Rare Diseases Clinical Research Network

Effect of Increasing Doses of Cystine Binding Thiol Drugs on Cystine Capacity in Patients with Cystinuria

Rare Kidney Stone Consortium

Study Chair

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iv. RDCRN Protocol Template

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1. Protocol Synopsis

Interventional Synopsis

Protocol Number:	6413
Protocol Title:	Effect of Increasing Doses of Cystine Binding Thiol Drugs on Cystine Capacity in Patients with Cystinuria
Study Chair:	Dr. David Goldfarb
Statistician:	
Consortium:	Rare Kidney Stone Consortium
Participating Sites:	New York University Medical Center, New York, NY
Activation Date:	
Current Status:	
Sample Size:	10-15 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:	Eligilbilty: Patients between ages 18-80 with confirmed diagnosis of cystinuria with a medical regimen that includes tiopronin or D-penicillamine. 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 (if applicable)	
Agent-	Tiopronin or D-Penicillamine
Dosage, schedule, route of administration-	500mg PO BID x 7 days, then 1g PO BID x 7 days, then 1.5g 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):	
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 effect of increasing doses of cystine binding thiol drugs, including tiopronin and D-penicillamine, on urinary cystine capacity, which is a measure of the amount of cystine 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 cystine binding thiol drugs (CBTDs), which help increase the solubility of cystine in the urine (1). At present, the dosing of CBTDs is empiric, and the drugs are not titrated to a specific measured effect. We propose to measure the effect of increasing doses on urinary cystine capacity, in order to help guide treatment. Ultimately, we hope to minimize the amount of unnecessary larger dosages of the medications, which may decrease potential side effects as well as increase compliance with the medications by decreasing the burden of the large number of pills that need to be taken daily.

THIOLA® is FDA approved for the prevention of cystine (kidney) stone formation in patients with severe homozygous cystinuria with urinary cystine greater than 500 mg/day, who are resistant to treatment with conservative measures of high fluid intake, alkali and diet modification, or who have adverse reactions to d-penicillamine. CUPRIMINE is FDA approved in the treatment of cystinuria. Both drugs are used within the approved indications. The usual dosage of CUPRIMINE in the treatment of cystinuria is 2 g/day for adults, with a range of 1 to 4 g/day. The average dose of Thiola in some studies was 1000 mg (1g) but the package insert does not specify a dose range; many clinicians use doses between 500 mg and 3g per day based on clinical stone activity and 24h urine collection results.

2. Specific Aims (Hypothesis and Objectives)

Our primary objective will be to measure the effect of increasing doses of CBTDs on urinary cystine capacity. We predict that higher dosages of these medications will lead to a more positive urinary cystine capacity, or the ability of the urine to take up more cystine (and therefore decrease risk of stone formation). However, the dose at which increasing dosages of the medications cease to provide additional benefit is unknown. We propose to directly measure the cystine capacity of urine in response to increasing doses of medications to determine if there is a dose at which the maximum benefit of the drugs exists.

This protocol was previously conducted at Lenox Hill Hospital, New York, and approved by the Feinstein Institute IRB. The Feinstein Institute conducts research oversite for North Shore Long Island Jewish Health System.

We plan to transfer 2 previously enrolled Lenox Hill participants to NYU. No further enrollment into this protocol will occur.

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. 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 for several reasons. For one, the assays cannot reliably distinguish between the thiol groups of cystine and the drugs used to bind cystine (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 cystine capacity assay accurately measures cystine solubility in the presence of CBTDs (5). The test is widely used by clinicians throughout the USA and in standard care for patients with cystinuria under the care of Dr. Goldfarb.

Current treatment strategies to prevent stone formation in patients with cystinuria include increasing fluid intake, alkalinizing urine with alkali therapy, and cystine-binding thiol drugs (CBTD) such as tiopronin (Thiola), D-penicillamine, and captopril. These medications have sulfhydryl groups that can reduce the disulfide bond in the cystine and produce mixed disulfides with cysteine that are more soluble than the homodimer itself. A study by Dolin, et al, showed that CBTDs significantly increased the cystine capacity of urine compared to the control period without CBTDs (1). However, this preliminary study did not include a dose-response algorithm so the minimum effective dosage of each drug is still unknown. We propose a study of CBTDs in patients with cystinuria to measure the change in cystine capacity in the urine in response to different dosages of the drugs currently used to treat the disorder, with a goal to help guide therapy and ultimately minimize unnecessary side effects caused by large dosages.

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. We plan to enroll 10-15 patients in the study and perform a crossover trial in which patients receive escalating dosages of cystine binding thiol drugs (CBTDs).
All participants were recruited at Lenox Hill Hospital and enrollment is completed. Two remaining participants will be transferred to NYU to complete this protocol.

Patients will be recruited from the clinical practice of the principle investigator at routine clinic visits at Lenox Hill Hospital. 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. In the first part, patients will stop taking CBTDs for seven days and perform a 24-hour urine collection on day 7. In part 2, patients will take their usual CBTD, either tiopronin or d-penicillamine, 1g per day for 7 days, taken as 500 mg twice a day. They will perform another 24-hour urine collection on day 7 of this study period. In part 3 of the study, patients will take a total of 2g of tiopronin or D-penicillamine daily for 7 days and in part 4 they will take a total of 3g/d of tiopronin or D-penicillamine, also for a 7 day period. 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 the CBTDs. With the exception of CBTDs, the patients will continue all of their regular medications including alkali therapy.

Patients will 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 Corp (Chicago, IL), for analysis.

The urine pH, sodium, urea, and creatinine will be measured. 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 $37^{O}C$ 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 mean cystine capacities in each part of the study (0 g/d of D-penicillamine, 1g/d, 2 g/d, and 3 g/d) performed will be compared to determine the effect of drug dosage on urinary cystine capacity. Urine urea will be measured as a surrogate of protein intake to ensure diets are

replicated correctly, and urine pH will be 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, one 3 ml EDTA tube of blood) and urine test (urinalysis) within one month of completing the study to monitor for any potential adverse effects of changing the dosages of medication. The laboratory tests may either be performed at an outside lab at the patient's convenience, or in a routine office visit at Kidney Stone Prevention Clinic at NYU. If laboratory tests are performed at an outside laboratory, subjects will be asked to send the results to Dr. Goldfarb for review.

Subjects will be reimbursed for any additional medication costs that they incur as a result of participating in the study, but otherwise will not receive compensation for participation in the study.

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 either tiopronin or D-penicillamine
- 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 Protocol 6401 (Cystinuria Registry, NYU IRB #09-0425)

4.2 Exclusion Criteria

- Patients with renal colic
- Patients who are scheduled to undergo a surgical procedure
- Inability to give informed consent
- Patients that are not enrolled in Protocol 6401 (Cystinuria Registry, NYU IRB # 09-0425)

4.3 Recruitment of Participants

No additional participants will be recruited into this protocol. Two remaining participants will be transferred from Lenox Hill to NYU.

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4.4 Retention Strategies

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

4.5 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	
Blood test (CBC) and urinalysis						x

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 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 (Observational) Safety Monitoring Board (D/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 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 D/OSMB. 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. A separate report detailing protocol compliance will also be available from the DMCC for 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.

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

It is not anticipated that randomization to taking "no CBTD" or doses greater or less than what was taken outside of the study will expose subjects to any risks greater than what is already encountered from routine use of CBTDs.

The period off CBTDs 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 CBTD is extremely unlikely to lead to cystine stone formation. That is particularly true since dosing of CBTDs 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.

CBTDs are associated with allergy and other side effects, most of which are considered idiosyncratic and not clearly dose-related. Patients will take 1-3g, which is likely to exceed their usual doses. The duration at each dose is a week and half-life is 12 hours. 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. In our practice, we have patients that take daily up to 3g of CBTDs without any reported AE.

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. Within

four weeks after finishing this protocol, patients will undergo blood testing (CBC, comprehensive metabolic and urine protein) to monitor for adverse events.

5.4 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 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 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

5.7 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).

5.8 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.

7. Data Management

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

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.

7.1 Registration

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 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 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 Subjects

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 CBTDs in the future.

8.3. Risks

The potential risks of this study are:

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.

It is not anticipated that randomization to taking "no CBTD" or doses greater or less than what was taken outside of the study will expose subjects to any risks greater than what is already encountered from routine use of CBTDs. Although it is possible that some doses in the study may exceed the usual dose of medication in subjects, the doses used in this study are within the range of recommended doses for the treatment of cystinuria, and not known to be associated with a higher risk of developing side effects.

8.4. Recruitment

Patients will primarily be recruited from the clinical practice of the principle investigator, Dr. David Goldfarb. 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:

Each investigator is responsible for ensuring that informed consent is obtained from each participant using a current consent form according to the guidelines of its local 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 at the site responsible for informed consent (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 via a combination of the phone and mail. In these circumstances, the investigator will discuss the study in detail with the potential subject either in person or on the phone. After the discussion, the potential subject will be mailed a copy of the consent for review. The study investigator will then perform the informed consent process via telephone with the potential subject. If the subject desires to participate in the study, they will sign and date the consent form and send it back to the study investigator, who will then sign and date the document as well. In this situation, the requirement for a witness signature is waived. The investigator will send a copy of the signed form back to the subject and retain the original in the study records. The investigator will be sure to also properly document the entire process, including phone conversation, in the study records.

Since the study also requires a review of the most recent blood work and medical record information to confirm eligibility, the study team will make attempts to have this information sent to them from the treating physician for all remotely consented subjects. In regards to the one month post-procedure visit that includes a blood test and urine test, subjects consented remotely will have the option to come into the study office for these tests or offered the ability to have the tests performed locally with the results being forwarded to the study investigators. In either case, there will be no additional costs 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

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 and legal 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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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