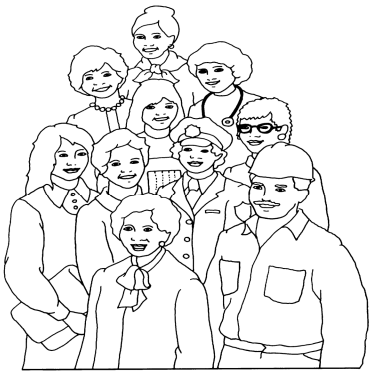
Protocol #1: A Randomized, Multicenter Clinical Trial to Evaluate the Efficacy of Oral Elmiron, Oral Hydroxyzine and the Combination of Oral Elmiron and Oral Hydroxyzine in Patients with Interstitial Cystitis (IC)

Second Edition – Effective April 12, 1999



Interstitial Cystitis Clinical Trials Group (ICCTG)

Sponsored by the

National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK)

National Institutes of Health

ICCTG Protocol for Randomized Clinical Trial #1

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1 Introduction

Interstitial cystitis (IC) describes a typically painful, debilitating and chronic syndrome of the urinary bladder. A broad, clinical definition of IC includes any patient who complains of urinary urgency, frequency, nocturia, and/or pelvic/perineal pain in the absence of any obvious cause, such as bacterial infection or carcinoma (1,2). The presentation of symptoms can be quite variable among patients, leading several authors to posit that IC is a complex of diseases, rather than just one (3) (4). IC, which predominately afflicts females, is a serious health problem that leaves many patients unable to cope with basic daily functions (5-8).

Recognizing that the clinical definition of IC as a "symptom complex" was inadequate for research purposes, the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIADDK) held a workshop in 1987, in which a research definition of IC was formalized (9). Based on results of pilot studies, the criteria were revised at a subsequent workshop in 1988 (10). The NIADDK criteria, (Appendix A), were designed to create some degree of uniformity among IC patients in research studies. However, these criteria were not designed to use as a clinical definition of IC. (It is important to note that specific pathological findings are omitted from the criteria, since there is a lack of consensus as to which pathologic findings, if any, are required for a tissue diagnosis (1,9,11-13)). In the Interstitial Cystitis Data Base (ICDB) cohort study, of the patients thought by investigators to "definitely" or "very likely" have IC, only 30-40% met all of the NIADDK criteria (14).

Since *IC is defined by what it is <u>not</u>*, several different etiological theories, each with at least some scientific support, can be found in the literature. Many authors believe that a combination of etiologies is likely (15,16). Since the etiology of IC remains unclear, directing treatments towards the specific cause(s) of the symptoms is problematic. Physician and patient, therefore, typically take on a trial-and-error approach with hopes of alleviating the symptoms, rather than curing the disease. This approach to treating IC is consistent with the findings from the ICDB Study, in which 582 females reported usage of more than 180 different treatments during baseline screening alone (17).

The importance of IC research is demonstrated in the number of patients whose lives could be significantly improved by conclusive information about IC therapies. In 1987, researchers at the Urban Institute and the University of Pennsylvania estimated that the number of people in the U.S.A. who were diagnosed with IC ranged from 44,000 to 90,000 (8). More recently, using 1989 National Household Interview Survey data and 1990 Census data, Jones *et al.* estimated that the number is closer to 1,000,000 (18). The most conservative estimate of 44,000 suggests that, in 1987, IC-related medical care costs and lost economic production were at least $116.6 million and $311.7 million, respectively (8). Clearly, if the most recent estimate of 1,000,000 patients with IC symptoms is closer to reality, the economic impact is considerably larger in today's economy.

Since there is no one standard therapy which is currently effective for the majority of IC patients, the primary goal of the Interstitial Cystitis Clinical Trials Group (ICCTG) trials will be the rapid identification of "active" therapies which provide a clinically significant improvement in patient symptoms without triggering unacceptable adverse events.

In order to accomplish this goal, the NIDDK convened five clinical centers throughout the United States, and a Data Coordinating Center, to conduct a series of randomized clinical trials under standardized protocols. The ICCTG elected to limit the first clinical trial to oral medications, rather than intravesical and other modalities, since, in general, oral medications have the most appeal to IC patients, in contrast to treatments that require invasive approaches such as catheterization. Likewise, there are several oral preparations for the treatment of IC that are available and currently in use, but had only been subjected to limited studies. Initially, therefore, the ICCTG chose to select currently available pharmaceutical agents for the first clinical trial. The group further elected to investigate a combination therapy to determine if there is an advantage to combining two drugs with different modes of action, in contrast to single drug therapy.

Pentosan polysulfate (Elmiron®) was chosen for one of the oral agents because of its unique property of "coating and sealing" the injured mucosa in IC. Furthermore, this drug, although the only approved oral medication for IC, has had limited studies and conflicting results. Another oral agent that was chosen was the antihistamine preparation -- hydroxyzine. The ICCTG selected this drug because of its reported specific action in inhibiting mast cells, a product of allergic reactions, a presumed pathophysiology of IC. Although this drug has not been subjected to any randomized placebo controlled trial among IC patients, recent open label studies suggest some usefulness in abating IC symptoms.

The second phase of this protocol will be to pursue further testing of one or more of these treatment arms if initial results warrants such action.

2 Study Design and Objectives

This ICCTG protocol #1 for the randomized clinical trial (RCT) will utilize a 2 x 2 factorial design to evaluate: 1) placebo, 2) oral Elmiron® 3) oral hydroxyzine, and 4) the combination of oral Elmiron® and oral hydroxyzine as displayed in Figure 1. All participants who meet eligibility criteria at baseline screening will be randomized to one of the four treatment arms, and followed for 24 weeks, including an initial three week dose escalation period for hydroxyzine to be increased from 10 mg. to 50 mg. daily. The primary objectives of this trial are:

Figure 1. 2 x 2 Factorial Design

Placebo + Placebo	**Placebo + Elmiron**
Hydroxyzine + Placebo	**Hydroxzine + Elmiron**

Hydroxyzine increased from 10 to 50mg during run-in
Elmiron 100mg TID
Placebo TID

1. To demonstrate that the ICCTG network can accrue, follow and retain IC participants and collect relevant clinical trial data in an acceptable timeframe.

2. To demonstrate safety and tolerability (including acceptable drop-out rates) for oral Elmiron® and oral hydroxyzine.

3. To conduct an initial efficacy evaluation of oral Elmiron® and oral hydroxyzine to determine whether any of the proposed treatments, either singly or in combination, are worthy of further study in a larger comparative trial.

Approximately 136 participants, 34 per treatment arm, will be treated and followed for 24 weeks. The total time required for this trial will be approximately 16 months, including the 24 weeks of follow-up on all participants. If there is evidence of significant efficacy for any of the three treatment arms in this trial, accrual to those arms plus placebo may be expanded.

3 Study Background and Prior Clinical Studies

3.1 Elmiron®

Normal human urine has many qualities that make it irritating, even lethal, to cells. These include non-physiologic pH, extremes in osmolarity, and high concentrations of potassium, ammonium, and other noxious components. Therefore, it is crucial that the bladder epithelium serve as a protective barrier. The normal epithelium is covered by a layer of large sugar molecules (glycoconjugates) which are thought to contribute to the barrier. One possible etiologic theory for IC is that the bladder epithelium is permeable ("leaky"). This idea is suggested by several indirect studies (19), (20), and (21). However, in the only direct study published so far, IC patients' bladder permeability was not shown to be significantly greater than healthy controls' (22). Thus, the "leaky bladder" hypothesis remains an unresolved issue.

If the IC bladder is permeable, one possible reason is that the epithelial glycoconjugates are deficient (23). Because of this theory, IC patients have been treated with glycosaminoglycans (GAGs), which are thought to replace the deficient glycoconjugates and "coat" the bladder wall (23). Oral pentosan polysulfate (Elmiron®) represents a GAG which has the advantage over other GAGs (such as heparin and hyaluronic acid) in that it can be taken orally. Elmiron® has been evaluated in several clinical studies (see below) and it is clear that some patients have good symptom relief with Elmiron®. However, the mechanism of symptom relief is still unknown. Since bladder permeability has not been proven to increase in IC, nor to correlate with any deficiencies in epithelial glycoconjugates, the assumed mechanism of "GAG replacement" to restore the permeability barrier may not be correct. Other possible mechanisms include: (1) placebo effect, (2) nonspecific binding to urine components (such as potassium) which would otherwise irritate the bladder, and (3) modulation of bladder inflammation or tissue repair.

Elmiron® has been evaluated in several clinical studies, both through case series and four randomized clinical trials. The first case series (24) used a dose of 50 mg qid or 150 mg bid in patients who had previously failed treatment with bladder distention or DMSO. Within four to eight weeks, 20 out of 24 patients had at least 80% reduction in pain, urgency and nocturia. In another open label study, Fritjofsson et al. (25) used a dose of 200 mg bid. Most patients reported decreased pain within four weeks. For 33 patients with bladder ulcers, there was no significant improvement in frequency, nocturia or voided volume. In contrast, all three of these outcomes improved in the non-ulcer patients (n=48). A third open-label study was reported by Hanno (26). Outcomes were based on questionnaires and included pain, urgency, overall IC symptoms, frequency and nocturia.

Depending on which outcome was tested, 42% to 62% of patients reported at least moderate improvement in symptoms.

Elmiron® was also tested in four placebo-controlled randomized clinical trials: three by Parsons *et al*. (27), (28), (29) and one by Holm-Bentzen et al. (30). The first Parsons study (27) used a dose of 100 mg tid in a double-blind, cross-over design with three months on each treatment. All patients had glomerulations or Hunner's ulcer. The percent of patients with at least 50% improvement for pain, urgency and frequency were 18%, 19% and 39% respectively, in the placebo group and 45%, 40% and 63% respectively, in the Elmiron® group. All three of these differences were statistically significant. The average voided volume increased from 85 to 102 ml in the Elmiron® group, but from 80 to 85 ml in the placebo group (p=0.009). The second study (28) was a multi-center study of 110 patients with cystoscopic findings of IC who had failed treatments with clorpactin, DMSO, or bladder distention. The dose of Elmiron® was 100 mg tid for three months. A self-reported overall improvement (better than 25%) was found in 28% of the Elmiron® patients and 13% of the placebo group (p=0.04). The investigator assessment of global response was similar (26% for Elmiron®, 11% for placebo, p=0.03). For other outcomes (pain, pressure, urgency, voided volume) the two groups did not differ significantly. The third study (29) was a multi-center trial of 148 patients who had the cystoscopic findings of IC. This study did not require failure of any specific prior treatments. The Elmiron® dose was 100 mg tid for three months. The percents of patients who reported at least a 50% improvement in overall condition, pain and pressure were 32%, 38% and 30% respectively, in the Elmiron® group and 16%, 18% and 18% respectively, in the placebo group. The Elmiron® patients also were more likely to have at least a 1-point decrease on 5-point scales for pain and urgency. Voided volume increased by at least 20 ml in 40% of Elmiron® patients and 24% of placebo patients (p=0.02). In summary, all three of the above studies showed significant differences between the Elmiron® groups and the placebo groups. These results were used as part of the rationale for the approval of Elmiron® as treatment for IC in 1996.

A fourth study was an European multi-center trial of Elmiron® (200 mg bid) for four months (30). This study showed no significant differences in symptoms (pain, dysuria, frequency, nocturia, total symptom score) or urodynamic features (volume at first sensation, bladder capacity) between the two patient groups. Possible reasons for the different conclusions between this study and Parsons' studies include: (1) the European study population had a higher percentage of patients with Hunner's ulcers, and Elmiron® is known to be less effective in this group (25), (2) the dose 200 mg bid may have different effects than 100 mg tid, (3) the European study did not specify that Elmiron® was taken on an empty stomach, so absorption may have been poor, (4) the European study looked at mean scores for the entire patient groups (e.g. mean pain score) while the other studies looked at percent of responders. If a subset of patients did respond to Elmiron® in the European study, their improved scores may not have significantly changed the mean scores for the entire group.

The conflicting results of the two sets of randomized clinical trials of Elmiron®, combined with the relatively low response rates which suggest that only subsets of patients may

respond positively to Elmiron® treatment, leave some question as to the overall efficacy of Elmiron® for all IC patients. Therefore, additional well-controlled clinical trials, using standardized symptom endpoints, which demonstrate the superiority of Elmiron® over placebo will greatly contribute to the acceptance of Elmiron® as a standard IC therapy.

3.2 Hydroxyzine

A number of findings support the suggestion that mast cells are important in the pathophysiology of IC (31). Mast cells are involved in allergic and late phase reactions (32)in which immunoglobulin E (IgE) bound to specific receptors on the surface of mast cells is bridged by antigen (Ag) leading to exocytosis. However, mast cell secretion can also be triggered by many other substances, such as neurohormonal secretagogues (33) and adherent bacteria (34). Hydroxyzine is a heterocyclic piperazine histamine$_1$-receptor antagonist (antihistamine), with anticholinergic, anxiolytic and sedative properties (35), which may also reduce bladder mast cell activation (36). Hydroxyzine has been reported to inhibit connective tissue mast cell (CTMC) secretion in rats (37) and in humans (38,39). Hydroxyzine also inhibits secretion from rat basophilic leukemia (RBL) cells (40), which are considered equivalent to mucosal mast cells (MMC) (41). Interestingly, the major hydroxyzine metabolite cetirizine (Zyrtec) appears to lack hydroxyzine's inhibitory effect on mast cells (42).

Hydroxyzine reaches a peak serum concentration in about two hours after oral administration and is almost entirely metabolized and cleared through the kidneys and liver. The half-life averages 16 hours in adults (35,43). The clinical use of hydroxyzine is mostly limited to the treatment of atopic dermatitis (44) and urticaria (45), even though it is also effective in the treatment of allergic rhinitis (46). The use of hydroxyzine at bedtime is indicated not only by its long half-life, but also by the fact that evening dosing of hydroxyzine reduces its adverse effects (47), while its beneficial actions are maintained during the day (35,43).

Although to date no one has conducted a controlled clinical trial to establish the usefulness of this medication in IC treatment, recent studies suggest its use as a treatment for the symptoms of IC. The observation that hydroxyzine can reduce bladder mast cell activation (36), may help explain why oral hydroxyzine has been suggested to reduce symptoms of IC in recent case series (48,49). Hydroxyzine's effectiveness is not due to its antihistaminic properties since other common H_1-receptor antagonists were ineffective, (36)as also observed clinically in IC (50). Hydroxyzine's possible effectiveness in reducing the pain associated with IC, may also be explained by the fact that parenteral hydroxyzine given together with morphine has been shown to augment analgesia in the treatment of postoperative pain (51).

3.3 Combination of Elmiron® and Hydroxyzine

The rationale for the combination use of Elmiron and hydroxyzine is based on the putative pathogenesis of IC. The normal impermeable bladder surface urothelium becomes more permeable in IC either as a primary defect or following inflammatory changes in the bladder wall. The potassium sensitivity test described in (19)is a surrogate marker of increased permeability in IC. Defective surface urothelial glycosaminoglycans (GAGs) are

thought to contribute to this increased permeability. Elmiron®, a synthetic heparinoid compound with GAG properties, is used in IC based on its postulated effect in restoring or augmenting the bladder surface GAGs.

Hydroxyzine is used to treat IC because of its effect on inhibition of mast cell activation (predominately neurogenic). Histologically, mast cells are noted in the submucosal and detrusor layers of the bladder wall in IC. Conceptually it is possible that the pathogenesis of IC is based on a vicious circle of 1) an abnormal bladder urothelium (abnormal GAGs), increased permeability, 2) diffusion of urine into the bladder wall, 3) activation bladder sensory afferent neurons resulting in release of mast cell activation, inflammation and release of tachykinis (neuropeptides such as substance P).

Mast cell metabolites (e.g. leukotrienes, TNF, histamines) may aggravate the damage to the bladder lining, which further compounds the damage/permeability defect in the bladder urothelium. Combination use of Elmiron® and hydroxyzine aims to interrupt the above pathogenic pathway at two points: namely, the surface urothelium (Elmiron®) and the bladder wall inflammation (hydroxyzine). Such combination therapy may well lead to a shorter time for clinical response and augmentation of the clinical efficacy of a single agent therapy.

4 Study Organizations

The ICCTG Study organization includes 5 main Clinical Centers, 2 Satellite Centers, and 1 Affiliate Center. In total, there will be 8 clinical sites recruiting for this study (Appendix B). In addition the study includes a Data Coordinating Center (DCC), a Steering and Planning Committee, Working Groups, Publications Policy and Ancillary Studies Committee, an External Advisory Committee, and NIDDK Project Scientists. The responsibilities of each component as related to the current protocol are described below.

4.1 Clinical Sites

There are 5 main Clinical Centers, 2 Satellite Centers, and 1 Affiliate Center recruiting participants for the ICCTG Study. All Clinical Centers and Satellite Centers will maintain their own computing hardware for direct data entry into the study database at the DCC. These 7 sites will be referred to as *Randomization Sites*. The 1 Affiliate Center will coordinate the transfer of Case Report Forms (CRFs) of participant data to the appropriate primary Clinical Center for data entry into the Data Management System (DMS). Throughout this document, the 8 centers recruiting for this study will be referred to as *Clinical Sites*.

The responsibilities of each clinical site include:

1. Recruiting, screening, enrolling and following participants throughout the course of the clinical trial.
2. Confirming eligibility of each participant based on the study criteria identified in the protocol.
3. Adhering to study protocol and the Manual of Procedures in the implementation of procedures and the acquisition of data.

4. Collecting data of high quality according to Good Clinical Practice (GCP) guidelines.
5. Collaborating with other study investigators in the development of the Manual of Procedures, acquisition of high quality data, and the analysis and publication of study results.

4.2 Data Coordinating Center (DCC)

The Data Coordinating Center (DCC), located at the University of Pennsylvania Medical Center, will provide administrative, biostatistical, and data management/computing leadership for design/conduct of the clinical trial.

Responsibilities include:

1. Overall leadership regarding study design and conduct of the clinical trial.
2. Preparation and distribution of the study protocol and Manual of Procedures, based on collaboration with the Steering and Planning Committee and NIDDK Project Scientists.
3. Collaboration with other study investigators in the development, testing, and use of all case report forms (CRFs) and study procedures.
4. Provision of an efficient data management system (DMS) to enter data directly into the central database at the DCC, and to implement double data entry with verification.
5. Development and application of quality assurance procedures including data tracking and validation, query processes, and maintenance of related documentation.
6. Development of tracking and storage procedures for laboratory samples.
7. Training of clinical site staff and coordination of the site monitoring.
8. Coordination of Steering and Planning Committee and External Advisory Committee meetings.
9. Preparation of detailed reports regarding participant recruitment and retention, data collection activities, and interim results to the External Advisory Committee.
10. Collaboration with study investigators in the analysis and publication of study results.

4.3 Steering and Planning Committee

The Steering Committee is the primary governing body of the ICCTG Study. Steering and Planning Committee members include the NIDDK Project Scientists, the Principal Investigators and Co-Investigators from each of the clinical sites, and the Principal and Co-Principal Investigator of the Data Coordinating Center. Although other study investigators will often attend meetings, all major scientific decisions will be made by the Steering and Planning Committee. The primary responsibilities of the Steering and Planning Committee include:

1. Identifying the specific aims of the clinical trial.
2. Determining eligibility criteria, including exclusion and deferral criteria, developing the study plan, study protocol and Manual of Procedures, participating in case report forms development, and establishing the timeline.

3. Overseeing standardized implementation of the study protocol.

4. Monitoring overall study quality assurance and quality control.

5. Reviewing and approving all publications based on any data collected as part of the trial.

6. Approving outside study investigators for access to data and stored specimens for their own epidemiological and clinical studies.

7. Establishing the time line for the study.

In addition, various working groups and committees have been formed to deal with specific protocol and group issues as follows.

4.3.1 Working Groups

The Steering and Planning Committee has established working groups to carry out various tasks related to protocol development (see Appendix C). To date, working groups include the 1) Master Protocol Working Group; the 2) Treatment and Study Design Working Group; the 3) Outcomes Working Group and the 4) Novel Therapy Working Group. Additional working groups may be formed in the future as needs arise.

4.3.2 Publications, Presentations and Ancillary Studies (PP&AS)

From within the membership of the ICCTG, the Publications, Presentations, & Ancillary Studies (PP&AS) Committee addresses issues regarding the presentation and dissemination of study information. The preparation of all publications or presentations must be assigned by the Steering and Planning Committee to specifically appointed writing groups. The authorship policy of the ICCTG Study is to recognize all participants of the ICCTG professional staff, as well as to recognize individual effort. The Chairman of the PP&AS Committee will establish a schedule and formal review process for all materials submitted, according to specific guidelines described in the Manual of Procedures.

Any ancillary study must be undertaken with careful consideration of its impact on the objectives of the protocol. To protect the integrity of the primary study, a proposal to conduct an ancillary study must be reviewed by the PP&AS Committee before its initiation. Guidelines describing the format, submission and approval process for ancillary studies are outlined in detail in the Manual of Procedures.

4.4 External Advisory Committee

The External Advisory Committee is an independent advisory group composed of experts in relevant medical, biostatistical, and bioethical fields. The primary responsibility of the Committee is to periodically review the progress of all ICCTG protocols, provide advice to the NIDDK Project Scientists regarding the scientific merit of the study, and serve as the Data Safety and Monitoring Board reviewing interim analyses of study results.NIDDK Project Scientists

4.5 NIDDK Project Scientists

The NIDDK Project Scientists' primary responsibility is to provide scientific support in all aspects of the ICCTG Study, including protocol development, quality assurance and quality control, interim data monitoring, final data analysis and interpretation, preparation of publications, and group performance. All clinical sites and the DCC are subject to official NIH site visits.P**articipant Criteria**

5 Participant Criteria

5.1 Study population

The study population for this RCT protocol will be drawn from patients with a diagnosis of IC, confirmed sometime in the past with the results from a cystoscopy/hydrodistention. Any IC patient presenting with symptoms of urinary frequency in conjunction with urinary pain/discomfort persisting for at least 24 weeks will be considered a candidate for enrollment into the study.

5.2 Number of participants and study duration

This RCT will require the accrual of 136 participants, randomizing 34 participants to each of the 4 treatment arms. Assuming an annual accrual rate of approximately 35 participants for each of the 5 primary Clinical Centers (includes Satellite Centers and Affiliate Center), the total accrual for this protocol is expected to require 10 months. Allowing for a minimum of 24 weeks follow-up on all participants, this yields a total study length of approximately 16 months.

5.3 Inclusion criteria

Participants are required to fulfill the following criteria:

1. Participant must be at least 18 years of age.
2. Participant must sign and date the informed consent.
3. Participant (male or female) must agree to use an effective method of birth control.
4. Participant must report a urinary frequency of at least 11 times per 24-hour day, on average over the previous four weeks. This frequency criterion must be met at each of the two baseline-screening visits as reported by the participant.
5. Participant must report a pain/discomfort score of 4 or greater on a 0 - 9 Likert scale. This pain/discomfort criterion must be met at each of the two baseline-screening visits.
6. These reported urinary symptoms of frequency and pain/discomfort must have been present for at least the previous 24 weeks prior to the first baseline screening visit (B1).

5.4 Exclusion criteria

Any participant satisfying one of the following criteria will not be eligible to participate in the ICCTG Study:

1. Currently participating in another intervention study.
2. Any imminent change in residence outside the driving distance of the ICCTG network within the next 24 weeks.
3. Participant unlikely to be compliant due to medical or psychological problem.
4. A history of having been previously treated with Cytoxan®/cyclophosphamide.
5. A history of pelvic radiation treatment.
6. Having been previously treated with at least 100 mg TID of Elmiron® or greater than 10 mg of hydroxyzine per day for greater than 12 consecutive weeks.
7. Having had augmentation cystoplasty.
8. Having had a cystectomy or cystolysis.
9. Having had a neurectomy (i.e. hypogastric nerve plexus ablation) or implanted peripheral nerve stimulator which has affected bladder function.
10. A history of a bladder calculus.
11. A history of tuberculous cystitis.
12. A history of neurologic disease or diabetic cystopathy.
13. A history of malignant bladder tumors.
14. A history of urethral cancer.
15. Reports a urinary void with a maximum volume > 350 cc, as measured by a 24 hour-voiding diary.
16. Currently has an active urethral calculus.
17. Currently has a ureteral calculus.
18. Symptomatic urethral diverticulum.
19. Has an LFT > 1.5 times the respective institution's upper limits of normal at the Baseline 1 screening visit.
20. Has abnormal blood coagulation tests results: PT or PTT (aPTT).
21. Has platelet test results outside the respective institution's normal range.
22. Reports any allergies to Elmiron® or hydroxyzine.
23. Currently taking cimetidine or currently on intravesical heparin.
24. Chronic use (more than 3 out of 7 days each week) of greater than one gram of acetylsalicylic acid (e.g. aspirin, Bayer®, Anacin®, Excedrin®, etc.).
25. Chronic use (more than 3 out of 7 days each week) of aspirin replacement products (acetaminophen, NSAIDs, etc.) of more than the amount of milligrams in the

maximum single dose allowed by the Physicians' Desk Reference for prescription use, spread out over 24 hours.

26. Chronic use (more than 3 out of 7 days each week) of sedating histamine-1 receptor antagonists (only those containing diphenhydramine, brompheniramine, or chlorpheniramine).

Exclusion criteria for men only:

27. Having a residual urine volume >150 cc by ultrasound or catheter.

28. Having had a TURP, TUIP , TUIBN, TUMT, TUNA, balloon dilation of the prostate, open prostatectomy or any other prostate surgery or treatment such as cryotherapy or thermal therapy.

29. Currently being treated for chronic bacterial prostatitis as documented by a positive urine culture.

Exclusion criteria for women only:

30. Having had uterine, cervical or vaginal cancer during the past 3 years.

31. Having active vaginitis.

32. Currently pregnant.

33. Currently breastfeeding.

5.5 Deferral criteria

There are several physical conditions for which a participant will be deferred from entry into the ICCTG Study. Once it is formally ascertained that the condition is not present or has subsided according to the time frame identified, the participant will be reconsidered for entry into the ICCTG Study. The following list identifies the conditions for deferment and the criteria that a participant must meet in order to be evaluated further for entry into the study:

1. If a participant has initiated any new medications for IC during the past 4 weeks, he/she will be deferred until he/she has been on the same dose for at least 4 weeks.
2. If a participant has undergone any of the following during the past 6 weeks: urethral dilation, cystometrogram, urodynamics, bladder cystoscopy /hydrodistention under general or regional anesthesia, or bladder biopsy under general or regional anesthesia, he/she will be deferred until at least 6 weeks from the date of the procedure.
3. If a participant has had a positive urine culture and/or clinical evidence of bacterial UTI during the past 6 weeks, he/she will be deferred until the participant has been without the condition for at least 6 weeks.
4. If a participant has had gross hematuria during the past 12 weeks, he/she will be deferred until the participant has been without the condition for at least 12 weeks.
5. If a participant has active genital herpes or has had active genital herpes during the past 12 weeks, he/she will be deferred until the participant has been without the condition for at least 12 weeks.

6. If a participant has received treatment with Elmiron® or hydroxyzine, he/she will be deferred until the participant has been off drug for a minimum of 12 weeks prior to study entry.

7. If a participant has had any intravesical treatment, other than BCG during the past 12 weeks, he/she will be deferred until at least 12 weeks after the last treatment received.

8. If a participant has received intravesical BCG during the past 24 weeks, he/she will be deferred until at least 24 weeks have passed since the last dose of BCG.

9. If a participant has had a cystocele, rectocele, or urinary incontinence surgery, he/she will be deferred until at least 24 weeks from the date of the procedure.

Deferral criteria for women only:

10. If a participant has had any form of transvaginal surgery, hysterectomy, prolapse, vaginal delivery or C-section, she will be deferred until at least 24 weeks from the date of the procedure.

6 Participant Recruitment, Consent and Confidentiality

6.1 Participant recruitment, consent, and confidentiality

Participant recruitment will be conducted through the urology clinic at each of the participating clinical sites. Participants may be self-referred or referred through their primary physician (either solicited or unsolicited by the urology clinic). Participants referred to the clinics with symptoms suggestive of IC will be introduced to the ICCTG Study by the Research Coordinator and by a one-page brochure (Appendix D) describing the RCT for protocol #1. Potentially eligible participants will then be asked whether they are interested in participating in the study.

6.2 Informed consent

Each clinical site will prepare an informed consent form following the guidelines of their local Institutional Review Board. The form will, at a minimum, contain a description of the potential risks, benefits, and expense to the subject, and identify risk management procedures and the risk-benefit ratio and alternative treatment (see basic elements of the proposed informed consent in Appendix E).

If the patient expresses interest in participating, he/she will be asked to sign the informed consent form. This form will provide consent for both the screening procedures and the follow-up procedures. Prior to signing the informed consent, the Research Coordinator will review the details of the consent form orally with the participant, and answer any questions that the participant has concerning participation in the ICCTG Study. The original signed consent form will be kept in the participant study file at the clinical site, while a copy of the signed consent form will be given to the participant.

6.3 Participant confidentiality

Extensive efforts will be made to ensure that the participant's confidentiality is maintained. Any forms or documents sent to the DCC will have all personal information removed. Each participant will be assigned a unique study identification number. A log of the participant names, participant ID numbers, and pertinent registration information (e.g. home address, telephone number, and emergency contact person) will be maintained in a locked file cabinet at each clinical site. The staff at the DCC will not have access to this log. Only the participant ID number and initials will be given to the Data Coordinating Center staff and entered into the ICCTG Study data base. Any communication between the Data Coordinating Center staff and the clinical site staff regarding participant data will occur via this participant ID number.

7 Endpoints

7.1 Primary Endpoints

The primary endpoint will be a participant-reported global evaluation of improvement at 24 weeks or withdrawal, whichever comes first, relative to overall baseline symptoms. A seven point scale centered at zero will be used: –3) markedly worse; –2) moderately worse; –1) slightly worse; 0) no change; +1) slightly improved; +2) moderately improved; and +3) markedly improved. Participants who answer either +2) moderately or +3) markedly improved on the primary endpoint will be considered to be responders. Participants who withdraw from the study for any reason (e.g. adverse events or participant choice) prior to the 24 week endpoint exam will be considered treatment failures. Following standard "intent-to-treat" methods, these withdrawals will be included in the denominator of the response rates for evaluation of the primary endpoint (see details in section 15 of this protocol).

7.2 Secondary Endpoints

A number of secondary outcome measures related to both specific symptoms and overall symptom scores will be used to supplement the analysis based on the primary endpoint. Two symptom questionnaires will be evaluated over time for all participants entered in the trial and compared to the overall assessment of response. The IC Symptom and Problem Index was validated in IC participants studied from multiple clinical centers, using gynecologic outpatients as controls (52). The University of Wisconsin Symptom Score was recently validated by Ken Peters and his group, using data from the BCG trial (53). Both of these instruments will be utilized to assess responsiveness to change over time as measured by the primary endpoint.

In addition to overall symptom scores collected via these questionnaires, participants will report their three primary symptom domains of pain/discomfort, urgency, and frequency repeatedly over time. These measures are identical to those used in the ICDB Study (6,54). Briefly, pain/discomfort and urgency are rated by the participants on a 10-point (0 – 9) Likert scale, and frequency (and related volume measures) is assessed via a 24-hour voiding log. A series of ongoing analyses of these ICDB data using latent variable

modeling of multiple measures of pain/discomfort suggest that this overall 10-point Likert scale for pain/discomfort has high internal consistency (55).

Additional secondary analyses will be conducted to compare the impact of initiation or increased usage of narcotics during the follow-up period, and examination of the effects of other IC treatments that may represent "rescue medication" to compensate for lack of efficacy of the study agents. Details of both the primary and secondary analyses are described in section 15 of the protocol.

8 Treatment Procedures

Participants meeting all inclusion criteria at Baseline Visit 2 will be randomized to one of the four treatment arms as displayed previously in Figure 1 (Section 2). Each participant will receive a four-week supply of blister packs containing green capsules (hydroxyzine or its matching placebo) and one sealed bottle containing white capsules (Elmiron® or its matching placebo). The study medications will be labeled according to regulatory requirement per Code of Federal Regulations (CFR) 312.6 (56). This supply is designed to provide adequate medication for the dose finding/stabilization phase for the green capsules and the fixed daily supply for the white capsules for the three weeks prior to the first follow-up clinic visit. The Research Coordinator will provide explicit instructions to the participant at the time of randomization and dispensing of study drugs.

The participant will be instructed to take three white capsules per day. If possible, he/she should try to take his/her white capsules eight hours apart, depending on his/her schedule. For example, the participant might take them at 6:00 a.m., 2:00 p.m. and 10:00 p.m. The participant should also take them on an empty stomach, either one hour before or two hours after a meal.

Secondly, the participant will be instructed to take one or two green capsules per day, at bedtime. He/she may take the green capsule at the same time that he/she takes the third white capsule of the day. In order to find the maximal tolerable dosage for the green capsules, the blister cards will be prepared and labeled separately for weeks 1, 2 and 3. The blister card for week 4 will be identical to the card for week 3, and is provided to ensure a continuous supply prior to the 3-week clinic visit, which may not fall exactly on the 21st day of follow-up.

- Ø The blister card for week 1 will contain only 1 row of 7 green capsules, labeled as "Dose 1". The participant will be instructed to take only one green capsule per day, at bedtime.
- Ø The blister card for week 2 will have two rows, labeled as "Dose 1" and "Dose 2". The participant will be instructed to begin week 2 by taking one green capsule per day, at bedtime, labeled "Dose 2". If for any reason, the participant can not tolerate "Dose 2", he/she will be instructed to call the Research Coordinator, and get approval to switch back to "Dose 1" for the remainder of week 2.
- Ø The blister card for week 3 will have three rows, labeled "Dose 1", "Dose 2", and "Dose 3". For participants successfully completing week 2 on "Dose 2", they will be instructed to progress to "Dose 3" IN ADDITION to "Dose 2". That is, participants will be instructed during week 3 to take 2 green capsules per day at bedtime, the capsule in the "Dose 2" column AND the capsule in the "Dose 3" column. This will be clearly labeled on the week 3 blister pack. If for any reason, the participant cannot

tolerate "Dose 3", s/he will be instructed to call the Research Coordinator, and get approval to switch back to "Dose 2" for 2 days then re-attempt "Dose 3" for the remainder of Week 3. This process will be monitored closely by the Research Coordinator so that the participant may comfortably be established on the dose that they can tolerate for the maintenance phase of the study.

- Ø Each participant will be provided with an extra blister card (Week 4) for use during week 4, in the event that he/she cannot schedule his/her 3 week follow-up clinic visit within exactly 21 days after the first visit. The participant should continue taking his/her medication until the next office visit.

Participants will be instructed to take one or two green capsules each day, at bedtime. As a result, there may be one unused capsule left over for each day of week 2, and one or two unused capsules left over for each day of week 3. In an attempt to find the maximum tolerable dosage of the green capsules, the participant may request, and the Research Coordinator may agree, to change the participant's target dose for either weeks 2 or 3. However, the participant will be instructed not to make this change in dose without consultation and approval from the Research Coordinator. The participant will be informed that dose stabilization is a crucial aspect of the first 3 weeks of follow-up. The RC will contact the participant at the end of weeks 1 and 2 to determine treatment tolerability.

Prior to the clinic visit at the end of three weeks of follow-up, the Research Coordinator will contact the participant to determine the maximum tolerable dose (either dose 1, 2 or 3) for the green capsules. Depending on this response, the drug distribution center will ship one sealed bottle of green capsules (at the selected dose) to the clinical center in overnight mail on time for the 3 week follow-up visit. An additional sealed bottle will be dispensed to the participant at clinic visits at weeks 10 and 17. The supply of green capsules in each sealed bottle is designed to be adequate for taking one or two green capsules each day, at bedtime, for the following 7-8 weeks until the next clinic visit.

If during this drug maintenance phase, participants determine that the sedative adverse experience is unpleasant, participants may request to de-escalate their drug dose one time only. This decision can only be made in consultation with and approval from the study Principal Investigator and Research Coordinator. The participant and Research Coordinator will then determine if and when the participant can escalate the drug dose to the original level. These changes will be documented by the participant in his/her Daily Medication Log, and by the Research Coordinator in the participant study file.

The participant will be instructed that if at any time he/she should miss a daily dose, he/she should take the next dose at the usual time. The participant may not "double-up" a dose. The participant will be instructed to save the blister cards (during the first 3 weeks) and bottle, even if they are empty, and return all study medications at each follow-up visit, to assist the study in compliance monitoring.

8.1 Elmiron®

8.1.1 Dosing schedule and justification

The prescribed dose for Elmiron® (PPS) will be one 100 mg capsule, three times a day (TID). This dose corresponds to that used in the placebo-controlled clinical trials which showed a significant difference between PPS and placebo

(27-29). It is recommended from these studies that Elmiron® be taken at least two hours after a meal and at least one hour before the next meal. The white capsules will be provided in sealed bottles.

8.1.2 Drug manufacturing and packaging

Elmiron® will be manufactured centrally in one complete batch of active drug by the pharmaceutical manufacturer (ALZA™ Corporation located in Mountain View, CA). The entire quantity of active drug capsules will be shipped to the drug packaging and distribution center for packaging into sealed bottles, labeling and distribution directly to the clinical center, with the participant's five-digit randomization number on the label.

8.2 Placebo for Elmiron®

8.2.1 Dosing schedule

The placebo capsules are manufactured to appear identical to the Elmiron® capsules and will be taken on the same schedule of one capsule three times a day (TID), two hours after and one hour before a meal.

8.2.2 Placebo manufacturing and packaging

A matching placebo (identical white capsules containing microcrystalline hydroxymethl cellulose, magnesuim stearate) for Elmiron® will be manufactured centrally in one complete batch by the pharmaceutical manufacturer (ALZA™ Corporation). The entire quantity of placebo capsules will be shipped to the drug packaging and distribution center for packaging into sealed bottles, labeling and distribution directly to the clinical center, with the participant's five-digit randomization number on the label.

8.3 Hydroxyzine

8.3.1 Dosing schedule and justification

The target dose of hydroxyzine will be two green 25 mg capsules per day, taken at bedtime. However, in order to minimize loss of participants due to inability to tolerate the potential adverse experiences (drowsiness), the dosage of hydroxyzine will be titrated up slowly from 10 mg per day (week 1), to 25 mg per day (week 2), to 50 mg [{2} 25 mg capsules] per day (week 3). By the end of week 3, each participant, in close consultation with the Research Coordinator, will select their maximal tolerable dose. This dose will be selected to be the maintenance dose for the remainder of the 21 weeks of the follow-up period.

Although all participants are expected to develop some initial adverse experiences from this medication, predominately sedation, it has been shown that participants tend to become tolerant to these effects if a slow titration is used (48). In addition, the entire dose of hydroxyzine will be given as one or two capsules before bedtime to minimize sedation effects during waking hours the following day.

Participants will be instructed to increase their dose at the beginning of each new week during the dose stabilization phase (weeks 1-3) of the follow-up period, if they are not experiencing adverse experiences. The titration upward will be stopped if the participant reports that the adverse experiences are unacceptable. The dose of the study drug will then be reduced to the previously tolerated next lower dose for the remainder of that week. A second attempt to increase the dose by one step will be attempted. If this produces unacceptable adverse experiences, the dose will be lowered to the next lower level and maintained for the duration of the remaining weeks of follow-up. If the participant tolerates the higher dose, doses will be increased a step every week up to a maximum of 50 mg. The titration will be governed by the following rules:

- Participants will be encouraged to take the highest dose of medication tolerated.
- If a participant reports mild to moderate sedation at a particular dose, s/he will be kept on that dose for an extra week before restarting titration.
- If the participant reports severe adverse experiences, they will be encouraged to reduce their dose by one level, but continue on the medication.
- If there are adverse experiences and there is adequate time, participants will be encouraged to try a higher dose.
- All doses should be stabilized by the end of 3 weeks.

The highest tolerated dose will be used throughout the remainder of the trial.

8.3.2 Drug manufacturing and packaging

Hydroxyzine will be purchased from a certified supplier by the drug packaging and distribution center. An adequate supply of 10mg and 25 mg capsules will be purchased, and over-encapsulated into green “look alike” capsules containing either 10 mg (Dose 1), 25 mg (Dose 2), of hydroxyzine. These green capsules, almost identical in size to the Elmiron capsules, will be packaged into blister cards, labeled separately for weeks 1, 2 and 3. The blister card for the first week will contain only one 10 mg capsule for each day. The card for the second week will contain a separate row of one 10 mg (Dose 1) and one 25 mg (Dose 2) capsule for each day. The card for the third week will contain all three doses, 10 mg (Dose 1), 25 mg (Dose 2), and 25 mg (Dose 3). An additional Week 4 card will be provided to each participant to ensure a continuous supply prior to the 3-week clinic visit, which may not fall exactly on the 21st day of follow-up. At the end of the titration period, during his/her follow-up clinic visit, each participant will receive his/her maintenance dose in a sealed bottle .

8.4 Placebo for hydroxyzine

8.4.1 Dosing schedule

The placebo capsules will be manufactured to appear identical to over-encapsulated capsules of hydroxyzine and will be taken on the same schedule of one or two capsules per day, at bedtime.

8.4.2 Placebo manufacturing and packaging

A matching placebo (identical green capsules containing microcrystalline cellulose powder only) for hydroxyzine will be manufactured centrally in one complete batch by the drug packaging and distribution center. The entire quantity of placebo capsules will be packaged into blister packs, with the same sequence for weeks 1, 2 and 3, for the titration period. Hydroxyzine placebo will be packaged in sealed bottles for the maintenance phase of the trial with the participant's five-digit randomization number on the label.

9 Concomitant Medications

Hydroxyzine should be used with caution because of increased sedation when administered together with central nervous system depressants, such as narcotics, non-narcotic analgesics, barbiturates, benzodiazepines and sedating antihistamines. Anti-cholinergics should also be used with caution because hydroxyzine may increase their anticholinergic effect and induce retention. Finally, hydroxyzine should preferably not be used with medications that inhibit the ability of the liver to metabolize drugs such as cimetidine as the serum concentration of hydroxyzine will be increased because it, too, is metabolized by the liver.

Elmiron® should also be used with caution when other drugs metabolized by the liver are administered.

9.1 Excluded Medications

Participants will be excluded from this clinical trial if they are on the histamine-2 receptor antagonist cimetidine (e.g. Tagamet) at the time of screening. Participants will be withdrawn from the study if they initiate cimetidine usage.

Participants will be excluded from this clinical trial if they are on intravesical heparin. Participants will be withdrawn from the study if they initiate intravesical treatment.

Participants will also be excluded if they report chronic use (more than 3 out of 7 days per week) at the time of screening, of greater than one gram of acetylsalicylic acid (e.g. aspirin Bayer®, Anacin®, Excedrin®, etc.). In addition, participants will also be excluded if they report chronic use (more than 3 out of 7 days per week) at the time of screening, of aspirin replacement products (e.g. NSAIDs, acetaminophen, ibuprofen, Motrin®, Advil®) of more than the amount of milligrams in the maximum single dose allowed by the Physicians' Desk Reference for prescription use, within a 24 hour period.

In addition, participants will be excluded from enrollment in this clinical trial, if at baseline screening visit 2 they report chronic use (more than 3 out of 7 days per week) of sedating

histamine-1 receptor antagonists (only those containing diphenhydramine, brompheniramine, or chlorpheniramine) (Appendix F).

10 RCT Tests, Procedures and Participant Withdrawal

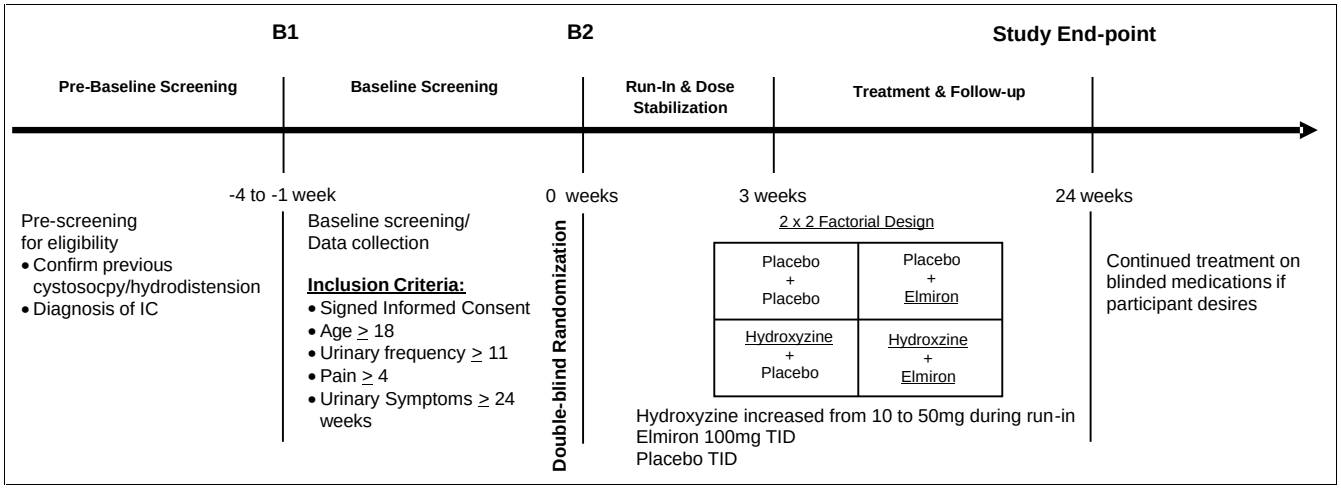
10.1 Procedural Summary

This RCT will utilize a 2 x 2 factorial design to evaluate the effectiveness of 1) placebo plus placebo, 2) placebo plus Elmiron® 3) hydroxyzine plus placebo 4) hydroxyzine plus Elmiron® in the improvement of moderate to severe symptoms of pain/discomfort and frequency in IC participants. Approximately 136 participants with clinically diagnosed moderate to severe IC will be recruited from eight clinical sites throughout the United States.

Prior to baseline screening, potential participants must have been diagnosed with IC, confirmed sometime in the past with the results from a cystoscopy/hydrodistention.

This study is comprised of two distinct phases for each participant: i) the *screening phase* and ii) the *treatment and follow-up phase* (Appendix G). The screening phase, which assesses a participant's eligibility via inclusion, exclusion and deferral criteria, will consist of two "baseline" visits no more than 4 weeks and no less than 7 days apart. Any candidate failing any of the inclusion or exclusion criteria will be considered ineligible for the protocol and treated according to usual clinical care. Some participants who initially fail study entry criteria may later be reconsidered for inclusion if the exclusionary conditions resolve (section 5.3-5.5). Any participant meeting all of the criterion will then be eligible for randomization to one of the four treatment arms. After randomization, participants are asked to return to the clinic for follow-up visits at weeks 3, 10, 17 and 24. Study medications will be dispensed at each clinic visit and participants will be asked to complete several quality of life and symptom scale questionnaires. At week 24, any participant requesting to continue on study medication will be provided masked medication until the study is closed. These participants will be followed every 12 weeks.

Figure 2. Treatment Design Schema



10.1.1 Baseline Screening Period: First Baseline Visit

Prior to any screening measure, informed consent for participation must be obtained. If consent is obtained, participants will continue with a thorough screening process (Appendix G).

The Baseline Visit 1 is considered to be conducted at –4 to –1 weeks, relative to Baseline Visit 2 (Day 0), which includes randomization. If the participant has been found to be eligible based on the data collected during this visit, s/he will undergo the Baseline Symptoms questionnaire and the following examinations: a complete medical history, physical exam, a urine sample for urinalysis and culture, a serum pregnancy test (when applicable), liver function tests (LFTs), blood coagulation tests, platelet test, and a residual urine volume test for men. Each participant will be provided with a Voiding Diary and a measuring container to take home and complete prior to Baseline Visit 2. He/she will be instructed to select a typical day and record the time and amount of each urination during a complete 24-hour period. The participant will be asked to return the completed Voiding Diary at Baseline Visit 2. In addition, the participant will be asked to maintain a daily medication diary for each week that elapses between clinic visits. These diaries will be returned and replaced with additional diaries at every clinic visit.

This screening period may not exceed 4 weeks between the two baseline visits. If a potential participant is not randomized within 4 weeks after the first baseline visit, the participant must re-enter the screening period, and have all the Baseline Visit 1 procedures and data collection repeated, in order to be considered eligible for randomization.

10.1.2 Second Baseline Visit and Randomization

At the Baseline Visit 2 (Day 0), the participant will return the Voiding Diary and complete a second Baseline Symptoms questionnaire. The participant will also

be instructed to remember his/her overall urinary symptoms on this day. He/she will be informed, that upon completion of the study, or withdrawal, whichever comes first, he/she will be asked to compare the overall symptoms experienced at Baseline Visit 2 to that at week 24. This visit must occur no less than 1 week and no more than 4 weeks after the first baseline visit. In order to meet eligibility criteria, the participant must report a voiding frequency of at least 11 times in a 24 hour day, and a pain/discomfort score of at least 4 at both Baseline 1 and Baseline 2 Visits (see all inclusion/exclusion/deferral criteria in Sections 5.3 to 5.5).

If it is determined that the participant meets all eligibility criteria, then randomization to one of the four treatment arms is implemented. Participants will be stratified by randomization site and randomized in equal proportions to one of the four treatment arms, using a randomized block design with varying block sizes.

At the time of randomization, the participant will be provided with both study medications and thorough instructions on how to take each of them. The RC must approve and document any changes in study medication dosages during the 3 week titration/dose stabilization for the green capsules. The following questionnaires will also be administered: Symptom Ranking Cards, IC Symptom & Problem Index, University of Wisconsin Symptom Survey, Health Status Questionnaire (MOS SF-36), and the MOS Sexual Functioning Scale. In addition, a urine sample will be collected, processed, frozen and shipped to the Core Pathology Laboratory, for storage (Appendix H). In addition, the participant will be asked to maintain a daily medication diary. This diary will be returned and replaced with another booklet at every clinic visit.

10.1.3 Treatment and Follow-up

Participants will return for follow-up visits at week 3 and every seven weeks following (Appendix G). At weeks 3, 10, 17, and 24 participants will complete the IC Symptom & Problem Index, the University of Wisconsin Symptom Survey, the Follow-up Symptoms form, and return the Voiding Diary and Daily Medication Diaries. The participants will receive a telephone call from the RC at weeks 1, 2, 3, 6, 14, and 20. At each scheduled contact, they will be asked about excluded/restricted medications, any possible adverse events, and initiation of IC treatments. In addition, study medication compliance will be calculated at weeks 10, 17 and 24.

At the final clinic visit on week 24, participants will be asked to complete the Symptom Ranking Cards, the Health Status Questionnaire (MOS SF-36), the MOS Sexual Functioning Scale, the Patient Close-out Form, and undergo a physical examination. Urine samples will be collected, processed, frozen and shipped to the Core Pathology Laboratory for storage. In addition, at week 24, LFTs, the blood-coagulation tests and platelet test will be performed (Appendix G).

10.1.4 Post Treatment Period

Any participant requesting to continue on study medication will be provided masked study medication until the study is closed to all accrual and follow-up visits. Every 12 weeks, these participants will be asked the Follow-up Symptoms measure, IC Symptom Problem Index, University of Wisconsin Symptom Survey, and return the Voiding Diary. Adverse events, serious adverse events, addition of excluded/restricted medications or IC treatments will also be recorded.

10.1.5 Participant Withdrawal

Under certain circumstances, a study participant may have his/her treatment terminated prior to the 24 week clinic visit. These circumstances include: unacceptable concomitant medications/treatments (e.g. cimetidine, or intravesical heparin), a positive pregnancy test, and unacceptable adverse events as determined by the Principal Investigator (P.I.). In addition, if a participant has 2 consecutive abnormal LFT tests (2.5 X's > than the respective institution's upper limits of normal) or 2 consecutive abnormal blood coagulation test results post randomization, the subject will be withdrawn. In addition, any participant who acquired a serious or life-threatening medical condition while participating in the study may have the study treatment terminated early at the discretion of the P.I. Participation in the study may also be terminated early as a result of participant dissatisfaction with treatment or participant disinterest in continued study participation.

A participant may also undergo early study termination because of a change of residence outside the driving distance of the ICCTG network.

10.2 Clinical and Laboratory Procedures

10.2.1 History and Physical Examination

Each participant will undergo a physical examination including height, weight and blood pressure. For females, the physical examination will include a bimanual exam and external genital exam. For males, this examination will include an external genital exam and rectal exam.

10.2.2 Urine Sample

Two urine samples will be obtained for the purpose of maintaining a study specimen bank containing urine collected from all participants at the Baseline 2 Visit and the week 24 visit. The urine specimens will be collected, processed, and frozen at the study site at –70° C. Periodically, the frozen urines will be shipped in batches to the Core Pathology Laboratory for central storage and future research investigating selected biomarkers. Details of procedures for urine collection, processing, and shipping are given in Appendix H.

Elevated levels of three markers of bladder mast cell activity have been found in IC urine specimens: methylhistamine, tryptase and IL-6. Methylhistamine is

the major metabolite of histamine which is released by activated mast cells. Although histamine levels were only slightly increased in spot urine specimens from IC patients, methylhistamine levels were shown to be greatly elevated, suggesting that they may serve as an important marker of disease activity. Tryptase is a proteolytic enzyme also released by activated mast cells; unlike methylhistamine which can be excreted intact into the urine, urine tryptase is thought to be specific for urinary tract pathology, and elevations in urine tryptase in IC patient specimens were therefore taken as evidence of increased urinary tract mast cell activity. However, the measurement of tryptase by itself is not as sensitive of a marker for IC as is methylhistamine, making it desirable to measure both substances. IL-6 is a cytokine which has also been shown to be elevated in the urine of IC patients, and which can be elevated in the absence of detectable mast cell degranulation. The measurement of all 3 substances should therefore provide a very sensitive indication of bladder mast cell activity.

Another marker for IC has been described which appears to be very specific and sensitive for the disease itself - a urine "antiproliferative factor" or "APF". This factor is a low molecular weight peptide that inhibits the proliferation of primary normal human bladder epithelial cells in vitro. Because the bladder epithelium is abnormally attenuated in this disease, it is thought that the APF may be causally related to the disease process. Levels of this factor by IC patients have recently been shown to be decreased following bladder hydrodistension, a treatment currently used for IC and beneficial in some patients, making it another potential indicator of disease activity.

Because the primary parameters to be measured for this study are subjective in nature, potential objective measurements of disease activity were thought to be desirable. It is thought that the first 3 markers (methylhistamine, tryptase, and IL-6) may serve as objective indicators of whether the antihistamine in this study has an effect on bladder mast cell activity, and the fourth marker (APF) may serve as an objective indicator of whether the antihistamine and/or Elmiron have a measurable effect on another aspect of the disease process.

10.2.3 Urinalysis and Culture and Other Urine Tests

The urinalysis and culture is useful in the evaluation of renal, urinary, and metabolic disorders. A chem-strip 9 will be used. The parameters that will be assessed are Nitrite, Blood, Hemoglobin, Leukocytes, and Urine Culture. A residual urine volume test will be performed on men via ultrasound or catheter.

10.2.4 Blood Draw Procedures

A serum pregnancy test will be performed on all women at risk for pregnancy (still menstruating). If the test is positive, the subject will be excluded. In addition, Liver Function Tests (LFTs) (AST, ALT, Glutamyltransferase, and Alkaline Phosphatase), blood coagulation tests (PT and PTT) and platelet test will be performed at Baseline 1, and week 24.

If either the LFTs or blood coagulation tests are abnormal on two separate occassions post randomization, the participant will be withdrawn from the study.

11 Risks and Benefits to Participants

This is a phase III, double-masked, placebo-controlled randomized clinical trial (RCT) evaluating the efficacy and safety of Elmiron®and hydroxyzine in participants with interstitial cystitis (IC). After evaluation of previous study data and physician participant records using these drugs in relation to IC, it is anticipated that there will be a direct benefit to the participants, however, direct benefits are not guaranteed. The information gained from this study may eventually prove beneficial to the treatment and diagnosis of other IC participants. Potential risks to the participants are limited to risks related to venipuncture and the use of the study drugs.

12 Adverse Events and Participant Withdrawals

The Investigator (s) will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, adverse events, or precautions pertinent to the safety of the drug under investigation.

12.1 Types of adverse events

An adverse event is any unfavorable and unintended sign, symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product (57)**.**

The term "adverse event" could include, but not be limited to, any of the following events, which develop or increase in severity during the course of the study:

- Any signs or symptoms whether thought to be related or unrelated to the condition under study;
- Any clinically significant laboratory abnormality;
- Any abnormality detected during physical examination.

These data will be recorded on the appropriate CRFs, regardless of whether they are thought to be associated with the study or the drug under investigation. (Associated with the use of the drug means that there is a reasonable possibility that the event may have been caused by the drug.)

Any event reported by the participant, other than mild sedation, that the participant considers an adverse event, will be immediately reported to the treating urologist.

Signs and symptoms will be graded by the Research Coordinator as mild, moderate, or severe.

Adverse events will be addressed at each participant visit and if noted by the participant, a detailed description of the adverse event will be recorded on the Adverse Event CRF. Adverse Event CRFs will be reviewed regularly by the DCC and reports will be produced

on a monthly basis summarizing the adverse events by clinical center and masked treatment assignment.

The following drug reactions may have been reported:

Elmiron®: Adverse events with Elmiron® tend to be infrequent, mild and transient. Known adverse events include: diarrhea, nausea, alopecia (reversible upon discontinuation), headache, rash, dyspepsia, abdominal pain, liver function abnormalities, and dizziness. The above mentioned adverse events occurred at a frequency of 1% to 4%.

Hydroxyzine: Adverse experiences seen with hydroxyzine include temporary drowsiness and dry mouth. 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, participants may have urinary retention (inability to urinate), nightmares, weight gain or some shakiness in their hands.

Placebo: Inactive agent—No adverse events expected

12.2 Serious adverse events

A serious adverse event (SAE) is any adverse event occurring during the course of a clinical investigation, whether or not determined to be related to exposure to the test article, that is fatal or life-threatening, is persistent or significantly disabling/incapacitating, requires in-patient hospitalization or prolongs hospitalization, or is a congenital anomaly. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (58)

12.2.1 Reporting obligations

Serious adverse events, whether or not unexpected or considered to be associated with the study, must be communicated to (see list below) immediately upon discovery of the event either by telephone, or fax.

The RC will evaluate the potential SAE in consultation with the corresponding clinical site P.I. The NIDDK will notify the FDA. The reporting of serious adverse events in this study will involve recording any and all SAEs on the Serious Adverse Events form. Within 1 working day the following people or groups need to be notified via phone call. In addition, a fax of the SAE form, and mailed hard copy of the SAE will also be sent to these contacts:

- Clinical Site Principal Investigator
- Respective Clinical Site IRB office
- Data Coordinating Center

The DCC will keep records of all SAE reports and report them to both the NIDDK and the External Advisory Committee. The details of the reporting of

the serious adverse events will be provided in the Study Manual of Procedures. The Investigator must promptly inform the IRB or Ethics Committee of any serious, unexpected adverse event that is considered possibly related to the study. **Serious adverse experiences (deaths) need to be reported for a period of 30 days following cessation of study medication.**

12.3 Follow-up of adverse events

All serious adverse events must be followed with appropriate medical management until resolved.

12.4 Unmasking of treatment

At the end of Baseline Visit 2, participants will be randomly assigned to one of the four treatment groups: 1) placebo and placebo, 2) placebo and Elmiron®, 3) hydroxyzine and placebo, or 4) Elmiron® and hydroxyzine, by a randomization schedule generated by the DCC. Neither the Investigator nor the investigational site personnel will know the treatment group to which any participant is randomized. If there is a serious adverse event which is thought by the clinical site staff to be possibly or probably related to the coded medication, the clinical site staff, when necessary for the safety of the participant, will unmask treatment group assignment upon conferring with the clinical site's Principal Investigator. In this event, the clinical site staff must promptly contact the DCC with an explanation of the need for unmasking the treatment group assignment. A detailed report must also be submitted to the DCC within 3 working days of the initial DCC contact by the Principal Investigator. Unmasking of treatment assignment is anticipated to be an uncommon occurance and is highly discouraged.

13 Administrative Aspects

13.1 Institutional Review Board

It is the responsibility of the Principal Investigator to provide the appropriate Institutional Review Board (IRB) with all pertinent material, including a copy of the informed consent. Approval of the protocol and the informed consent form must be obtained and forwarded to the sponsor prior to screening or enrolling any subjects. The Investigator also maintains the responsibility of initiating protocol reapproval, notification of protocol and/or consent form changes, notification of adverse reactions, and termination of the study according to the appropriate IRB requirements. A sample consent form is included in Appendix E.

13.2 Laboratory accreditation

The Principal Investigator must maintain documentation of adequate licensure or accreditation for all clinical laboratory facilities used for study samples analysis. In addition, the clinical laboratory's normal values for test results must be forwarded to the DCC prior to study initiation. This documentation should cover the entire period the protocol is active.

13.3 Sponsor monitoring/on-site monitoring

The progress of the study will be carefully monitored by an experienced site-monitoring firm, for compliance with applicable government regulations and ICCTG protocol. These individuals will have access to all records necessary to ensure integrity of the data and the regulatory documents at the clinical sites.

13.4 Compliance with agencies

The sponsor will ensure this study is performed in compliance with applicable regulations associated with the Food and Drug Administration (FDA), the International Conference on Harmonization (ICH) (56)Guidelines and the Declaration of Helsinki. The sponsor will also keep a 1572 (Statement of Investigator), and current CVs of all Principal Investigators and Research Coordinators on file.

13.5 Record retention

The DCC must maintain all trial records for a period of 7 years**.**

13.6 Direct access to source documents

Investigators will maintain, on-site, in an orderly fashion, for a period of no less than 7 years, and make available to the sponsor or the sponsor's representative, the following documents: the signed study protocol, amendments, informed consent documents, investigator brochure, approval letters from the IRB, drug accountability forms, CRFs, all primary source documentation, and all letters of correspondence.

14 Data Management and Analysis

The Data Coordinating Center (DCC) will coordinate all ICCTG activities pertaining to:

1. Design, development, production, testing and distribution of case report forms (CRFs) over the internet to the client workstations at each clinical center;
2. Collection, entry, verification, validation and query resolution of data; and
3. Quality assurance monitoring and reporting.

Data management issues, especially those concerning data quality and integrity in multicenter trials, as discussed extensively in Meinert (59) DeMets (60) Neaton (61) Bailey (62), and McFadden (63), will be addressed within the Manual of Procedures (MOP) and emphasized during the Research Coordinator (RC) training prior to protocol initiation.

The DCC will develop and maintain a computerized Data Management System (DMS) for this ICCTG Protocol, that will be deployed on client workstations within each of the main Clinical Centers and Satellite Centers. Case report forms (CRFs) will be available to be printed locally at the clinical centers from Portable Data Files (PDF). Originals of these forms will be retained by the clinical sites. Double data entry will be performed at the main Clinical Centers and Satellite Centers, utilizing the DMS tools available on the clients workstations. In particular, for the Baseline Visit 2, there will be a manual back-up system for implementing randomization of

participants, in the event the DMS system is not functional at the moment that a new randomization is required.

Validation checks will be performed at the centralized database to verify data accuracy and identify missing, unclear, illogical, or problematic responses. Queries will be generated to resolve discrepancies. Confidentiality will be strictly adhered to by assigning a unique participant identifier that will not identify the subject by name. The Manual of Procedures will define these processes in detail.

Details describing the transfer of urine specimens between the clinical sites and the Core Pathology Laboratory are presented in Appendix I.

15 Statistical Considerations

The proposed study design is a four-arm, double-blind, randomized clinical trial (RCT) utilizing a 2×2 factorial design to evaluate the effect of oral Elmiron® and/or oral hydroxyzine on IC symptoms. An inactive placebo will be used for both Elmiron® and hydroxyzine. The four treatment arms will be 1) placebo plus placebo, 2) placebo plus Elmiron® 3) hydroxyzine plus placebo 4) hydroxyzine plus Elmiron. A total of 136 participants will be enrolled. Details of the design considerations and statistical analysis, including sample size calculations, are described in the following sections.

15.1 Randomization and Stratification

The five treating Clinical Centers plus the two Satellite Centers compose the seven *Randomization Site*s. To ensure balance across treatment groups within each Randomization Site, a stratified randomization will be used. Within each of the seven strata, subjects will be randomly allocated in equal proportions to the four treatment arms using a permuted block randomization procedure with variable block sizes. In order to maintain blinding, each subject will be given a unique identifier number. The treatment code will be known only to the University of Pennsylvania Medical Center Investigational Drug Service and the Data Coordinating Center Quality Assurance Director until the completion of treatment and data collection on all participants.

15.2 Sample Size Calculations

This first ICCTG randomized clinical trial (RCT) represents a “pilot study” for which the primary goals are: (i) to demonstrate that the ICCTG network can accrue, follow and retain IC participants and collect relevant clinical trials data in an acceptable timeframe, (ii) to demonstrate safety and tolerability (including drop-out rates) for oral Elmiron®and oral hydroxyzine, and (iii) to conduct an initial efficacy evaluation of oral Elmiron® and oral hydroxyzine to determine whether any of the proposed treatments are worthy of further study in a larger comparative trial. As discussed subsequently, if there is evidence of sufficiently high efficacy for any of the proposed treatments at the completion of this pilot study, accrual to some or all of the treatment arms may be expanded to provide adequate statistical power for the comparison of response rates. Approximately 136 participants, 34 per treatment arm, will be treated and followed for 24 weeks. The total

time required for this trial will be approximately 16 months, including the 24 weeks of follow-up on all participants.

Although the primary objectives of this study are feasibility, safety and tolerability, the primary analysis on which sample size requirements are based is the comparison of response rates. Response will be defined based on the primary outcome of participant assessment of improvement as measured at 24 weeks or withdrawal, whichever comes first. Participants who report being "moderately" or "markedly" improved at 24 weeks, as compared to their overall symptoms at the time of randomization, will be considered "responders". Participants who withdraw from the study for any reason (e.g. adverse events or participant choice) will be considered treatment failures. All treatment failures will be included in the denominator for evaluation of response rates.

For each of the two primary comparisons (Elmiron® versus no Elmiron®, hydroxyzine versus no hydroxyzine), we desire adequate numbers of participants to detect a difference in response rates between 30% and 65% (difference of 35%). The baseline response rate of 30% is based on previous IC studies and other studies suggesting that this is a typical placebo rate for symptom-related outcomes. Assuming 80% power to detect the specified difference between groups at a two-sided $\alpha = 0.05$ level of significance using the Fisher's exact test, a minimum of 72 total participants are required for the two primary comparisons. After adjustments to allow for multiple comparisons in the factorial design (50% increase), clustering within Randomization Site (20% increase), and interim monitoring (5% increase), a total of 136 participants or 136/4 = 34 participants per arm will be required. Total required sample sizes for alternative response rate differences are shown in the table below.

Smaller Response Rate	Larger Response Rate								
	30%	35%	40%	45%	50%	55%	60%	65%	70%
10%	276	196	144	112	92	76	68	56	48
20%	1168	572	344	236	168	132	104	84	72
30%	-	5360	1424	664	392	260	184	**136**	108
40%	-	-	-	5952	1540	704	408	264	184
50%	-	-	-	-	-	6068	1540	688	392

In addition, for each individual treatment arm of 34 subjects, the width of a 95% confidence interval for adverse event and other rates will be no wider than ± 17.5%. It is expected that these 136 participants can be accrued within approximately 10 months. Allowing for an additional 24 weeks of follow-up on all participants, the entire study should require 16 months for completion.

15.3 Intent-toTreat Analyses and Missing Data

An *intent-to-treat* analysis, in which all available data on all randomized participants are included, will be used for the primary comparison of treatments. All attempts will be made to keep missing data to a minimum and participants who withdraw from treatment will be encouraged to continue on study in order to provide complete follow-up information. However, it is expected that up to 30% of the randomized participants may withdraw prior to the final assessment of response at 24 weeks. These participants will be included in the denominator for evaluation of the response rate primary endpoint. The characteristics at time of randomization for those participants without complete follow-up will be examined; however, there will be limited statistical power to detect any but major differences between these participants and those with complete follow-up. In addition, in order to assess the potential biases introduced by differential withdrawal among treatment arms, a comparison of withdrawal rates and time to withdrawal will be included as an ancillary analysis to the primary endpoint comparison.

15.4 Statistical Analyses

In addition to the analyses described subsequently, descriptive statistics will be used during the course of the project as part of data management procedures for monitoring data quality. A brief overview of some of the statistical methods that may be used at the time of analysis, both for descriptive purposes and in more comprehensive analysis of the primary research questions, is summarized in the following sections. It is recognized that these methods may be revised and additional ones considered as the details of the specific analyses are developed.

Descriptive Analyses: Standard descriptive statistics will be used to describe baseline characteristics and follow-up measures, both overall and within each treatment group. Examination of baseline characteristics will include estimates of the distribution of age, race, and other demographic characteristics, baseline severity based upon pain/discomfort, urgency and frequency, and Randomization Site. These factors will be examined, both separately for each of the seven Randomization Sites, and combined across centers. Summary statistics such as means, medians, and ranges will be produced for all measured variables. Frequencies will be computed for all categorical and ordinal variables. Graphical methods including stem-and-leaf diagrams and boxplots will be used to examine distributions, identify potential influential points, and guide in the choice of transformations if warranted. The balance of baseline measures across the treatment groups will be compared using appropriate 2-sample and k-sample tests including analysis of variance (ANOVA), Wilcoxon and Kruskal-Wallis tests, and Fisher's exact tests.

Analysis of Primary Outcome: The primary analysis comparing response rates will make use of the exact conditional test (ECT) version of Mantel-Haenszel methods to adjust for within-center clustering, as implemented within the Proc-StatXact software system (64). Secondary analyses of the primary endpoint will rely on logistic regression and generalized estimating equation (GEE) methods to evaluate whether observed differences, if any, are attributable to imbalances in prognostic factors such as baseline symptom severity (65). Standard regression diagnostics will be used to assess model adequacy and examine potential outlying or influential data points. In addition, time to

response will be compared among groups using standard methods for failure-time data, including Kaplan-Meier curves, logrank tests, and Cox proportional hazards modeling (66).

Secondary Analyses: A number of secondary analyses will be conducted both to evaluate the secondary symptom-related outcomes and to supplement the primary endpoint comparison. Secondary outcomes include pain and urgency measured on the Likert scales, urinary frequency and volume measures obtained from the voiding diary, the IC Symptom and Problem Index, the University of Wisconsin Symptom Survey, the Health Status Questionnaire (MOS SF-36), and the MOS Sexual Functioning Scale. Other outcomes to be used in the final assessment include withdrawal rates and the use of narcotic medications for pain control.

Profiles of symptom changes over time as collected from the symptom questionnaires and voiding logs will be compared among treatment groups using methods for longitudinal data analysis (67). These methods will include random effects regression models for continuous outcomes and GEE methods for categorical and ordinal outcomes (67). Both within- and between-participant variability in these outcomes will be carefully assessed to provide pilot data for future clinical trials. For measures obtained only at baseline and one follow-up time point, change from baseline will be compared among groups using analysis of variance (ANOVA) and regression methods. When applicable, additional analyses of the symptom outcomes will include evaluation of time to response defined by specific changes in symptoms (e.g. 50% drop in symptom score). Associations between longitudinal changes in secondary outcomes and the overall participant assessment of improvement will be used to supplement the primary endpoint analysis and evaluate the validity of the symptom scales for assessing change.

Changes in the distribution of "worst" symptoms from baseline to 24 weeks; as recorded on the symptom ranking cards, will be evaluated using a marginal homogeneity test (64). Withdrawal rates will be compared among arms using standard methods for failure-time data as described above (66). As the use of narcotic medications to control pain may provide information on the effectiveness of the treatments under study, a secondary analysis of the primary endpoint will evaluate narcotic usage. For this secondary analysis, participants who initiate narcotics or increase narcotic usage 33% or more above baseline will also be considered "failures". The secondary analysis will include these failures in the denominator for assessment of response rates and also compare narcotic usage among the treatment arms.

15.5 Data Safety and Monitoring and Interim Analyses

In addition to the final data analysis and standard monitoring for adverse events and data quality, one interim analysis will be conducted for the primary safety and efficacy data after approximately one half (n = 68) of the participants have been accrued and followed for 24 weeks. Given the projected accrual rates, it is expected that this will occur approximately 10 months into the conduct of this study. The results of these analyses will be presented to the External Advisory Committee. The goal of this analysis is to identify major differences among treatment arms that might lead to early study closure for ethical reasons. The endpoints to be considered at the interim time point include the primary response endpoint, toxicity and adverse events, and withdrawal rates. For the

primary endpoint, the Lan and DeMets (68) analog to an O'Brien-Fleming boundary (69) will be used to calculate the nominal significance level to which interim p-values are compared. Only an "upper" boundary, which allows for closure in the case of evidence of a treatment difference, will be used at this interim analysis. Assuming this analysis is conducted using 24-week data on 68 participants, corresponding to an information time of 50%, the boundary significance level to which the observed p-value will be compared is 0.0031. As described above, sample sizes have been adjusted to account for this interim monitoring.

15.6 Final analysis

The final analysis of the data will take place after the completion of accrual, follow-up, and data collection and validation on all subjects. At this time, a decision will be made as to whether there is sufficient evidence of clinically significant differences between any of the treatments to warrant expanding two or more of the treatment arms to allow adequate power to detect smaller differences in response rates. Although the sample size is based on a comparison of response rates between 30% and 65%, it is recognized that a treatment difference of this magnitude is unlikely to be observed in this study. Ideally, it would be desirable to have adequate statistical power to be able to detect a difference between a baseline response rate of 30% and a rate of 50% for an effective treatment (difference of 20%). A study to detect a clinically significant difference of this magnitude will require a total of 100 – 200 participants per arm, depending on the number of arms and including those participants in the initial pilot study.

A conditional power analysis will be used at the time of final analysis to decide whether there is sufficient evidence to continue accrual to two or more of the treatment arms (70,71) (72). This type of sequential analysis of a randomized clinical trial, also known as "stochastic curtailment", allows an assessment of the likelihood of observing a specified results in the future, given the current data and the target sample size for an extended trial. In particular, the probability of observing a difference in response rates of 30% versus 50%, if accrual to two or more arms were to be extended, can be calculated given the observed data and response rates at the time of final analysis of the current trial.

If the observed results are unlikely to change after accruing additional participants, the trial will be considered completed. Alternatively, if there is evidence that one or more of the treatments may yield a clinically significant improvement over placebo with the addition of subjects, these arms will be considered for extension. Careful consideration of withdrawal rates and adverse events will also be used to aid in this decision making.

15.7 Statistical Computing

The appropriate ASCII and SAS data files will be extracted from the Oracle database for use in statistical analysis. Primary analyses, including graphical methods, will be implemented using various commercially available statistical packages including SAS (73), (74), (75), (76), (77), (78), (79), (80) and S-plus (81). The Proc-StatXact for SAS Users software (64) will be used to compute the exact tests of discrete measures between groups. All software is currently available through the networked computing environment within the DCC.

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Appendix A

Appendix B

Appendix C

Appendix D

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Appendix F

Appendix G

Appendix H

Appendix I

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