Appendix E

P.I. Name and Department
Telephone Numbers(s)
Co-P.I. Name(s)
Day Telephone Number(s)
24-Hour Emergency Number
IRB # of protocol

SUGGESTED SUBJECT CONSENT FORM

A RANDOMIZED, MULITCENTER CLINICAL TRIAL TO EVALUATE THE EFFICACY OF ORAL ELMIRON®, ORAL HYDROXYZINE AND THE COMBINATION OF ORAL ELMIRON® AND ORAL HYDROXYZINE FOR THE TREATMENT OF INTERSTITIAL CYSTITIS (IC)
ICCTG PROTOCOL #1

INTERSTITIAL CYSTITIS CLINICAL TRIALS GROUP

INVITATION TO PARTICIPATE: You are being asked to participate in a research study because you have been diagnosed with interstitial cystitis (IC) and have been informed that you may be eligible for the investigational study known as:"A Randomized, Mulitcenter Clinical Trial to Evaluate the Efficacy of Oral Elmiron®, Oral Hydroxyzine and the Combination of Oral Elmiron® and Oral Hydroxyzine for the Treatment of Interstitial Cystitis (IC)"

The Interstitial Cystitis Clinical Trials Group (ICCTG) has been established by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) to identify and study treatments for people with symptoms of IC. It is hoped that such a study will eventually lead to improvement in the treatment of IC.

PURPOSE OF THIS STUDY: The purpose of this study is to investigate the efficacy of pentosan polysulfate sodium (trade name: Elmiron®), a clinically available drug, oral hydroxyzine (trade name: Atarax, Vistaril) to treat the symptoms of IC. This study will attempt to determine if any of these treatments is effective in providing relief for IC: pentosan polysulfate sodium (Elmiron®), oral hydroxyzine (Atarax®), or the combination of these two drugs. Elmiron® has been approved by the United States Food and Drug Administration (FDA) for the treatment of IC. Although hydroxyzine is an antihistaminic drug marketed for pruritus (itching) and urticaria (hives), it is not approved for the treatment of IC and is considered investigational for this study. However, based

on previous use of hydroxyzine, there are indications it may be helpful in relieving IC symptoms. In addition, the combination therapy of Elmiron® and hydroxyzine has not been formally tested for the treatment of IC, and thus represents another experimental aspect of this study. But based on the potential methods of action, and the promising effects of Elmiron® and hydroxyzine when taken alone, this combination therapy may also be helpful in the treatment of IC.

Approximately 136 participants with clinically diagnosed interstitial cystitis will be involved in this study at the following clinical centers: University of Maryland, Baltimore, Maryland; New England Medical Center, Boston, Massachusetts; Henry Ford Hospital, Detroit, Michigan; University of Oklahoma, Oklahoma City, Oklahoma; Graduate Hospital, Philadelphia, PA; University of Pennsylvania, Philadelphia, PA; University of Rochester, Rochester, New York; and William Beaumont Hospital, Royal Oak, Michigan.

If you choose to participate, your involvement in the study will last at least 6 months and at most 16 months. While you are participating in this study, you must agree not to begin any other therapy for your IC or participate in any other intervention (clinical trial involving randomization to treatment) trial.

PROCEDURES AND CONDUCT OF THE STUDY:

Prescreening: If you choose to participate in this study, and after you have signed the consent form, the clinical research coordinator will evaluate your eligibility for the study.

Baseline 1 Visit: At this visit you will be asked to complete a questionnaire about your symptoms. You will also talk to the Research Coordinator and your physician about your medical history. At this time you will be given a physical examination. You will give a urine sample, and have about one to two teaspoons of blood drawn from your vein. Laboratory tests on your urine include a urinalysis and urine culture. Laboratory tests on your blood include a serum pregnancy test, if applicable, and tests to determine if your liver is functioning within acceptable limits and if your blood is clotting normally. If you are male, you will be given a residual urine volume test either by ultrasound or catheter.

You will be given a voiding (urination) diary and a measuring container to take home. In this diary you will record the following information covering a 24-hour period: the time you void, the amount, whether you awoke to void, and the times you went to bed and awoke. You will be asked to bring this diary to your Baseline 2 visit.

Baseline 2 Visit: Prior to selection, you will be asked to complete a series of questionnaires that will evaluate your IC symptoms, general health status and sexual functioning. You will also be asked to provide a urine sample, which will be frozen and shipped to the University of Pennsylvania and stored for a period of 5 or more years for future research analyses.

Another evaluation will be made at this time to determine if you are still eligible for this study. If so, you will be randomly assigned to one of four treatment groups. Random assignment is like flipping a coin. Neither your physician nor you will know to which treatment group you will be assigned. Group One will receive two oral placebos. Group Two will receive oral Elmiron® plus an oral placebo. Group Three will receive oral hydroxyzine plus an oral placebo. Group Four will receive oral hydroxyzine plus oral Elmiron®.

Neither the clinical staff nor you will know which treatment or placebo is being given. However, information regarding which treatment you are receiving will be made available to your physician in case of an emergency.

You will also be given a medication diary to take home. In this diary you will record the names of all over-the-counter and prescription medications you take each day and how much you take. You will need to record in this diary every day for as long as you are on the study. You will need to bring this diary with you to each of your clinic visits.

Some participants may experience drowsiness as a result of the study medications. It is expected that this drowsiness will go away after a few weeks. The full therapeutic effect of Elmiron® may take several months; therefore, you are encouraged to remain on the study for its duration. Your physician will continue to assess and treat your urinary symptoms.

Treatment Period: After randomization, you will be given a bottle containing study medication. You will be instructed to take three (3) white capsules each day, spaced eight (8) hours apart (morning, afternoon and evening). You should take these capsules on an empty stomach, either one hour before or two hours after you eat.

You will also receive four (4) "blister cards" containing enough green capsules for the first three weeks of the study (one blister card for each week), plus an additional week in case your next clinic visit cannot be scheduled exactly 21 days after your Baseline 2 visit. A blister card is the package which holds the capsules inside a plastic and foil barrier. The Research Coordinator will instruct you to take one (1) capsule at bedtime from one of three columns depending on the week of the study and the agreed dose for that week.

During your clinic visit after week 3, you will return all of the blister packets, even if they are empty or still have some capsules left in them. You will then receive a bottle of green capsules. You will take one (1) capsule from this bottle at bedtime in addition to the white capsules you have been taking morning, afternoon, and evening. The bottle will contain enough capsules to get you through until you return for your next scheduled clinic visit.

You will be given a voiding (urination) diary and a measuring container to take home at week 3 and then every seven weeks during the treatment period. Beginning at week 3 and at weeks 10, 17 and 24, you will come to the clinic to return your voiding diary and

complete several symptom questionnaires. You will also need to bring all blister cards and bottles of study medication (empty or not) to all clinic visits. At week 24 you will be asked to provide a urine sample which will be frozen and shipped for storage. Laboratory tests on your blood will be repeated at week 24. At that visit you also will complete a health status questionnaire, sexual functioning questionnaire, and have a complete physical examination.

The Research Coordinator will contact you by telephone at weeks 6, 14, and 20 to ask you some questions about how you are feeling, how often you are taking your study medication, if there has been a change in your non-study medications or if you have added any other treatments for IC.

Because of the risks associated with pregnancy and the study drugs you may be taking, your doctor may order a pregnancy test at any time throughout the study for applicable participants. You must agree to use an effective method of birth control during your participation in this study and for one month afterward.

Post Treatment Follow-up Period: You will have the option of continuing with the study medication after your week 24 visit. If you choose to continue, you will come into the clinic every 12 weeks to bring in your bottles of study medication and completed voiding diary. You will also be asked to complete several symptom questionnaires.

You may continue until the study is closed which may be as long as 16 months or as short as a few weeks depending on whether you are one of the first participants entered into this study or one of the last. At the close of the study, you will be able to find out which medications you were taking.

RISKS:

Participation in this study may involve some risks, complications, unforeseen hazards, or discomforts. These may include the side effects of the drugs or procedures, or the inconvenience and time involved in participating in this study.

The risk of serious complications resulting from the ingestion of oral Elmiron® or oral hydroxyzine are low. These complications can include, but are not limited to, the side effects listed below. The side effects and risks associated with the combined use of Elmiron® and hydroxyzine are unknown.

Because of possible drug interactions, you must not take the following medications while participating on this study: Cimetidine (Tagamet®). Chronic daily use of greater than one gram of aspirin; chronic daily use of more than the maximum, single dose of acetaminophen or aspirin-replacement products (NSAIDs) in a 24-hour period (some examples are ibuprofen, ketoprofen); chronic daily use of medications containing diphenhydramine, brompheniramine, or chlorpheniramine (some examples are Benadryl®, Tylenol®, Unisom®, Actifed®, and Excedrin P.M.®). Chronic use is defined as, more than three (3) days out of seven (7) days per week.

In addition, you must not receive intravesical (instilled into the urinary bladder) heparin while participating in this study.

Pentosan polysulfate sodium (Elmiron®):

Side effects tend to be infrequent, mild and temporary. Side effects reported in a large, open label trial were diarrhea (4%), nausea (4%), reversible hair loss (4%), headache (3%), rash (3%), indigestion (2%), stomach pain (3%), liver function abnormalities (1 – 4 %) and rarely, dizziness (1%). Elmiron® is a weak blood thinner, therefore you should not take this drug if you are planning to undergo surgery and/or certain dental procedures. If you are taking blood thinners (anticoagulant drugs) such as Coumadin®, the dose may need to be adjusted and your physician will need to check your clotting tests more frequently.

Hydroxyzine (Atarax®, Vistaril®):

Side effects seen with hydroxyzine include temporary drowsiness and dry mouth. You should not drive a car or operate machinery until the drowsiness passes. You should have someone drive you, take a taxi or other transportation if you need to travel the first days after starting study drug. This drowsiness usually disappears after a few days in most people. This drug should not be taken together with alcohol, or other central nervous system depressing drugs, sedatives or sleep inducing medicines, including over-the-counter cold medicines that contain antihistamines, because there may be pronounced drowsiness. In dosages considerably higher than the study medication, people may have difficulty urinating, nightmares, weight gain or some shakiness in their hands.

Placebo:

A placebo is a capsule that contains inactive ingredients.

VENIPUNCTURE PROCEDURE AND RISKS:

Approximately one to two teaspoons of blood will be needed at the Baseline 1 and week 24 visits. If the results are not within acceptable limits, the procedure will be repeated. This procedure involves placing a needle in a vein in your arm to take blood and will require no more than a few minutes. There is minor transient pain when the needle is being inserted. Occasionally, there are minor complications and you may experience fainting, bruising, swelling, black and blue marks, and/or infection at the site.

PREGNANCY AND BREAST-FEEDING ISSUES:

You must agree to practice effective birth control during the time you are taking the study medications and for one (1) month afterward.

_____ Participant Initials _____ Date

If you are pregnant or become pregnant there might be risk or harm to your unborn child. If you are pregnant, you must inform your physician and you will not be included in the study. If you are still capable of becoming pregnant, you will be given a serum pregnancy test prior to entry into the study and at any time during the study that your doctor advises. Further, while you are taking these drugs, you should not become pregnant. If you do become pregnant, you must discontinue the study drugs.

Due to the effect of these drugs, there could be serious harm to unborn children or children who are breast-feeding and it could also jeopardize the health of the mother. In addition, it is possible that harmful side effects that are not yet known could occur to both the mother and unborn or breast-feeding child.

ICCTG – URINE SPECIMEN (BANKING):

You will also provide a urine sample two different times during this study (at the Baseline 2 and the week 24 visits). These samples will be frozen and shipped to the University of Pennsylvania where they will remain frozen and stored for a period of five (5) or more years. The purpose of this repository is to make specimens available for use in research. Your identity will be kept strictly confidential.

BENEFITS:

The purpose of this study is to determine the effectiveness of Elmiron®, hydroxyzine, and the combination of Elmiron® and hydroxyzine to improve the symptoms of IC. Even though you may receive Elmiron®, hydroxyzine, both, or a placebo there is no

assurance that you will receive any benefit from participating in this study. Your symptoms may even worsen while participating in this study. At the present time no representation can be made that your participation will be of certain benefit.

COSTS:

You will not receive any financial compensation for participation in this study except as outlined in this consent form.

Labs, and clinic visits required as part of this study and outlined in this consent form will be paid for by the Interstitial Cystitis Clinical Trials Group under a grant from the National Institutes of Health. This includes blood test/s, urine analysis and culture, urine residual volume (males only), pregnancy test/s, all study medications, and clinic visits.

ALTERNATIVES:

Although there is no single method of treating IC, there are several therapies that have been effective for some patients. These include oral anti-inflammatory agents (Advil®, Motrin®), oral antidepressants (Elavil®), oral antispasmodic medications (Ditropan®), hydrodistention of the bladder, instilling of dimethyl sulfoxide (DSMO) or heparin into the bladder, oral pain medications, Pyridium® (a urinary tract analgesic), or adjusting diet. Of these options, only instilled DMSO, in addition to Elmiron®, has received FDA approval for the treatment of IC symptoms.

You may choose not to participate in this study and, if you decide not to participate, you will receive the usual standard of medical care for your interstitial cystitis.

CONFIDENTIALITY:

All information collected in this study including your identity will be kept strictly confidential, except as may be required by law. Representatives of _____ *(RESPECTIVE INSTITUTION)*, the Interstitial Cystitis Clinical Trials Group, the National Institutes of Health (NIH), as well as the Food and Drug Administration (FDA) will have access to all your medical records and data collected about you during all phases of this study. This includes medical records from other institutions. If any publication results from this research, you will not be identified by name.

DISCLAIMER/WITHDRAWAL:

You are voluntarily agreeing to participate in this study and understand the possible effects or hazards that might occur as a result of participating in this study as described in this consent form. Should your physician find it necessary, and/or in your best interest, s/he may withdraw you from the study at any time.

You may choose not to participate or to withdraw from the study at any time without penalty or loss of benefits to which you are otherwise entitled, and without prejudicing your present or future medical care by your physician, Dr. _____ *(NAME OF RESPECTIVE P.I.)* or _____ *(RESPECTIVE INSTITUTION).*

COMPLICATIONS:

Complications may arise during the course of therapy either due to your disease or due to the treatment. Therapy for any such complication/s will be carried out by your doctors and costs associated with such care may be provided by third party payers. No compensation for injury will be provided to you as a result of your participation in this study. If you have questions regarding medical treatments or costs associated with injuries or complications, contact _____ *(NAME)* by calling _____ *(PHONE NUMBER).*

ADDITIONAL INFORMATION:

If any significant new findings develop during the course of the study about IC or the treatment you are receiving that may relate to your willingness to continue in this study, this information will be provided to you.

SUBJECT RIGHTS:

If you wish further information regarding your rights as a research subject, you may contact _____ *(RESPECTIVE INSTITUTION).*

If you have any questions pertaining to your participation in this research study, you may contact Dr. _____ *(NAME OF RESPECTIVE P.I.)* by calling _____ *(PHONE NUMBER).*

PARTICIPANT'S DECLARATION:

I have been given the opportunity to ask questions and have had them answered to my satisfaction. I have read (or have had the consent form read to me) and understand the consent form. I understand that any questions that I might have in the future will be answered verbally or, if I prefer, with a written statement. I understand the possible benefits and risks of involvement in this protocol and I hereby agree to voluntarily participate in this research study. Upon signing below, I will receive a copy of the consent form.

_____	_____	_____
Name of Subject (print)	Signature of Subject	Date
_____	_____	_____
Name of Investigator (print)	Signature of Investigator	Date
_____	_____	_____
Name of Witness (print)	Signature of Witness	Date