Rare Diseases Clinical Research Network (RDCRN)

Effect of Increasing Doses of Tiopronin on Cystine Capacity in Patients with Cystinuria

Rare Kidney Stone Consortium

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1. Synopsis

Protocol Number:	6421
Protocol Title:	Effect of Increasing Doses of Tiopronin on Cystine Capacity in Patients with Cystinuria
Study Chair:	Dr. David Goldfarb
Statistician:	Frank Modersitzki
Consortium:	Rare Kidney Stone Consortium
Participating Sites:	New York University Langone Health, New York, NY
Activation Date:	09/10/2018
Sample Size:	15 subjects
Target Enrollment Period:	1 year
Study Design:	Crossover trial of escalating doses
Primary Study Objective:	To evaluate the effect of escalating doses of cystine binding thiol drugs on the cystine capacity of the urine. The overall goal will be to help guide therapy and ultimately minimize unnecessary side effects caused by larger dosages.
Secondary Study Objective(s):	None.
Study Population and Main Eligibility/ Exclusion Criteria:	Eligibility: Patients between ages 18-80 with confirmed diagnosis of cystinuria with a medical regimen that includes Tiopronin who are willing to complete a 24h urine collection and food diary. Female patients at childbearing age who are willing to use a contraception method. Exclusion Criteria: Patients who are unwilling or unable to provide informed consent, pregnancy, patients with renal colic or patients who are scheduled for a urological procedure.
Treatment	
Agent-	Tiopronin
Dosage, schedule, route of administration-	500mg PO daily x 7 days, then 500 mg PO BID x 7 days, then 1g PO BID x 7 days
Safety Issues-	Allergy or drug side effects
Primary Outcome Measures:	Urine cystine capacity
Secondary Outcome Measures:	Urine volume, pH, urea, sodium, creatinine, cystine concentration, and urinary cystine supersaturation
Statistical Considerations (sample size and analysis plan):	The impact of CBTD dose on CysCap will be analyzed with a mixed effects model, with subject as a repeated factor, and including dose and period effects.

Sponsors (federal, state, foundation and industry support):	National Institutes of Health (NIH), NIDDK, ORDR

1.1 Overview:

The purpose of this study is to determine the minimum effective dose of the cysteine binding thiol drug (CBTD) Tiopronin on urine cystine capacity, which is a measure of cystine solubility in the urine, in patients with cystinuria.

Cystinuria is a rare genetic disease that can lead to significant morbidity in affected patients due to the recurrent nature of the disease. As a result, a significant part of treatment is focused on prevention of stone formation. Current methods of prevention include increasing fluid intake, dietary modifications, alkali therapy, and CBTDs, which help increase the solubility of cystine in the urine.[1] At present, the dosing of Tiopronin is empiric, and the drug not titrated to a specific measured effect. We propose to follow the level of urine cystine capacity in order to help guide treatment and to use lower than usually prescribed Tiopronin doses to decrease the potential side effects while keeping the same therapeutic benefit. This will increase adherence with the medications by decreasing the burden of the large number of pills that need to be taken daily.

2 Specific Aims (Hypothesis and Objectives)

Our primary objective is to compare the effect of different Tiopronin doses on urinary cystine capacity (CysCap). A positive urinary cystine capacity reflects the ability of the urine to take up more cystine and therefore decrease the risk of stone formation. In a previous study, we demonstrated that Tiopronin improves cystine capacity and that the change in cystine capacity was minimal with doses above 1g.
We propose comparing the effects of lower doses of Tiopronin on cystine capacity.

3 Background

Cystinuria accounts for approximately 1% of kidney stones in adults and 6% to 8% in children.[2] It is an autosomal recessive disorder that leads to an impairment in the renal and intestinal transport of cystine and dibasic amino acids: ornithine, arginine, and lysine. As a result of the poor solubility of cystine, the increased urinary excretion leads to precipitation of cystine in the renal tubules, resulting in nephrolithiasis. The recurrent nature of the stones in this disorder can lead to significant morbidity in these patients.

Measurements of cystine excretion in the urine are inaccurate. The assays cannot reliably distinguish between the thiol groups of cystine and the thiol groups of CBTDs either free or bound to cysteine.[3] Prior studies also found that measurements of cystine solubility varied with pH, and therefore nomograms to determine cystine supersaturation could not accurately be made.[4] A recent assay for cystine capacity is a promising new tool that directly measures the ability of the urine to take up additional cystine from a preformed solid phase (undersaturation,

or positive cystine capacity) or give it up to the solid phase (supersaturation, or negative cystine capacity).[3] In contrast to previous assays, the CysCap assay accurately measures cystine solubility in the presence of CBTDs.[5]
Current treatment strategies to prevent stone formation in patients with cystinuria include increasing fluid intake, alkalinizing urine with alkali therapy, and CBTDs such as Tiopronin (Thiola), D-penicillamine, and Captopril. These medications have sulfhydryl groups that can reduce the disulfide bond in the dimer cystine and produce mixed disulfides with the monomer cysteine that are more soluble than the homodimer itself.

Our study by Dolin, et al, showed that CBTDs significantly increased the cystine capacity of urine compared to the control period without CBTDs.[1] We tested the effect of different doses of CBTDs used in clinical practice (1g, 2g, 3g) on cystine capacity in a previous study and concluded that there was no change in cystine capacity with doses above 1g. The higher doses were well tolerated but had little efficacy in changing CysCap. We also retrospectively realized that measuring Tiopronin in the urine would have been useful; in the current study, we will collect urine for that purpose.

We propose testing the minimum effective dose of Tiopronin by comparing doses lower than 2g. Reducing Tiopronin doses will ultimately minimize unnecessary side effects while keeping the same benefit.

4 Study Design and Methods

Due to the low prevalence of cystinuria in the population, the number of patients available to participate in this study precludes the ability to conduct a randomized controlled trial with satisfactory probability to achieve a projected sample size. As in our recently completed study, we plan to enroll 5-10 patients in the study and perform a crossover trial in which patients receive escalating dosages of CBTDs.

Patients will be recruited from the clinical practice of the principle investigator at routine clinic visits at the Kidney Stone Prevention Clinic at NYU Langone Health. After completing informed consent, the patient will have an initial visit that will be a screening interview. During this interview, the patient will be screened for symptoms of renal colic (which if present would exclude him/her from eligibility), as well as asked about any scheduled urologic procedures. A medication history will be taken at this time, and the subject's most recent bloodwork (including a complete blood count) and most recent urinalysis will be reviewed. The total time for this visit should be approximately 20 minutes. The remainder of the study will be performed at home.

There will be four parts to the study. Each part will be divided into a 7-day period in which patients will be taking different dosage of Tiopronin and will have a urine collection at the end of each period. Patients will stop taking their medications for one week in the first part. The dosage of Tiopronin in the following parts will be as follow: 500 mg for the second part, 1g for the third part and 2g for the third part. Unlike the previous study, there will not be a 3g dosage week.

A 24-hour urine collection will be performed on day 7 of each study period. The order in which the four parts of the study are performed will be randomized for each subject, in order to prevent an order effect. After a subject is enrolled in the study, the order in which he/she will perform the study periods will be determined by a computer program that generates a random order of the numbers 1-4. There will not be a specified wash-out period in between study periods due to the short half- life of Tiopronin. With the exception of Tiopronin, the patients will continue all of their regular medications including alkali therapy.

Patients will continue on their self-selected ad-lib diets. They will keep a food diary during the day before the urine collection and during the urine collection. They will then replicate the diet during each of the subsequent parts of the study, repeating the same diet on the day before and the day of the urine collection. We will collect the food diaries at the end of the study to ensure compliance and to keep a record of what the subjects were eating.

The urine will be collected with thymol and gentamicin as preservatives, and maintained at room temperature. The urine will be alkalinized at home with 10g of $NaHCO_3$ as per the usual Litholink protocol for cystine measurement. Study participants will be asked to measure the volume of their urine and then mail an aliquot of their urine to a commercial laboratory, Litholink Corporation (Chicago, IL), for analysis. Another specimen will be mailed to Mayo Clinic for liquid chromatography mass spectrometry (LC/MS) testing.

The urine pH, sodium, urea, and creatinine will be measured by Litholink. Additionally, the cystine supersaturation, 24h urine cystine excretion and cystine capacity of each urine sample will be measured by the following method, the "solid phase" cystine assay[3]. Measured amounts of cystine crystals will be incubated in the urine at 37°C for 48 hours with stirring. The residual solid phase will then be harvested by centrifugation at 3800 rpm for 20 minutes at room temperature and then dissolved in 25ml of high-pH buffer (0.1 M sodium carbonate; pH 9.9). The cystine concentration will be measured in both the supernatant liquid and the buffer to determine the change in solid phase, which is known as the cystine capacity.

The primary outcome of the study is to determine the effect of drug dosage on urinary cystine capacity. Thus, the mean cystine capacities in each part of the study (0 g/d, 500 mg/d, 1 g/d, and 2 g/d) will be compared. Urine urea, a surrogate of protein intake and urine sodium will be measure and compared to ensure diets are replicated correctly throughout the study period. Urine pH will be also measured to make sure similar amounts of alkali therapy are used in each part of the study.

Subjects will be asked to undergo a blood test (for complete blood count) and urine test (urinalysis) within one month of completing the study to monitor for any potential adverse effects of changing the dosages of medication. In our previous study of doses up to 3g no adverse effects were anticipated and none occurred. The laboratory tests may either be performed at an outside lab at the patient's convenience, or in a routine office visit at the Kidney Stone Prevention Clinic at NYU Langone Health. If laboratory tests are performed at an outside laboratory, subjects will be asked to send the results to Dr. Goldfarb for review.

As in the previous study, subjects will be reimbursed for any additional medication costs that they incur as a result of participating in the study. They will be compensated for the amount of $25 per week, a total of $100 only if they completed all 4 stages of the study. Litholink and Mayo Clinic testing will be performed at no cost to the patients and their insurance will not be billed.

4.1 Inclusion Criteria:

- Age between 18 and 80 years.
- Patients with a confirmed laboratory diagnosis of cystinuria who meet the following criteria: (1) stone analysis demonstrating cystine as a component, or (2) increased urinary cystine excretion (>250mg/24hrs in adults).
- A medical regimen that includes Tiopronin.
- Female patients who are willing to use a birth control method.
- Ability to reliably urinate in a collection vessel and measure urine volume.
- Ability to give informed consent.
- Documentation of a stable complete blood count (CBC) and urinalysis (UA) in the six month period prior to the date of enrollment.
- Enrollment in Rare Kidney Stone Consortium (RKSC) Protocol 6401 (Cystinuria Registry)

4.1 Exclusion Criteria:

- Pregnant patients.
- Patients with renal colic
- Patients who are scheduled to undergo a surgical procedure
- Inability to give informed consent

4.2 Recruitment of Participants:

Patients from Dr Goldfarb's clinic and those who are enrolled in the RKSC protocol 6401 (Cystinuria Registry) will be contacted either by phone, mail, or email and recruited.

4.3 Retention Strategies:

Due to the short duration of the study (4 weeks), we do not anticipate the need for extensive retention strategies. Patients will be called periodically at least once a week during the 4-week study period to answer any questions they may have, and to ask about any adverse effects they may be experiencing.

4.4 Schedule of Events:

	Baseline (Visit 1)	Day 7	Day 14	Day 21	Day 28	Day 29-60
Demographics (sex, date of birth)	x					
Baseline stone history (diagnosis date and method of diagnosis, review of current symptoms)	x					
Medication history (Current medications including Alkali therapy, and history of CBTDs including side effects, allergic reactions)	x					
Dietary history (fluid intake, low sodium, low protein, etc)	x					
24-hour urine collection		x	x	x	x	
Pregnancy Test	X					

5 Data and Safety Monitoring Plan

The study protocol will be reviewed and approved by the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) before submission to NYU Langone Health IRB for approval. Participant enrollment may only begin with IRB approved consent forms. This is an interventional pilot study that meets the federal definition of low risk.

5.1 Study Oversight:

The Study Chair has primary oversight responsibility of this clinical trial. The NIH appointed Data Safety Monitoring Board (DSMB) has oversight responsibility of the Data Safety Monitoring Plan (DSMP) for this clinical trial. The DSMB will review accrual, patterns and frequencies of all adverse events, and protocol compliance every 6 months. The D/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. Either the Principal Investigator or one of the co-Investigators will call each subject weekly during the study period to remind them to change the dose of medication, and to assess for any potential adverse events. All subjects will undergo a blood test for complete blood count and urine test for urinalysis within one month of completing the study to monitor for any adverse effects from the changes in medication dosages. The results of the blood and urine tests will be reviewed by the Principal Investigator. All adverse events will be reported to the DSMB. 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. The research

team will then evaluate whether the protocol or informed consent document requires revision based on the reports.

5.2 Adverse Event 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.

5.3 Expected/Known Risks/Discomforts/Adverse Events Associated with Study Intervention and Procedures: Definition of Expected Adverse Events:

The period off Tiopronin is only a week. During that period, the patients will continue their alkali therapy, if prescribed, and their usual fluid intake and dietary restrictions. Therefore the week off Tiopronin is extremely unlikely to lead to cystine stone formation. That is particularly true since dosing of Tiopronin is completely empirical and not based on cystine supersaturation values; in other words, the doses have not been titrated to a particular level to achieve a particular therapeutic effect. In the previous study, no episodes of renal colic occurred during the week off Tiopronin.

Tiopronin is associated with allergy and other side effects, most of which are considered idiosyncratic and not clearly dose-related. Patients will take 0.5-2g, which is less likely to exceed their usual doses. The duration at each dose is a week. Since all patients are taking the drugs for inclusion, it is again very unlikely that patients will experience any important allergy or toxicity of the drugs in the short time they take doses different than their usual doses.

Patients will be closely monitored during the time in the study and will have frequent contact with the investigators in order to report any AEs in the course of the study. Patients will be contacted by phone at least weekly to be asked about any potential adverse effects.

5.4 Reporting Timeline:

Within 24 hours (of learning of the event), investigators must report any reportable Serious Adverse Event (SAE) that:
o Is considered life-threatening/disabling or results in death of subject-OR-
o 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 GCRC oversight committee and the FDA, if appropriate, remain the responsibility of the treating physician and the Study Chair.

5.5 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 back-up notification system is in place so that any delays in 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 a bi-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.

5.6 Unanticipated Problem Reporting

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research

protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Per the definition, only a subset of adverse events would be characterized as unanticipated problems. There are other types of incidents, experiences, and outcomes that are not considered adverse events, but are characterized as unanticipated problems (e.g., breach of confidentiality or other incidents involving social or economic harm).

Incidents or events that meet the OHRP criteria for unanticipated problems are to be reported to the IRB, per local institutional reporting requirements. Local institutional reporting requirements to IRBs, any GCRC oversight committee and the FDA, if appropriate, remain the responsibility of the treating physician and the Study Chair.

5.7 Study Discontinuation:

The NIH, RDCRN DSMB and local IRBs (at their local site) have the authority to stop or suspend this trial at any time. This study may be suspended or closed if:
- Early stopping rules have been met. The early stopping rule will be that the study will end if any apparent toxic effect of the medications occurs. These toxic effects include allergic manifestations, including rash, and including nausea, vomiting, or other symptoms that lead a patient to not tolerate the medication.
- Accrual has been met.
- The study objectives have been met.
- The Study Chair / Study Investigators believe it is not safe for the study to continue.
- The RDCRN DSMB suspends or closes the trial.
- The NIH suspends or closes the trial.

5.8 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
- Intercurrent illness or event that precludes further visits to the study site or ability to evaluate disease (e.g.-mental status change, large pleural effusion).

5.9 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 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.

6 Statistical Considerations

The impact of CBTD dose on CysCap will be analyzed with a mixed effects model, with subject as a repeated factor, and including dose and period effects.

6421 Sample Size

The primary endpoint is defined as a mean change in Cystine Capacity (CysCap). In a previous study, we saw the highest change in CysCap between dose 0mg/d vs. dose 1mg/d. With this large effect size, we would need 9 participants (P=0.05, power 85%) in this protocol. We plan to enroll 15 participants in this protocol. This should account for potential patient withdrawal or other unforeseen protocol issues.

Statistical Considerations

Standard descriptive, repeated-measure ANOVA (Friedman test), and GLS regression will be applied.

7 Data Management

Collection of all study data will comply with all applicable guidelines regarding patient confidentiality and data integrity.

7.1 Registration:

All study data will be collected through REDCAP and will comply with all applicable guidelines regarding patient confidentiality and data integrity. REDCAP is a secure, web-based application for building and managing online databases. On-line forms will be developed that contain the requisite data fields.

Registration of participants on this protocol will employ an interactive data system in which the clinical site 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 site.

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 accessionnumber. 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 system, 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.

8 Human Subject

8.1. GCP Statement:

This clinical trial 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. Benefits:

The potential benefits of this study are:

There are no direct benefits to participating in this study. However, if there is a maximal beneficial dose of Cystine Binding Thiol Drugs, then physicians will be able to minimize potential side effects of the drugs by prescribing lower doses overall, and patients will not be burdened with taking extra unnecessary pills. The results of the study may help guide treatment of patients with cystinuria with Tiopronin in the future.

8.3. Risks:

The potential risks of this study are:

CBTDs are associated with allergy and other side effects including fever, central nervous system depression, anorexia, nausea, vomiting, loss of taste, abdominal pain, and myalgia. More serious adverse effects include nephrotic syndrome, hypersensitivity reactions, transient blood dyscrasias, aplastic anemia, neutrophilic agranulocytosis, neutropenia, thrombocytopenia, bronchiolitis obliterans, rashes, dystonia and various autoimmune responses (polymyositis, myasthenia gravis, SLE, Goodpasture's syndrome, thyroiditis). Although the side effects are considered idiosyncratic and not clearly dose related, there is a risk that a patient could develop a

new side effect at a drug dose that is higher than their usual dose. Since all patients are already taking the drugs for inclusion and demonstrated good tolerance, it is very unlikely that a patient will develop a significant new allergy.

Performing multiple 24-hour urine collections over the course of four weeks may be burdensome, but it is non-invasive and should not cause any pain or discomfort.

8.4. Recruitment:

Patients who are enrolled in the RKSC protocol 6401 (Cystinuria Registry) as well as patients from Dr Goldfarb's clinic will be recruited. They will be contacted by phone, mail or email or during their regular clinic visits. There will be no restrictions on recruitment with regards to gender, socioeconomic background, educational level, or ethnicity.

8.5. Written Informed Consent:

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.

8.6. Process of Consent:

The investigator is responsible for ensuring that informed consent is obtained from each participant using a current consent form according to the guidelines of NYU Langone Health Institutional Review Board (IRB) and in accordance with the Common Rule (45 CFR Part 46 subpart A Protection of Human Subjects). The informed consent form must be obtained and on file (signed and dated by the participant) prior to initiation of any study related activity. In all cases, an attempt will be made to obtain written informed consent in-person. In extenuating circumstances, informed consent may be obtained over the phone or through the mail. In these circumstances, the investigator will discuss the study in detail with the subject either in person or on the phone. After the discussion, the subject will be mailed a copy of the consent to review and may sign and return the consent to the investigator via the mail. The investigator will then co-sign the consent and return a copy of the signed consent to the subject.

The Informed Consent form must provide the following information to each participant:
- A statement that the study involves research, and explanation of the purposes of the research and expected duration of the participant's involvement.
- A description of any benefits to the participants or to others which may reasonably be expected from the research.
- A description of any foreseeable risks or discomforts to the subject.

- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained.
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights.
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled and the participant may discontinue participation at any time without penalty.
- Written and/or oral information about the study in a language understandable by the participant will be given to all participants.

8.7. Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify the participant in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless the participant has consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if the participant consents to the disclosure, including for their medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research participants.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the U.S. Department of Health and Human Services and/or the National Institutes of Health, which is funding this project or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA). The Certificate of Confidentiality does not prevent a participant from voluntarily releasing information about themselves or their involvement in this research. If a participant wants research information released to an insurer, medical care provider, or any other person not connected with the research, the participant must provide consent to allow the researchers to release it.

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. The Certificate of Confidentiality will also not be used

to prevent disclosure as required by federal, state, or local law, such as reports of child abuse and neglect, or harm to self or others.

9 References

1- Dolin DJ, et al. Effect of Cystine-Binding Thiol Drugs on Urinary Cystine Capacity in Patients with Cystinuria. J Endourol 2005; 19: 429-432.
2- Chillaron J, Font-Llitjos M, Fort J, Zorzano A, Goldfarb D, Nunes V, Palacin M. Pathophysiology and Treatment of Cystinuria. Nat Rev Nephrol 2010; 6: 424-434.
3- Goldfarb D, Coe F, Asplin J. Urinary Cystine Excretion and Capacity in Patients with Cystinuria. Kidney Int 2006; 69: 1041-1047.
4- Nakagawa Y, Aspin J, Goldfarb D, Parks J, Coe F. Clinical Use of Cystine Supersaturation Measurements. The J Urol 2000; 164: 1481-1485.
5- Coe F, Clark C, Parks J, Asplin J. Solid Phase Assay of Urine Cystine Supersaturation in the Presence of Cystine Binding Drugs. J Urol 2001; 166: 688-693.

10 Appendices

NYU Informed Consent Form