sample size and broaden our subject population, we intend to merge data from the existing UCDC data set with two additional registries maintained by: 1) the Studies of Pediatric Liver Transplantation (SPLIT) Research Group, housed at the EMMES Corporation and 2) National Urea Cycle Disorders Foundation (NUCDF) patient stakeholders. To study the two UCD patient cohorts, one managed conservatively and the other treated by liver transplantation, we will use covariate balanced propensity score matching to greatly reduce bias in this non-randomized study. Propensity score matching is widely recognized as a best practice alternative when an RCT is not feasible.

In the qualitative component of this study (**Aims 2 and 3**), we intend to enroll a representative sample of pediatric patient caretakers (guided by referrals from the NUCDF) and medical providers, including the treating physician and other clinicians on the team (guided by referrals from UCDC site coordinators) to participate in semi-structured interviews that will explore how decisions about UCD treatment are being made. Patient caretakers will also be asked to take part in focus groups to provide feedback on themes that emerged from the semi-structured interviews and to discuss effective strategies for the dissemination of evidence-based information obtained in this study.

4.1. Inclusion Criteria

Aim 1 (UCD patients):

- Age 18 and under
- Diagnosed with the following Neonatal-type urea cycle disorders:
    - CPSD, OTCD, ASD or ALD, as defined as follows:
        - Diagnosis of CPS I deficiency, defined as decreased (less than 20 % of control) CPS I enzyme activity in liver, and/or an identified pathogenic mutation, and/or hyperammonemia and first-degree relative meets at least one of the criteria for CPS I deficiency
        - Diagnosis of OTC deficiency, defined as the identification of a pathogenic mutation, and/or less than 20% of control of OTC activity in the liver, and/or elevated urinary orotate (greater than 20 uM/mM) in a random urine sample or after allopurinol challenge test, and/or hyperammonemia and first-degree relative meets at least one of the criteria for OTC deficiency
        - Diagnosis of AS deficiency (Citrullinemia), defined as a greater than or equal to 10-fold elevation of citrulline in plasma, and/or decreased (less than 20% of control) AS enzyme activity in cultured skin fibroblasts or other appropriate tissue, and/or identification of a pathogenic mutation in the AS gene, and/or hyperammonemia and first-degree relative meets at least one of the criteria for AS Deficiency
        - Diagnosis of AL deficiency (Argininosuccinic Aciduria, ASA), defined as the presence of argininosuccinic acid in the blood or urine, and/or decreased (less than 20% of control) AL enzyme activity in cultured skin fibroblasts or other appropriate tissue, and/or identification of a pathogenic mutation in the AL gene, and/or hyperammonemia and first-degree relative meets at least one of the criteria for AL Deficiency
- Willing to participate in at least 1 neurocognitive assessment and 1 quality of life assessment
- Permit access to medical records and medical providers

Aims 2 & 3:

- Primary caretaker(s) of a patient age 25 and under who has been diagnosed

with either CPSD, OTCD, ASD or ALD (broadly defined as those individuals who are responsible for making the child's treatment decisions and who also provide the majority of the child's physical and emotional care)
- Considered, are currently considering, or opted for, liver transplantation as a treatment for UCD.
- Willing to participate in a 60-minute semi-structured interview and/or a 60-90 minute focus group discussion

OR

- Health care provider (e.g. metabolic disease physician, liver transplant surgeon, gastroenterologist, genetic counselor, or nurse) that participates in treating patients diagnosed with either CPSD, OTCD, ASD or ALD,
- Willing to participate in a 60-minute semi-structured interview and/or a 60-90 minute focus group discussion

4.2. Exclusion Criteria

Aim 1:
- Rare and unrelated comorbidities (e.g., Down's syndrome, intraventricular hemorrhage in the newborn period, and extreme prematurity)

Aim 2 and 3:
- None

4.3. Recruitment of Participants

Aim 1: De-identified data from the Longitudinal (natural history) Study (LS) of the Urea Cycle Disorders (UCD) will be supplemented with data from subjects identified from two sources: the Studies of Pediatric Liver Transplantation (SPLIT) Research Group and the National Urea Cycle Disorders Foundation (NUCDF).

Longitudinal Study participants will not be recruited to participate in this study, but their data used for this analysis, as is permissible per the LS consent form.

By agreement, when this project is implemented, SPLIT will contact its respective transplant centers to describe the study and its eligibility criteria indicating the number and descriptive characteristics of eligibility based on SPLIT anonymized records asking study staff to contact eligible patients and provide general recruitment materials. NUCDF will also distribute recruitment materials and directly enroll eligible participants to the study. In all cases, interested patients will contact one of the study sites to express their interest in participating in the study.

Enrollment in the UCDC LS will be offered to any patient not already enrolled, so that they can take advantage of the rare disease protocol to capture laboratory data, neurocognitive function and quality of life information, using the resources already in place through the UCDC. Participants interested in enrolling in the LS will be put in

touch with the study coordinator and PI at the nearest (or preferred) UCDC site. The PCORI site coordinator will work closely with LS coordinators to ensure that contact with interested participants is not delayed. We anticipate that a large proportion will agree to participate in the PCORI study, which will require only two visits for neuropsychological testing and self-reported quality of life questionnaire.

Aim 2 and 3: UCD patient primary caretakers (typically a parent) will be recruited for interviews and focus groups from NUCDF's outreach to the UCD community and its membership (over 2000 UCD family members) and consented and enrolled by GW staff. We will work collaboratively with NUCDF and Children's National on the content of recruitment materials and means of distributing the materials most effectively, as well as recruiting approximately 40-50% of our primary caretaker interview and focus group sample from families attending NUCDF's Virtual Family Conferences, held annually in July, with a webinar and distribution of recruitment materials and a breakout session for interested families. Additional recruitment will also be conducted on a rolling basis through NUCDF's communication portals, social media site, and discussion boards, and one-on-one outreach, in order to capture families that are unable to attend this conference and thus minimize selection bias. NUCDF has begun to gauge preliminary interest among its membership and has identified approximately 65 families, with varying levels of access to expert care, disease severity, and transplant status, who have expressed interest in participating. NUCDF has established a patient stakeholder research working group, the Patient Powered Research Team (PPRT). Additional families will be invited to participate in the PPRT to expand the representative diversity of the group to meet the aims of the study. Additional recruitment outreach may be conducted on a rolling basis from the pool of patients recruited through SPLIT for Aim 1 of the study.

UCD providers, defined as treating physicians, nurses, and counselors, will be recruited for interviews from a population of approximately 55+ metabolic disease physicians, liver transplant surgeons, gastroenterologists, genetic counselors, and nurses within the 11 U.S. sites participating in the UCDC and additional participating SPLIT sites. GW will work with Children's to reach out to UCDC and SPLIT investigators to request their participation in interviews. NUCDF will identify and refer additional providers (with a focus on liver transplant surgeons) for participation in interviews.

We will use a purposeful sampling strategy (via the NUCDF conference and via the NUCDF communication portals) to recruit a representative sample of 32-48 patient primary caretakers (roughly 20-30% of the available target population) for participation in semi-structured interviews about their experience making treatment decisions for their child with UCD. With the assistance of NUCDF, we will also stratify our sample by 1) access to expert care, 2) disease severity, and 3) transplant status (see section 6.1).

In stage 2 of qualitative data collection, primary caretakers and providers of participants will be asked to take part in focus groups to provide feedback on themes that emerged from our structured interviews and to discuss effective strategies for the dissemination of evidence-based information obtained through this study. Additional patient caretakers will be recruited via NUCDF outreach as described above for participation in these focus

groups until a sample size of 64-80 has been reached. We will conduct 6-8 focus groups with 8-10 participants per group. Additional provider focus groups will be conducted after interviews to further discussion treatment decision making and dissemination strategies.

4.4. Retention Strategies

Aim 1: Since this component comprises only 2 visits for neuropsychological testing, we expect a high retention rate among highly motivated patients referred from and enrolled by NUCDF. In comparison, we have observed ~90% retention in the LS protocol since enrollment began in 2006; the LS is more demanding with regard to laboratory and neuropsychiatric testing. UCD appears to affect equally all ethnic groups, except African American, who are underrepresented (~3%). We will make every effort to enroll African American patients in this study.

Aim 2: As this component consists of 60-90 minute interviews and/or participation in focus groups, after which subjects exit the study, retention is anticipated to be near 100% (barring the rare occasion when a participant may voluntarily terminate the interview and/or participation in the focus group).

4.5. Data Elements and Schedule of Events

Aim 1:

Baseline Visit
Confirmation of Eligibility: Once enrolled into the study, the participant's diagnostic testing will be reviewed to assure that the correct UCD diagnosis has been made and eligibility requirements are met based on study inclusion and exclusion criteria.

Baseline Assessment: Historical and new data will be collected at baseline as summarized below. We will use a variety of methods to obtain these data. Certain information will be obtained from a historical review of existing charts and laboratory /treatment data. Careful attention will be paid to accurately note dates for historical information. Other data will be obtained from patients or their families through a standard interview. A Quality of Life survey will also be administered at the baseline visit or afterward by phone or through the RDCRN database. Neuropsychological testing will be performed at the same visit, or at another date.

Historical Data:

- Eligibility
- Enrollment/demographic information
- Review of past medical records, including:
    - growth charts
    - neurodevelopmental testing
    - neurological evaluation
    - biochemical and diagnostic testing (e.g., ammonia, plasma amino acids, DNA sequencing of UCD genes)

- history of hospitalizations
- medications and other treatments (e.g., dialysis)
- other comorbidities

Neuropsychological testing and Quality of life questionnaires:
Neuropsychological tests will be based on age-matched norms for the specific test used (Table 1). These tests overlap with those currently used in the UCDC LS. The findings will be discussed with the participant/parents at the time of the testing, and a report of the results of this testing will be provided to the participant/parent.

Table 1. Validated tests and scales to be used in this study

Test	Domain	6-35 mo.	3-5 y	6-16 y	≥17 y	Reference
Bayley-II/III	Overall Development (IQ/DQ)	X				[36]
WPPSI-IV			X			[37]
WASI/WASI-II				X	X	[38]
ABAS-II	Adaptive Skills	X	X	X	X	[39]
CBCL	Mood and Behavior		X	X		[40]
BRIEF	Attention/Executive Skills		X	X	X	[41]
TEA-Ch				X		[42]
RCFT				X	X	[43]
TOL-Dx				X	X	[44]
NEPSY	Attention/Executive, Language		X	X		[45]
D-KEFS				X	X	[46]
WRAVMA	Motor		X			[47]
Grooved Pegboard				X	X	
Grip Strength				X	X	[49]
Beery VMI	Visual Motor		X	X		[50]
CVLT-C/II	Learning and Memory		X	X	X	[51]
PedsQL	Quality of Life	X	X	X		[52]
SF-36				X	X	[53]
PROMISE					X	[54-56]

The Quality of Life questionnaires will be administered at the baseline visit to assess the impact the disorder has on the participant's quality of life. Parents of participants aged 1 month to 18 years old will be administered the PedsQL parent-report or parent proxy-report questionnaire. Participants between 13 and 18 years of age will complete the PedsQL child questionnaires for their age group. Adult participants (over 18 years of age) will respond to the SF-36v2 questionnaire and the Patient Reported Outcomes Measurement Information System (PROMIS) questionnaires annually (43, 44). PROMIS questionnaires: Satisfaction with Social Roles and Activities, Cognitive Function (previously called Executive Function), Anxiety, Depression, Emotional/Behavioral Dyscontrol. The site neuropsychologist and/or the site PI will review PROMIS questionnaires within 30 days of administration and follow up with the participant and his/her family, as appropriate, such as if there is any indication that the participant may harm himself/herself or others

Aim 2 & 3:

Once referred to the study, primary caretakers (mostly parents) and providers will initially be contacted by the study team to schedule an in person, telephone or video conference interview. Subjects will participate in a single semi-structured interview. Primary caretakers and providers that participate in a semi-structured interview will also be invited to participate in a follow-up focus group. Additional primary caretakers will also be recruited to increase the # of focus group participants and meet our proposed focus group sample size. Focus groups will be conducted during year 2 of the study. As described in detail in section 6.2, data from semi-structure interviews and focus groups will be rendered into codes and subcodes.

5. Data and Safety Monitoring Plan

The study protocol will be reviewed and approved by the National Institutes of Health (NIH) before submission to individual center IRBs for approval. Participant enrollment may only begin with IRB approved consent forms.

This is an observational study that meets the federal definition of minimal risk.

5.1. Study Oversight

The Study Chair has primary oversight responsibility of this clinical trial. The NIH appointed Data (Observational) Safety Monitoring Board (OSMB) has oversight responsibility of the Data Safety Monitoring Plan (DSMP) for this clinical trial. The D/OSMB will review accrual, patterns and frequencies of all adverse events, and protocol compliance every 12 months. The OSMB makes recommendations to the NIH regarding the continuation status of the protocol.

Each site's Principal Investigator and their research team (co-Investigators, research nurses, clinical trial coordinators, and data managers) are responsible for identifying adverse events. Aggregate report- detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures – will be available from the DMCC for site review. Adverse events will be reviewed every 12 months by the research team. A separate report detailing protocol compliance will also be available from the DMCC for a site review on a monthly basis. The research team will then evaluate whether the protocol or informed consent document requires revision based on the reports.

5.2. Definitions and Standards

The Rare Diseases Clinical Research Network defines an adverse event as: "…an unfavorable and unintended sign, symptom or disease associated with a participant's participation in a Rare Diseases Clinical Research Network study."

Serious adverse events include those events that: "result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects."

An unexpected adverse event is defined as any adverse experience, the specificity or severity of which is not consistent with the risks of information described in the protocol.

Expected adverse events are those that are identified in the research protocol as having been previously associated with or having the potential to arise as a consequence of participation in the study

All reported adverse events will be classified using the current version of the Common Terminology Criteria for Adverse Events (CTCAE) developed and maintained by CTEP at National Cancer Institute.

Only those events associated with the conduct of the study and as defined above are reportable.

5.3. Reporting Timeline

- Within **24 hours** (of learning of the event), investigators must report any reportable Serious Adverse Event (SAE) that:
  - Is considered life-threatening/disabling or results in death of subject

  -OR-
  - Is Unexpected/Unanticipated
- Investigators must report all other reportable SAEs within **5 working days** (of learning of the event).
- All other (suspected) reportable AEs must be reported to the RDCRN within **20 working days** of the notification of the event or of the site becoming aware of the event.

Local institutional reporting requirements to IRBs, any oversight committee, and the FDA, if appropriate, remain the responsibility of the treating physician and the Study Chair.

5.4. RDCRN Adverse Event Data Management System (AEDAMS)

Upon entry of a serious adverse event, the DMCC created Adverse Event Data Management System (AEDAMS) will immediately notify the Study Chair, site PIs, the Medical Review Officer, and any additional agencies (if applicable- industry sponsor, CTEP, etc) of any reported adverse events via email.

Serious adverse events: The NIH appointed Medical Review Officer (MRO) determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The MRO may request further information if necessary and possibly request changes to the protocol or consent form as a consequence of the adverse event. A backup notification system is in place so that any

delays in a review by the MRO beyond a specified period of time are forwarded to a secondary reviewer. The Adverse Event Data Management System (AEDAMS) maintains audit trails and stores data (and data updated) and communication-related to any adverse event in the study.

Non-serious expected adverse events: Except those listed above as immediately reportable, non-serious expected adverse events that are reported to or observed by the investigator or a member of his/her research team will be submitted to the DMCC in a timely fashion (within 20 working days). The events will be presented in tabular form and given to the MRO and RDCRN DSMB on an annual basis. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DMCC will post aggregate reports of all reported adverse events for site investigators and IRBs.

5.5. Study Discontinuation

This study will not have study discontinuation rules as it is purely observational as it exercises no control over treatment decisions or their outcomes. The NIH and local IRBs (at their local site) have the authority to stop or suspend this study at any time.

5.6. Subject Discontinuation

An intent to treat approach will be used. All data acquired prior to termination for the reasons outlined below will be included in the primary analysis unless patient withdraws consent. Every effort will be made to conduct a final study visit with the participant and participants will be followed clinically until, if applicable, all adverse events resolve.

- Withdrawal of consent
- Withdrawal by the participant
- Withdrawal by the investigator

5.7. Data Quality and Monitoring Measures

As much as possible, data quality is assessed at the data entry point using intelligent on-line data entry via visual basic designed screen forms. Data element constraints, whether in independent range and/or format limitations or ‘relative’ referential integrity limitations, can be enforced by all methods employed for data input. QA reports assess data quality post-data entry. As we note, data quality begins with the design of the data collection forms and procedures and incorporates reasonable checks to minimize transcription and omission errors. Of the more important quality assurance measures are the internal validity checks for reasonableness and consistency.

- Data Monitoring: The RDCRN DMCC identifies missing or unclear data and generates a data query to the consortium administrator contact.
- Data Delinquency Tracking: The Data Management and Coordinating Center will monitor data delinquency on an ongoing basis.

6. Statistical Considerations

6.1. Sample Sizes

Aim 1. Of the 185 projected members of the target population, 92 (49.7%) are expected to have received liver transplants and 93 (50.3%) to remain on conservative management. Based on previously published results and characteristics of the UCD patients currently enrolled in our longitudinal study, we expect these groups to be very comparable with respect to UCD severity. As described below, we will use the method of covariate-balanced propensity score matching to create additional groups that are more closely matched on additional severity indicators for the comparative effectiveness analysis. **Table 2** provides a detailed breakdown of the characteristics of study groups.

For **Aims 2 and 3**, we plan to recruit a representative sample of 32-48 patient primary caretakers for participation in semi-structured interviews on their experience making treatment decisions for their child with UCD and an additional 16-48 patient primary caretakers (until a sample of 64-80 is reached) for participation in focus groups to validate information obtained through interviews and to discuss effective dissemination strategies for the evidence-based information obtained through this study.

Table 2. Characteristics of Eligible Transplanted Cases and Comparable Controls

Group	Total	Type of UCD				Sex	Onset	Peak NH3 (µmol/l)		Surgery Age (mo.)
		CPSD	OTCD	ASD	ALD	M/F	(days)	# >200, %	Median, IQR	
Transplanted	**92**	12 (14%)	44 (47%)	22 (24%)	14 (15%)	62/30	2 (1-21)	90 (98%)	958, 938	11.7 (1.5-186)
Conservatively Managed	**93**	1 (1%)	21 (22%)	37 (39%)	34 (38%)	48/45	3. (1-21)	69 (74%)	403, 781	---

Interview and focus group participants will be stratified by their child's: 1) access to expert care (i.e. yes/no), 2) disease severity (i.e. neonatal onset/post-neonatal onset), and 3) transplant status (pre/no transplant, post-transplant,) (**Tables 3 and 4**). Although not included as an explicit level of stratification, we will also aim to recruit primary caretakers that are diverse in terms of their child's geographic distribution, socioeconomic status, and race/ethnicity.

Table 3. Sample Sizes for Stage 1 Patient Caretaker Interviews

		Pre/No Transplant		
		Access to Expert Care		Sample Size
		Yes	No	
Disease Severity	Neonatal onset	4-6	4-6	8-12
	Post-neonatal onset	4-6	4-6	8-12
	Post-Transplant			
	Neonatal onset	4-6	4-6	8-12
	Post-neonatal onset	4-6	4-6	8-12
TOTAL		**16-24**	**16-24**	**32-48**

Table 4. Sample Sizes for Stage 2 Patient Caretaker Focus Groups				
	Pre/No Transplant			
		Access to Expert Care		Sample Size
		Yes	No	
Disease Severity	Neonatal onset	8-10	8-10	16-20
	Post-neonatal onset	8-10	8-10	16-20
	Post-Transplant			
	Neonatal onset	8-10	8-10	16-20
	Post-neonatal onset	8-10	8-10	16-20
TOTAL		**32-40**	**32-40**	**64-80**

We will also recruit a national cross-section of 25-40 providers from the UCDC and SPLIT sites for participation in semi-structured interviews. Our provider sample will include metabolic disease physicians, liver transplant surgeons, gastroenterologists, genetic counselors, and nurses (**Table 5**).

Table 5. Sample Sizes For Provider Interviews & Focus Groups	
Type of Provider	**Sample Size**
Metabolic Disease Physician	5-8
Liver Transplant Surgeon	5-8
Gastroenterologist	5-8
Genetic Counselor	5-8
Nurse	5-8
TOTAL	**25-40**

6.2. Analysis Plan

For **Aim 1,** we will use covariate balancing propensity scoring based on the CBPS package in R [28] to create comparable (balanced) groups based on their risk factor (covariate) profile in subjects according to their propensity (probability) to move from conservative management to liver transplantation. This approach leads to a model that predicts treatment assignment (conservative vs. liver transplantation) and balances covariables, especially those related to study outcome(s), and offers the best opportunity to simulate RCT results from observational data. From prior experience, many through the UCDC [26,31,32}, we know many of the important risk factors, which include neonatal vs. late onset, number of prior hyperammonemic events, event severity in terms of hyperammonemic coma score [2], ammonia and glutamine levels at regularly scheduled clinic visits, and duration from birth to transplant or index date. In addition to these, we will consider comorbidities, organ function, and other laboratory assessments. The CBPS software will help us choose the model that maximizes covariate balance and generate the CBPS for each participant. The next steps will be to order the dataset according to the CBPS. It is useful at this point to select CBPS to cut points to form homogeneous strata to assess the number of subjects with a liver transplant and conservative management per stratum. Those strata where there are

insufficient numbers (mismatches) of conservative treatment or liver transplant subjects will be described, documented and excluded from the primary analysis due to lack of covariate balance. Before conducting model-based analyses for **Aim 1**, we will compare survival times based on the log-rank test in Kaplan-Meier analysis and the difference between mean scores based on t-tests by treatment for neurodevelopment and quality of life within each stratum to evaluate evidence of heterogeneity. Evidence of heterogeneity will provide clues to interactive effects based on UCD severity which will be modeled in regression analyses below by including a cross products term of treatment type with CBPS. Based on these results, we will develop general linear random effects longitudinal regression models in STATA 14 [http://www.stata.com/stata14/] to perform analysis of covariance that will enable us to evaluate **Aim 1** outcomes of neurodevelopment and quality of life. Each model will include treatment type, the baseline measurement of each outcome, as well as the CBPS and if necessary the cross product of treatment type by CBPS. When we address survival, we will implement Cox Regression models to predict survival time by treatment and will either control for CBPS or stratify on it in the case of heterogeneity.

We used PASS 12 [33] to evaluate statistical power to address study aims for sample sizes per group (liver transplantation vs. conservative management) of 90 and 80 in 2-tailed testing at an alpha of 0.05, which assumes some losses in the sample entering analysis in order to maintain adequate covariate balance between groups. For neurodevelopmental and quality of life assessments, we have 80% power to detect modest 0.4sd effect size differences between groups assuming two repeated measurements per person correlated at 70% (ICC). For mortality, assuming the rate in the conservatively treated group remains about 28%, the study will have 80% power to detect and increase in the liver transplant group of about 60% which is robust to differences in sample size between 80 and 90 per group. The study is well powered to detect any clinically meaningful difference in neurocognitive outcomes and QOL and adequately powered to detect a moderate difference in mortality between groups.

For **Aim 2**, interview data will be managed using QSR International NVivo 10 software [http://www.qsrinternational.com/products_nvivo.asp], a program that allows us to collect, organize, and code qualitative data sources. Although not explicitly a grounded theory study, our approach to the analysis of primary caretaker and provider interview data will borrow from aspects of Strauss and Corbin's systematic procedures for grounded theory work [34]. No existing framework or theory currently exists that describes the process which UCD patients and their families undertake when making the difficult decision to pursue liver transplant or continue conservative management. Thus, some of Strauss and Corbin's analysis techniques are suitable for this study aim, which seeks to describe a process/experience in a field where there is little pre-existing evidence.

Initial data abstraction will be conducted through the line-by-line open coding of a cross-section of 10-15 primary caretaker and provider interview transcripts. This will allow key issues regarding the liver transplant vs. conservative management decision-making process to emerge directly from the collected data and will ensure that important aspects of this phenomenon are not precluded through the use of a more selective

coding schema. We will use this initial process of open coding to generate a preliminary set of codes, which will be continuously refined via team consensus (i.e. merged, modified, and reduced) until a final structure of codes and sub-codes emerges. This coding structure will then be applied systematically across all interview transcripts, employing thematic content analysis to categorize data into recurrent or common themes [35].

Thematic content analysis will form the basis of our more sophisticated interpretation, which will move beyond a typology of participant accounts to look at the relationship between the themes we've identified and to build a framework that describes how primary caretakers of pediatric patients with UCD, their families, and their providers reach a shared treatment decision and the key clinical, social, and/or system level factors that influence this process. Our stratified purposive sampling strategy will allow us to examine differences and similarities among sub-populations of patients and their families in terms of how they experience this decision process. This will help facilitate the identification of issues that are common across groups as well as the factors that create differences in the way patients and families approach/experience this decision. To facilitate this level of analysis, we will employ common framework analysis techniques such as charting (i.e. reorganizing data according to thematic content in side-by-side charts to visualize/compare a range of perspectives across cases) and mapping and interpretation (i.e. using diagrams and tables to physically explore the relationship between themes) [35]. A team of 2-3 researchers will be used to code all interview data and inter-rater reliability scores will be calculated to assess agreement between coders. Members of the research team will code data independently but will collaborate to reach consensus on coding definitions as well as emerging key themes and the relationships between them.

For **Aim 3**, focus group data will be analyzed using thematic content analysis (see description above) to validate the decision-making framework developed through **Aim 2** and to identify key opportunities for improved dissemination of evidence-based information to families of UCD patients including when information should be delivered, who should deliver it, how it should be delivered, and what additional supports should be provided to improve the families' experience as they navigate the difficult decision to pursue liver transplant or continue conservative management. Focus group and interview data findings will be used in conjunction to draft a dissemination strategy that is responsive to the expressed needs of patients and their families, that aligns with the decision-making process illustrated through **Aim 2**, and that makes use of patient-preferred mechanisms of communication. Focus group participants will also be asked to provide feedback on portions of this dissemination strategy as it is being developed. Focus group data will also be managed using QSR International NVivo 10 software and coded by a team of 2-3 researchers as described above.

7. Data Management

Aim 1: All study data will be collected via systems created in collaboration with the RDCRN Data Management and Coordinating Center and will comply with all applicable guidelines regarding patient confidentiality and data integrity.

Aim 2 and 3: All qualitative study data (i.e. interview and focus group transcriptions) will be collected by research partners at the GW Milken Institute School of Public Health and managed by GW investigators using QSR International NVivo 10 software [http://www.qsrinternational.com/products_nvivo.asp]. After qualitative study data collection efforts are complete, data will be exported from NVivo to text files and submitted to the RDCRN Data Management and Coordinating Center.

7.1. Registration

Registration of participants on this protocol will employ an interactive data system in which the clinical sites will attest to the participant's eligibility as per protocol criteria and obtain appropriate informed consent. IRB approval for the protocol must be on file at the DMCC before accrual can occur from the clinical sites.

The DMCC will use a system of coded identifiers to protect participant confidentiality and safety. Each participant enrolled will be assigned a local identifier by the enrollment site. This number can be a combination of the site identifier (location code) and a serial accession number. Only the registering site will have access to the linkage between this number and the personal identifier of the subject. When the participant is registered to participate in the study, using the DMCC-provided web-based registration, the system will assign a participant ID number. Thus, each participant will have two codes: the local one that can be used by the registering site to obtain personal identifiers and a second code assigned by the DMCC. For all data transfers to the DMCC, both numbers will be required to uniquely identify the subject. In this fashion, it is possible to protect against data keying errors, digit transposition or other mistakes when identifying a participant for data entry since the numbers should match to properly identify the participant. In this fashion, no personal identifiers would be accessible to the DMCC.

7.2. Data Entry

Aim 1: Data collection for this study will be accomplished with online electronic case report forms. Using encrypted communication links, on-line forms will be developed that contain the requisite data fields.

Aim 2 and 3: Interviews and focus groups will be audio recorded with participant permission and transcribed. All audio recordings will be deleted following their transcription and transcriptions will be uploaded to a QSR International NVivo 10 software database, which will be password protected and stored on a secure hard drive with access limited to designated investigators.

8. Human Subjects

8.1. GCP Statement

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and all applicable regulatory requirements.

8.2. Risks (and Protection Against Risks)

The primary risk is a breach of confidentiality and privacy. However, the study staff is trained in procedures for maintaining the security and confidentiality of data. All files will be stored in a locked suite on a secure floor in the Children's Research Institute, or The George Washington University, or in a locked suite at the National Urea Cycle Disorders Foundation. However, the primary research coordinator at the Children's Research Institute will house copies of all relevant study materials. Study databases will be password-protected, and all staff will be trained in the importance of maintaining the confidentiality of study data.

While participation in interviews or focus groups does not pose any physical risks to subjects, caretakers, or providers, some questions may make subjects feel uncomfortable or anxious. Participants will be informed of their right to stop the interview at any time and/or decline to answer any question. We will facilitate online interviews and focus group discussions for patients and families who do not ordinarily attend NUCDF meetings and consider extra time and travel to be burdensome.

Because of neuropsychological testing, the participants could find out that they have an intellectual disability. However, developmental testing is also part of routine care; the participant might find out they have an intellectual disability regardless of involvement in the study.

8.3. Benefits

Participants will have access to neuropsychological testing that may assist in educational planning. Additionally, patients with UCD and their families will have access to reliable information on the outcome of conservative vs. liver transplant treatment for their conditions.

8.4. Written Informed Consent

Aim 1: Written informed consent will be obtained from each participant before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the participant with the date of that signature indicated. The investigator will keep the original consent forms and signed copies will be given to the participants. It will also be explained to the participants that they are free to refuse entry into the study

and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the participant will be given to all participants.

Aim 2 & 3: No written informed consent will be obtained for either interview or focus group participants. Instead, prospective subjects will be provided an information sheet about the study, as described in 8.5.

8.5. Process of Consent

The mechanisms described in section 4.3 will be used to recruit and consent participants. Any contact to recruit families will adhere to standards for ethical conduct of research and be fully HIPAA compliant.

After eligibility has been confirmed and the prospective participant has expressed interest in participating in the study, consent to participation will be obtained.

Aim 1
Consent to Participate in the Study:
Consent and assent forms will be given to potential participants prior to enrollment so that they have ample time to review the information and ask questions about the study. We will try to mail consent forms to the individuals in advance of their participation so that they can read and ask any questions before considering participating. Investigators will ensure that the participant or their legally authorized representative understands the information provided and obtain informed consent. Institutions may conduct consent by phone and receive the signed consent form by mail, fax, or electronic mail. All consent discussions will take place in private, closed-door locations.

Cognitive Impairment: Some of the prospective participants may be cognitively impaired. If the participant is 18 years old or older with significant cognitive impairments such that their mental age is younger than 18 years old, their legal guardian will consent to participation in the protocol. If the cognitively impaired participant is between the ages of 7 and 17, the parent or legal guardian will consent and assent will be waived. If the participant's mental age is the same as their actual age, we will follow the usual consent procedures with those 18 and over signing consent forms and 7-17-year-olds signing assent forms.

Aim 2 & 3:
Primary caretakers will first be approached for participation in interviews and focus groups by the NUCDF Study Staff (NUCDF Study Coordinator, NUCDF Genetic Counselor, or NUCDF Executive Director) via telephone and/or e-mail. Primary caretakers will be provided a preliminary information sheet about the study by mail or e-mail. If they express interest in participating, NUCDF's Staff will pass on their contact information (telephone and/or e-mail) to a member of the GW research team. A member of the GW research team will then reach out to schedule either an in-person, telephone or video conference interview with each primary caretaker, depending on availability and convenience.

Providers will first be approached for participation in interviews by their UCDC, SPLIT, or NUCDF site PI or coordinator. They will be provided a preliminary information sheet about the study in the digital or hard copy. If they express interest in participating, the NUCDF Study Staff, UCDC or SPLIT site coordinator will pass on their contact information (telephone and/or e-mail) to a member of the GW research team. A member of the GW research team will then reach out to schedule either an in-person, telephone or video conference interview either, depending on availability and convenience.

Primary caretakers and providers will be sent an information sheet by e-mail or mail at least 48 hours prior to their scheduled interview/focus group allowing them an opportunity to review the document.

At the scheduled interview/focus group time, a member of the GW research team will review the informational document with the participant, including their right to decline or withdraw participation at any time and respond to any questions or concerns. Each participant will be asked to provide their oral consent for participation before the interview/focus group begins. At the conclusion of the interview, participants will be informed that they will receive at $100 Amazon gift card for their contribution. Should they decline the gift card, this money will be utilized as a mini-scholarship for participating families to travel to the annual NUCDF conference to partake in focus groups for this study. All funds will be tracked by GW and Children's National.

All consent discussions and interviews/focus groups will take place in a private, closed-door location.

8.6. Certificate of Confidentiality

To help protect participant privacy, a Letter of Confidentiality has been obtained from the National Institutes of Health (NIH). With this Certificate, the researchers cannot be forced to disclose information that may identify a study participant, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify a participant, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally-funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

Even with the Certificate of Confidentiality, the investigators continue to have ethical obligations to report child abuse or neglect and to prevent an individual from carrying out any threats to do serious harm to themselves or others. If keeping information private would immediately put the study participant or someone else in danger, the investigators would release information to protect the participant or another person.

Department of Health and Human Services (DHHS) personnel may request identifying information for purposes of performing audits, carrying out investigations of DHHS grant recipients, or evaluating DHHS-funded research projects.

9. References

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