Interstitial Cystitis Clinical Trials Group (ICCTG)

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)

MANUAL OF PROCEDURES (MOP)

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(Version 2.0)
January 31, 2000

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Manual of Procedures
Table of Contents

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 (1, 2). IC, which predominately afflicts females, is a serious health problem that leaves many patients unable to cope with basic daily functions (1-4).

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. The first randomized clinical trial (RCT) to be conducted by the ICCTG, RCT #1, will involve the evaluation of oral pentosan polysulfate (Elmiron®), oral hydroxyzine, and the combination. The study background and results of pre-clinical studies with these agents are cited in the protocol.

1 STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

1.1 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:

1. To demonstrate that the ICCTG network can accrue, follow and retain IC patients and collect relevant clinical trials 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.

1.2 Study Time Line

Approximately 136 participants, 34 per treatment arm, will be treated and followed for a minimum of 24 weeks. The total time required for this trial should 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.

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

1.3 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. Participants who withdraw from the study for any reason (e.g. adverse events or participant choice) prior to the 24 weeks endpoint exam will be considered treatment failures.

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.

1.4 General Protocol Policy

1.4.1 Changing the Protocol

The objectives of the ICCTG RCT #1 are most likely to be achieved if the protocol does not require alteration. Any changes in the protocol will result in some degree of heterogeneity of the data, which complicates the analyses and may compromise the scientific integrity of the study. However, occasions may arise in which protocol changes are necessary. Therefore, changes in the protocol will be considered only if they are required to ensure participant safety or will significantly enhance the scientific validity of the study. (5)

1.4.2 Initiating a Protocol Change

Any member of the ICCTG may request a change to any portion of the study protocol. The member wishing to change the protocol should present the proposed change(s) in writing to either the Chair of the Steering Committee or the Principal Investigator of the Data Coordinating Center (DCC), who will then contact the other. The DCC Principal Investigator and the Chair of the Steering Committee will then jointly decide on the appropriate mechanism (letter, conference call, meeting) to handle the proposal depending on the implications of the proposed change. Proposed changes with only a minor impact on the current course of the ICCTG RCT #1 can be properly handled through a letter to each member of the Steering Committee. Proposed changes with a greater impact on the course of the ICCTG RCT #1 will be presented to the Steering Committee via conference call or formal meeting to allow all members to benefit from the scientific debate generated in these discussions. Proposed changes can be implemented only after the Steering Committee reaches a majority vote and the NIDDK Project Officer approves of the proposed changes. Once a proposed change has been approved, the DCC will coordinate all activities required to implement the change via the issuance of a protocol amendment document and revised protocol.

2 STUDY ORGANIZATION

The ICCTG Study organization includes 5 main Clinical Centers, 2 Satellite Centers, and 1 Affiliate Center. In total, there will be 8 centers recruiting for this study, referred to as Clinical Sites (Appendix A). Seven of these centers (main and satellite) will have primary responsibility for participant randomization; these seven sites will be referred to as Randomization Sites. 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 in the protocol.

2.1 Clinical Site Obligations

It is expected that each site will handle the ICCTG RCT#1 with integrity, professionalism, confidentiality and with reference to GCP guidelines. The RC is expected to provide the most complete and accurate data possible. The PI is expected to not just see the participant in the clinic, but to review CRFs for accuracy, safety and quality.

The responsibilities of each clinical site include:

1. Recruiting, screening, enrolling, 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. 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.

2.2 Staffing Requirements

Each clinical site is responsible for staffing one (1) RC to coordinate all activities at the site level required to achieve the goals of the ICCTG RCT#1. The RCs play an integral part in keeping the ICCTG RCT#1 on course, and therefore every effort should be made to retain these individuals throughout the course of the study. If an RC leaves the study, however, the PI is responsible for hiring a replacement immediately to ensure overlap among the relevant individuals. The departing RC is responsible for training the replacement on issues concerning the ICCTG RCT#1 specific to the clinical site. The new coordinator should attend a 1 - 2 day training session at the University of Pennsylvania. Each randomization site is responsible for staffing one (1) Data Entry person other than the RC. This person will only perform the first data entry process and will not review the data for correctness or completeness. That is the responsibility of the RC.

2.3 Participant Recruitment Requirements

ICCTG RCT#1 requires the accrual of 136 participants across the 5 Clinical Centers, resulting in a target accrual of 27.2 (136/5) participants per Clinical Center. Since we are assuming an annual accrual rate of approximately 35 participants for each of the 5 primary Clinical Centers (includes Satellite Centers and Affiliate Center), we are expecting to reach these recruitment goals within 10 months. Allowing for a minimum of 24 weeks follow-up on all participants, this yields a total study length of approximately 16 months. Depending upon the date of the last screening visit, participants will be involved in the follow-up phase for varying lengths of time. The attrition rate will be monitored by the DCC as well as by each randomization site.

2.4 Participant Retention

The success of the ICCTG RCT#1 depends heavily on the ability of the clinical sites to retain enrolled participants throughout their follow-up phase. The onus of keeping participants interested in the study, therefore, resides in the hands of the clinical site staff. Potential ways of accomplishing this are:

- emphasizing the advantage of having a dedicated RC available to answer phone calls
- emphasizing the advantage of receiving education about IC during participation in study and having first access to clinical trials
- emphasizing the impact their participation can have on helping other IC participants
- establishing a dedicated phone line and answering machine available to study participants
- offering reduced fees to study participants
- understanding that the participants are dealing with a conditions which have a negative impact on their lives, they are voluntarily participating and they may not always meet the staff's expectations, but they are human. Compassion, empathy and understanding go a long way.

2.5 Reporting to the DCC

Reporting to the DCC will generally be accomplished in two ways: (1) sending ***copies*** of completed sets of contact packets via Federal Express, when requested; (2) reporting via e-mail. Responses to DCC requests are expected in a timely fashion.

2.5.1 Additional Sets of Forms, Upon Request

Copies of completed forms or lab results sent upon request to the DCC should ***never*** contain participant names. Clinical sites will have to be especially careful to remove participant names from lab results before sending copies to the DCC.

2.5.2 Data Audits

Throughout the course of the study, the DCC periodically will request form submission on a random selection of participants and/or forms. These internal data audits will be conducted in an effort to ensure data quality across all randomization sites.

2.5.3 Monthly Participant Count

The monthly participant count will provide accountability for all assigned Patient ID numbers. It will also give the DCC an opportunity to track the participant accrual process and to identify reasons why participants choose not to participate in the ICCTG RCT#1. Since participants who refuse participation in the ICCTG RCT#1 are not assigned a Patient ID, these participants should be tracked on the Patient Refusal Log (**REF**) form. An e-mail template will allow each randomization site to report all participant activity on a monthly basis. This will consist of a manual count of participants according to the following categories:

- eligible, fully-screened and registered participants in the database for the given month
- deferred participants
- excluded participants
- screening failures, other than exclusions
- participants who refused to participate in the study, as well as a breakdown of why participants have refused

2.6 Additional Clinical Center Responsibilities

2.6.1 Computer Hardware

All randomization sites will maintain their own computing hardware for direct data entry into the study database at the DCC. The one (1) affiliate center will coordinate the transfer of participant CRFs to the appropriate primary randomization site for data entry into the DMS. A photocopy of all forms should be made before the CRFs are sent to the randomization site.

2.6.2 Clinical Site Institutional Review Board

It is the responsibility of the PI to provide the appropriate 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 PI also maintains the responsibility of initiating protocol re-approval, notification of protocol and/or consent form changes, notification of adverse reactions, and termination of the study according to the appropriate IRB requirements.

2.6.3 Clinical Site Laboratory Accreditation

The PI 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.

2.6.4 Direct access to source documents

Each randomization site will maintain, on-site, in an orderly fashion, for a period of no less than seven (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 letter and correspondence from the IRB
- drug accountability forms
- CRFs
- all primary source documentation
- all letters of correspondence
- CVs for all PIs and RCs participating on the ICCTG RCT#1 at that clinical site. These must not be older than two (2) years
- the signed 1572 form
- ICCTG RCT#1 MOP

These documents will be reviewed by the site monitors.

3 PARTICIPANT ENROLLMENT

This chapter provides a step-by-step approach to the activities required to recruit, screen, enroll, withdraw and transfer participants in the study.

3.1 Participant Population and Recruitment

The study population will be drawn from participants with a diagnosis of IC, confirmed sometime in the past with the results from a cystoscopy/hydrodistention. Any IC participant who presents with symptoms of urinary frequency in conjunction with urinary pain/discomfort will be considered a candidate for enrollment in the study.

3.1.1 Methods of Recruitment

One of the most important factors contributing to the future success of the ICCTG is the successful recruitment and retention of participants with interstitial cystitis. Although a set number of participants accrued to each Clinical Center has not been established, each clinical site is responsible to accrue as many participants as possible. Because the best methods to achieve the recruitment goals depend largely on the organizational structures of the individual clinics, each clinical site is also responsible for determining how best to recruit participants from its local population. Some recruitment methods are described below:

- **Investigator's Own Clinical Practice**

  Many potential participants can and will be identified simply by considering the current patient population in the urology practice. The success of this method depends largely on the number of individuals who are eligible and interested in the study. When considering this as the main source of potential study participants, investigators should not only evaluate how many participants will meet the study criteria, but also what percentage will be willing to participate in and comply with the study protocol.

- **Referral from the Medical Practice of Other Physicians**

  It is likely that each clinical site will need to rely on the referral of interstitial cystitis participants from the medical practices of other urologists. In order to succeed, this method of recruitment requires the support of colleagues more than any other method. If potential referring physicians are not advocates of the study, or fear losing their participants to the study, the number of referrals will be minimal, and the method not reliable for recruiting participants.

- **Interstitial Cystitis Association Web Site**

  The Interstitial Cystitis Association will announce the study on its web site which will refer interested participants and clinicians to the geographically appropriate investigator.

- **National Institutes of Health (NIH) Sponsored Press Release**

  Approximately one week prior to the start of the ICCTG RCT #1, the NIH will arrange a press release to introduce the study to the media and the public.

- **NIH Web Site**

  After the study has been officially introduced to the media and the public, ICCTG RCT #1 will be described on the NIH web site, NIDDK division, in the section "What's New at NIDDK" and/or the "NIDDK Health Information" section.

- **Brochure for Participants and Clinicians**

  In the brochure entitled "Information for Participants", the study is described and the general eligibility parameters are discussed. Clinical sites are encouraged to use these brochures which must be approved by a local IRB. They should be stamped with the name and contact information of the study coordinator or physician's office so that participants can contact researchers who will then provide study and enrollment details. Also, these brochures may be used at health fairs and other educational and promotional events to advertise the ICCTG study.

3.2 Pre-Screening

Every potential study participant should be pre-screened in order to confirm that s/he meets the minimal necessary criteria to be eligible to participate in this study. Pre-screening may be conducted over the telephone or in person. If the initial contact is by telephone, the RC placing the call should identify him/herself and inform the potential participant how s/he was selected.

The first contact with a potential participant will describe the purpose of the study, an overview of the requirements for participation (such as restricted and excluded medications, listed in Appendix B & C, and the Patient's Daily Medication Diary), and the length of time the participant may expect to be involved in the study. If the potential participant is interested, the RC will review selected eligibility criteria with him/her. The exclusion and deferral criteria may be reviewed with the potential participant in order to reduce the number of potential participants scheduled for a Baseline Visit 1. It is important that the RC **NOT** give the potential participant complete information about the study-specific inclusion criteria requirements (the grade of severity of symptoms or the specific length of time the symptoms must have been present). The potential participant should be given a copy of the informed consent or, if telephoning, a copy should be mailed or FAXed. The form must be signed in the presence of the PI or RC. If necessary, the RC should schedule a follow-up call to allow the potential participant time to consider the study obligations and discuss the study with his/her family members.

If it is determined that the potential participant is eligible and willing to participate, the RC should schedule a time to review and complete the informed consent and schedule the Baseline Visit 1. When scheduling the visit, the RC must remember to take into account the complete study schedule for this potential participant. Two visits must be scheduled; the second (Baseline Visit 2) must be 7 – 28 days from the first (Baseline Visit 1). Based on the proposed Baseline 1 date, the RC will review the resulting time windows for each of the remaining clinic visits.

If a visit is scheduled to complete the informed consent and the Baseline Visit 1, the RC will instruct the potential participant to bring all his/her medications (prescription and over-the-counter) to that visit.

3.3 Screening Phase

The Screening Phase consists, at a minimum of two (2) screening visits: Baseline Visit 1 and Baseline Visit 2. Participants must pass the study eligibility criteria before undergoing the procedures required prior to randomization at the Baseline Visit 2.

The time between Baseline Visit 1 and Baseline Visit 2, known as Contact Week Zero, is a period of stabilizing the participant on non-study medications and measuring symptom scores at two separate visits no less than 7 days and more than 28 days apart. **If a potential participant is not randomized within 4 weeks after Baseline Visit 1, the participant must re-enter the screening period, and have all Baseline Visit 1 procedures and data collection repeated.**

When a potential participant is re-screened, all forms and procedures must be repeated, except for the Patient LOG (**PTLOG**), beginning again at the Baseline Visit 1. A re-screened potential participant has already been assigned a Patient ID number following the consent process and, therefore, should not be assigned a new Patient ID number. Some participants who initially fail study entry criteria may later be reconsidered for inclusion as the exclusionary condition/s resolve. Pregnancy and breast-feeding are examples of these resolvable conditions.

Chapter 4 provides instructions for completing all Case Report forms referred to in this section.

3.3.1 Informed Consent

The informed consent MUST be obtained before any study information is collected or any study procedures are performed. The participant must be at least 18 years old at the time of signature in order to participate in the ICCTG RCT #1. The RC should provide the potential participant with a copy of the informed consent and ask him/her to read a few sentences out loud. This will help to ascertain whether the potential participant needs assistance with understanding written material. If this is the case, the RC should offer to read the informed consent document to the potential participant or to help him/her with the more difficult sections. This participant may be ineligible due to a low literacy level, since s/he may have difficulty identifying restricted or excluded medications and may have difficulty completing the Patient's Daily Medication Diary. (Appendix B & C).

The RC should allow ample time for the potential participant to thoroughly review the consent document. It is recommended that the potential participant be asked not to sign it until after s/he discusses its contents with the RC or the PI. The potential participant should be encouraged to write down all his/her questions. In this way, it is possible to have all questions answered before s/he is asked to make a decision regarding enrollment in the study. The RC should reaffirm the participant's willingness to accept a random treatment assignment before having him/her sign the form. The consent form should then be signed by the Principal Investigator in the presence of a third party (witness).

The RC will maintain the original consent document in the participant's study file, and will provide a copy to the participant. To ensure confidentiality, the RC will not send a copy of the consent form to the DCC.

In case of a protocol revision , the revised informed consent should be used as soon as the IRB approval is obtained. Revised procedures and forms reflecting the protocol change should be used only after the IRB approval is obtained.

3.3.2 Participant Confidentiality

The participant's confidentiality will be strictly enforced by means of an assigned Patient ID number. Any communication between the DCC staff and the randomization site staff regarding participant data will occur via this Patient ID number. This number will be obtained from the log of potential participants, which is kept at the randomization site under lock and key. Potential participants are those who have completed the informed consent process and have signed the consent document. In addition, pertinent registration information (e.g., home address, telephone number, emergency contact person, etc., recorded on the Patient Contact Information form) will be maintained in a locked filing cabinet at each randomization site. The staff at the DCC will not have access to this log. Only the Patient ID number will be given to the DCC and entered into the computer. All Case Report Forms and source documents that are sent to the DCC will have all participant identifiers, other than the Patient ID number, removed.

3.3.3 Assign Patient ID Number (PTLOG)

Because all communication with the DCC regarding individual participants must be via the Patient ID number, each randomization site needs a mechanism to cross-reference the participant's name and randomization (drug packet) number. Only after the participant has signed the informed consent document will the participant be logged in the Patient Log and assigned a Patient ID number. Each participant should be assigned the next available Patient ID number. Once a Patient ID number has been assigned, it should never, for any reason, be reassigned.

A Patient Log (**PTLOG**) has been developed for each randomization site. It includes columns for unique Patient ID number for ICCTG RCT #1, participants' names and initials, and randomization (drug packet) number. The Patient Log (**PTLOG**) should be stored in a secure, locked filing cabinet. A backup copy of this log should be made at the end of every other week and the copy stored in a separate, secure location. The Patient Log is a confidential document because it ties a Patient ID number to a participant name. It will be needed in case it is ever necessary to determine a participant's treatment assignment, either during or after the study. If a participant is deferred during the screening period and satisfies the deferral criteria at a later date, s/he should be tracked using his/her original Patient ID number.

The 5 digit Patient ID number is composed of three identifiers. The first digit indicates the ICCTG protocol number. The second digit indicates the randomization site. The last 3 digits are the sequential ordering of participants. Each randomization site will have a discrete range of ID number corresponding to the randomization site number listed below. For example Patient ID # 1 1 0 1 2 describes ICCTG Protocol #1, at the University of Pennsylvania, Patient ID #012. The randomization site numbers are as follows:

1 = University of Pennsylvania (includes Graduate Hospital)
2 = New England Medical Center
3 = University of Rochester
4 = University of Maryland
5 = University of Oklahoma
6 = William Beaumont Hospital
7 = Henry Ford Hospital

3.3.4 Baseline Visit 1 (B1)

In order to participate in ICCTG RCT #1, a potential participant must meet the required eligibility criteria, as described in the protocol. These are found in three eligibility checklists (**INCL**, **EXCL**, **DEF**). These are administrative forms that are not entered into the database but are used by the RC to collect initial screening information. The Baseline Visit 1 is estimated to take two hours, not including the time allotted for informed consent.

The RC will ask the participant to complete the Patient Contact Information (**PTCONT**) form. Its purpose is to collect pertinent participant information such as full name, address, and telephone number, as well as alternative contact information. This form also serves as source documentation proving the existence of the participant. This form is kept in a locked filing cabinet separate from the participant's study file. This form is not forwarded to the DCC.

The RC will ask the participant to complete the Baseline Symptoms 1 (**BSYM1**) form. Its purpose is to determine the participant's severity and duration of symptoms for inclusion for the study. (Note: **BSYM1**, along with the Urine Screening (**URINE**) and the Lab Results (**LAB**), is entered and verified in the Data Management System after Baseline Visit 1 for eligible participants). The RC then transcribes the answers from the **BSYM1** to questions #1, #3, and #4 onto the Inclusion Criteria (**INCL**) form. If the participant is ineligible, as indicated on the form, the visit should be stopped immediately.

If the participant satisfies all inclusion criteria, the RC will administer the Exclusion Criteria (**EXCL**) form. The last three questions on this form can only be answered after the results of the blood and urine tests are known. If the participant is ineligible, the visit should be stopped immediately.

If the participant satisfies all exclusion criteria, the RC will administer the Deferral Criteria (**DEF**) form. If the participant is deferred, the RC will complete the pertinent information on this form and will record the longest possible date of deferral until the participant will be eligible for re-screening. If there are no deferral issues, the RC will continue with the screening process.
The RC will administer the Medical History (**MED**) form. The Medical History form gathers basic information about past medical conditions. It is necessary to verify the responses of the Exclusion (**EXCL**), Deferral (**DEF**), and Medical History (**MED**) forms with the participant's medical records at the recruiting site or to try to obtain the participant's records from another treatment facility.

A one-day Voiding Diary (**VOID**) will be given to the participant at B1, to be returned at B2. The RC is responsible for explaining the diary and reviewing instructions and giving a standard

urine measuring cup to the participant. The RC will check the date of the onset of a female participant's menstrual cycle to see if a pregnancy test is indicated.

At this time, the RC should review with the participant, all the medications s/he is currently taking, to determine all the concomitant medications. (This will also help determine if s/he is taking any exclusionary or restricted medications.) Be sure to note the start dates of all concomitant medications. This master list of concomitant medications can be made on a copy of the Patient Medication Diary (**PTDIARY**) or a Medication Diary Record (**DIARYREC**), and will be updated at each clinic contact in the course of the study.

The RC will photocopy the master list of concomitant medications, and provide the copy to the patient. At this point, the Patient Medication Diary (**PTDIARY**) should be presented to the participant, and the RC should instruct him or her in completing the diary, using the photocopied master list as a reference. The patient should be instructed to bring the completed diary to Baseline Visit 2.

Blood tests including AST (SGOT), ALT (SGPT), Gamma GT (Glutamyltransferase), Alkaline Phosphatase, PTT (APTT), PT, a platelet count, and a serum pregnancy test will be measured at B1. No fasting is required. Blood samples should be sent to the clinic's designated laboratory for analysis. The PI will perform a pregnancy test on all women who have not been surgically sterilized via hysterectomy or tubal ligation. The results of the blood tests should be recorded on the Lab Results (**LAB**) form. The results of the pregnancy test should be recorded on the Eligibility Confirmation and Randomization form (**ELIG**). A urine sample should be taken for dipstick analysis and sent to the appropriate laboratory for urine culture. A physical exam should be performed by the PI or his/her designee. (A physician is identified as a designee by having been listed on the FDA form 1572.) A residual urine volume should be performed by the PI or his/her designee.

If blood and urine specimens cannot be obtained at the B1, the participant can return to the participating laboratory at another time, as long as the time constraints defined previously have been met. If the physical examination cannot be performed by an ICCTG participating physician at B1, another clinic visit may be scheduled as long as the time constraints have been met. If the residual urine volume (males only) cannot be performed at B1, another visit may be scheduled. If it is determined that the participant is not eligible based on information obtained from the labs or procedures, the screening process should be discontinued.

If any conditions have been identified which make the participant ineligible, the RC will end the visit. Otherwise, the RC will remind the participant that s/he must not begin any new treatments or medications (including herbs) for his/her IC between the B1 and B2 visits. The RC will schedule the B2 visit according to the parameters described in the previous chapter.

3.3.5 Screening Failures Determined Between the B1 and B2 Visits

There are certain eligibility requirements, determined between B1 and B2, which can make the potential participant ineligible for the ICCTG RCT #1. These include:

- Liver function tests (AST, ALT, glutamyltransferase, and alkaline phosphatase) that are greater than 1.5 times the institution's upper limits of normal.
- *Blood Coagulation Values:* (PT and PTT) that are **greater** than your institution's upper limits of normal.
- *Blood Coagulation Values:* (Platelets) that are **outside** the institution's lower and upper limits of normal.
- If the results of the urine culture taken at B1 are positive, the potential participant must be deferred until six weeks have elapsed since a negative urine culture has been recorded.
- If the Voiding Diary (**VOID**) that is returned by the potential participant shows a urinary void with a maximum volume greater than 350 cc, the potential participant is not eligible for this study.

3.3.6 Deferral

If the participant is deferred at either B1 or B2, the participant must begin the screening process again, beginning at the Baseline Visit 1. This includes all data forms and procedures normally scheduled at the Baseline Visit 1. Before scheduling the next clinic visit, it is recommended that the RC contact the participant by telephone close to the ending date of the deferral period. This will give the RC an opportunity to review the study with the participant and to determine whether the participant is still interested in beginning the screening process again.

To determine the re-screening date for a participant who has been deferred for more than one criterion, the RC will select one date that allows sufficient time for all deferral criteria to have resolved.

3.3.7 Baseline Visit 2 (B2)

The Baseline Visit 2 must occur no less than 1 week (7 days) and no more than 4 weeks (28 days) after the Baseline Visit 1. This is considered Day 0 of the study. The participant must not have initiated any new treatments or medications for his/her IC between the B1 and B2 visits. The Baseline Visit 2 is estimated to take 1.5 – 2 hours.

At B2, the potential participant returns the following completed forms to the clinic:

- Patient's Daily Medication Diary (**PTDIARY**)
- Voiding Diary (**VOID**)

The participant will have been given sufficient Patient Medication Diaries (**PTDIARY**) to be completed between B1 and B2. It is important to review the Patient Medication Diary with the participant at this visit, before randomization, to ensure that s/he understands the form, and how to complete it. When reviewing the Patient Medication Diary (**PTDIARY**), the RC should update the original master list of medications.

The RC also will collect the Voiding Diary (**VOID**) which was completed by the participant between B1 and B2. The RC will check the date of onset of a female participant's last menstrual

cycle to see if a pregnancy test is indicated. The RC will review the diary to determine if any void greater than 350cc would make the participant ineligible. This is an exclusion criterion. If the participant is ineligible, the visit should be stopped immediately. As with the Patient's Daily Medication Diary, the RC will review the Voiding Diary (**VOID**) while the participant is still in the clinic. The RC will note any errors and review instructions for completing the Voiding Diary with the participant.

The RC will give the Baseline Symptoms 2 (**BSYM2**) form to the participant, for completion. Its purpose is to determine participant's severity and duration of symptoms for inclusion for the study. (Note: **BSYM2**, along with the Crosscheck form (**CRSCK**) is entered and verified in the Data Management System during Baseline Visit 2 for eligible participants). The RC also transcribes the responses to questions #1 and #3 onto the Inclusion Criteria (**INCL**) form. If the participant is ineligible, the visit should be stopped immediately.

The RC will review with the participant the Exclusion Criteria (**EXCL**) form that was administered at B1. The RC will determine whether there have been any changes that would make the participant ineligible at this time. The last three questions on this form can only be answered after the results of the blood and urine tests are known. This should be completed prior to B2. If the participant is ineligible, the visit should be stopped immediately.

The RC will review with the participant the Deferral Criteria (**DEF**) form that was administered at B1. The RC will determine whether there have been any changes that would require a deferral period. If the participant is deferred, the RC will complete the pertinent information on this form and record the longest possible date of deferral until the participant will be eligible for re-screening. If there are no deferral issues, the RC will continue with the B2 visit.

The results of the screening process (**INCL**, **EXCL**, **DEF** from both B1 and B2) should be transcribed onto the Eligibility Confirmation and Randomization (**ELIG**) form. When the RC is confident that the participant is eligible to participate in ICCTG RCT #1, the RC should provide a quiet location for the participant to complete the symptom questionnaires while the RC is conducting the randomization process, which requires computer interaction. The following symptom questionnaires are required at the B2 visit:

- IC Symptom & Problem Index (**SYMPROB**)
- Health Status Questionnaire (**SF-36**)
- MOS Sexual Function Scale (**MOS**)
- University of Wisconsin Symptom Survey (**UNIVWIS**).

The participant should also complete the Demographics (**DEMO**) form at this time. Because the Symptom Ranking Cards (**CARDS**) form requires special instructions to the participant, it is recommended that these be completed after randomization when the RC and the participant are together.

3.3.8 Computer Randomization

At Baseline Visit 1, eligible patients are registered, into the Data Management System (**DMS**). Eligibility data collected at B1 (specifically the **BSYM1**, **URINE** and **LAB** forms) is entered and verified by the data entry person and the RC respectively, prior to the participant's B2 visit.

At Baseline Visit 2, if the participant meets all the eligibility criteria, the participant's eligibility data at B2 (specifically the **BSYM2** and **CRSCK**) is entered by the data entry person and verified by the RC. If the data entry person is unavailable at the time, a guest account is available to all the clinical centers for this process only. The RC then completes the on-line randomization process by entering the Eligibility and Randomization form (**ELIG**).

Only eligible participants can be randomized, and the system is designed to prevent ineligible participants from being randomized. If the eligibility data for a participant proves a participant is ineligible,, the system will not allow data entry. If the data entered is consistent with the requirements for randomization into the study, the computer application will assign a five-digit randomization number. This number will correspond to the drug packet number of all medications dispensed to the participant. The actual treatment that the participant is given will only be known to Penn Investigational Drug Service (**IDS**) and the DCC's Quality Assurance Director, for purposes of unmasking. If the computer system is non-functional at the time of a participant's randomization, a manual backup system has been established.

3.3.9 Back-up Randomization

In the case of a computer failure during randomization, the RC will call the DCC randomization pager number (**215 374-9931**), which will be available from 0900 to 1800 EST, Monday through Friday. A member of the DCC team will return the phone call and ask the RC all the questions on the Baseline Symptoms 2 (**BSYM2**), Crosscheck (**CRSCK**) and Eligibility Confirmation and Randomization (**ELIG**) forms, including the randomization (drug packet) number of the most recently randomized participant (the last randomization number assigned). The DCC representative will also ask the RC if data for B1 visit has been entered and verified. When the DCC representative confirms the participant's eligibility, the DCC representative will assign the next randomization number. At the earliest possible time, the DCC representative will enter the Baseline Symptom 2 (**BSYM2**), Crosscheck (**CRSCK**) and Eligibility Confirmation and Randomization (**ELIG**) data into the database. When the computer system at the randomization site is again operational, the RC should verify with the DCC that the database has been updated since the telephone randomization was performed, prior to entering data on new participants.

3.3.10 Continuing with B2 after Randomization

It is important that the RC review carefully each of the symptom questionnaires to make sure each question has been answered. The RC will ask the participant if s/he had any problems completing the forms and address these issues with him/her. If the Symptom Ranking Cards (**CARDS**) have not been completed, the participant should complete them at this point. All other data collected at the screening visits will be entered and verified on the computer as soon as possible. Administrative forms completed to process the visit and the collected data will be completed and a participant binder will be organized.

A sufficient number of Patient Medication Diaries (**PTDIARY**) should be distributed at the end of B2, to be completed by the participant between B2 and the next clinic contact at week 3. A photocopy of the updated master list of concomitant medications should be provided to the patient, for reference when completing the next set of diaries.

After the B2 contact, the RC should complete a Medication Diary Record (**DIARYREC**) form to include all medications the patient was taking at the time of randomization. This **DIARYREC** form should be marked "Administrative", as it does not get entered into the database. (**NOTE**: The **PTDIARYs** and **DIARYREC** completed for the screening contact are considered reference copies. However, they should still be kept with your patient's study binder, and copies sent to the DCC when requested.)

A thorough review of treatment procedures is described in Chapter 6.

3.3.11 Scheduling Telephone Contacts for the Run-In Phase

At the conclusion of B2 and before the participant leaves the clinic, the RC will schedule with the participant a date and time for the Run-in Phase telephone contacts. These appointments must be on (or as close to as possible) Day 8, 15 and 22, where the Baseline Visit 2 is considered Day Zero (0). Calls for the Run-in Phase should not be made before their due date.

Week 3 telephone contact on or after day 22 should be used to determine the maintenance dose for hydroxyzine or hydroxyzine placebo in order to get medication blister packs from Penn IDS, and to also confirm the Week 3 clinic visit, which should be scheduled between days 23 and 28.

3.3.12 Scheduling the Week 3 Visit

At the end of B2, the Week 3 clinic visit should be scheduled. In order to allow the participant to take the study medications for the full three weeks, this visit should be scheduled between days 23 and 28. The RC should remind the participant that s/he must not begin any new treatments for his/her IC. The RC will review the restricted and exclusionary medications (Appendix B & C). The RC will counsel the participant to call the RC with any unexpected problems.

3.4 Run-in Phase

Weeks 1 through 3 are considered the Run-in Phase of the study. The purpose of the Run-in Phase is to establish a maintenance dose of hydroxyzine or hydroxyzine placebo (green study medication). It is important that the participant attempt to achieve the maximum tolerated dose (two capsules total: one from column 2 and one from column 3) of the green capsules by the end of the Run-in Phase. The dose that the participant is taking at the end of the Run-in Phase will become his/her maintenance dose for the remainder of the study, barring any complications.

3.4.1 Telephone Contact and Monitoring of Dosage During the Run-in Phase

It is important that the participant communicate to the RC any unwanted side effects that would affect his/her compliance with the recommended dose. These side effects (Adverse Drug Reactions) should be recorded on the Adverse Event/Serious Adverse Event (**AESAE**) Form. Expected Adverse Drug Reactions (**ADRs**) listed in section 7.3 should not be recorded as Adverse Events/Serious Adverse Events (**AESAEs**). Through close monitoring and consultation, and upon PI approval, the RC can recommend a change in dosage. Telephone contacts between the RC and the participant are scheduled at the end of Week 1, Week 2, and Week 3. These regularly scheduled telephone contacts will be recorded on the Telephone Contact (**PHONE**) form. Information obtained about dosages during these telephone calls should be transcribed to

the Run-in Dosage Record (**RUNIN**). This form is also used to record the actual daily dose of the green capsules during the Run-in Phase.

In the event that a participant discontinues study medications due to a non-study condition during the run-in phase, the PI / RC will follow these guidelines in terms of re-titrating a participant on medication:

Study Drug	# of days off study drug	Result:
White pill	Any time limit	Restart participant at same dose
Green pill	< 3 days	Restart participant at same dose
Green pill	> 3 days, but < 7 days	• If participant was on 10 mg, restart at 10 mg; • If participant was on 25 mg, restart at 25 mg; • If participant was on 50 mg, restart on 25 mg for 2 days and then increase to 50 mg
Green pill	> 7 days	Participant is taken off drug for remainder of study.

3.4.2 Determining Final Dose and Ordering Week 4-11 Drug Supply

The dose that the participant is taking at the end of Week 3 (day 22) is documented on the Run-in Dosage Record (**RUNIN**) during the Week 3 telephone contact. This dose becomes the maintenance dose for the remainder of the study. The RC will notify Penn IDS of the dosage of green medication that should be dispensed for Weeks 4 – 11 via the Drug Request FAX sheet.

3.4.3 Week 3 Clinic Visit

The Week 3 visit should be scheduled as close as possible to day 23 but not on or before day 22. This date must also be coordinated with the shipping date of the study drug Penn IDS.

At this contact, the RC will collect and review for completeness the Patient Medication Diary (**PTDIARY**). When reviewing the diary, the RC should again update the original master list of medications. The RC should also, double check the white and green pill usage against the Run-in Dosage Record you have been completing for the week 1, 2, and 3 telephone contacts.

The participant should be given a sufficient number of Patient Medication Diaries to be completed between week 3 and next clinic contact at week 10, as well as a photocopy of the updated master list of concomitant medications, for reference.

Based on the Patient Medication Diary (**PTDIARY**) returned at week 3 and the administrative Medication Diary Record (**DIARYREC**) completed at B2, the RC should complete the Medication Diary Record (**DIARYREC**), to be entered into the database as follows:

- Record the ICCTG RCT#1 study medications
- Record all concomitant medications listed on the Administrative **DIARYREC**, from screening
- Record anything the patient has started, changed, or stopped since randomization, from the **PTDIARY**

The RC will also collect a Voiding Diary (**VOID**) which has been completed between the B2 visit and the Week 3 visit. The RC will review this form for accuracy and completeness and will review instructions with the participant, as needed. The RC will check the date of onset of a female participant's menstrual cycle to see if a pregnancy test is indicated.

See the Visit Schedule (**VTSCH**) for symptom questionnaires to be completed during this visit, and check instructions on how to complete the Standard Visit Inventory (**STVISIT**) form.

At the end of this visit, the RC will schedule a time for the Week 6 telephone contact and the Week 10 clinic visit. The RC will remind the participant not to begin any new treatments for his/her IC and will again review the restricted and excluded medications. (Appendix B & C).

3.5 Follow-up Phase

The Follow-up Phase consists of Weeks 4 though 24 of the study.

3.5.1 Follow-up Visit Schedule

Upon conclusion of the randomization process, the Data Management System (**DMS**) will generate a Patient Follow-up Contact Schedule to aid the RC in scheduling all follow-up contacts with participants. The Patient Follow-up Contact Schedule will be generated for each participant according to the date of the randomization (Day 0). This schedule indicates the sequence of follow-up contacts, target dates for each contact, and time windows in which the contact must be completed. At the close of each clinic visit, the RC will schedule the next phone contact and clinic visit, by referencing the Patient Follow-up Contact Schedule.

The *target date* for any follow-up contact is calculated by adding the correct number of days to the date of the participant's Baseline Visit 2 (randomization date). The *time window* for any follow-up contact is the time frame in which the contact should be completed. The time window for all contacts is defined as the interval of time starting on the target date and ending 7 days after the date of the contact. All dates are determined from the date of the Baseline Visit 2 (randomization date), without regard to whether they fall on a weekend or holiday.

3.5.2 Visit Windows and Missed Study Contacts

The visit schedule (Follow-up Contact Schedule) generated by the computer program lists the desired windows of +7 days. Days refer to calendar days, not business days. For purposes of scheduling initial clinical visits, there is no extended window beyond the +7 days. A participant must come to the clinic to make up a missed contact. This visit must be scheduled at the earliest available time and if possible, within the +7 day window. It is desirable to schedule initial visits early in the visit window in the event that it is missed due to unforeseen circumstances. If at all possible, a visit should not be split up so that some tasks are performed on a different day.

3.5.3 Telephone Contacts During Follow-up Phase

Each participant will receive a telephone call from the RC at Weeks 6, 14, and 20. The Telephone Contact (**PHONE**) form should be completed during the phone call. The Adverse Event/Serious Adverse Event (**AESAE**) Form is completed, as needed. It is recommended that the participant have his/her Daily Medication Diary (**PTDIARY**), completed to date, available during this telephone contact.

3.5.4 Clinic Visits During Follow-up Phase

These visits occur at Weeks 10, 17 and 24. The RC will collect a Voiding Diary (**VOID**). The RC will review this form for accuracy and completeness and review instructions as needed. The RC will check the date of the onset of a female participant's menstrual cycle to see if a pregnancy test is indicated. If indicated, **AESAE** form may be completed and Labs ordered. Lab results will be recorded on the **LAB** form.

At each follow-up clinic visit, the RC should collect and review the Patient Medication Diary (**PTDIARY**), double-checking the white and green pill usage against the pill count on the Standard Visit Inventory. The original master list of concomitant medications should be updated, and a photocopy of this list should be given to the participant with a sufficient number of Patient Medication Diaries (**PTDIARY**) to be completed for the next clinic contact. The RC should then complete the Medication Diary Record (**DIARYREC**), recording any changes in the ICCTG RCT#1 study medications or any concomitant medications that were started, changed, or stopped, as indicated in the Patient Medication Diary (**PTDIARY**)

3.5.5 Symptom Questionnaires

Each participant will complete a series of symptom questionnaires at each of the follow-up clinic visits, accordingly:

<u>Clinic Visits at Weeks 3, 10, and 17:</u>

- Follow-up Symptoms (**FUSYM**)
- IC Symptom & Problem Index (**SYMPROB**)
- University of Wisconsin Symptom Survey (**UNIVWIS**).

<u>Clinic Visit at Week 24:</u>

- Follow-up Symptoms (**FUSYM**)
- IC Symptom & Problem Index (**SYMPROB**)
- University of Wisconsin Symptom Survey (**UNIVWIS**)
- Health Status Questionnaire (**SF36**)
- MOS Sexual Functioning Scale (**MOS**)
- Symptom Ranking Cards (**CARDS**)

3.5.6 Standard Visit Inventory (STVISIT) form:

The purpose of this form is to collect information regarding compliance and dispensing, other IC treatments, and any adverse events or changes in non-study medications.

Part One: Capsule Counting and Compliance

Beginning at the contact visit at Week 10, capsules are returned and counted at each visit and compliance is calculated (see Part One, **STVISIT** form). When counting the capsules, it is advised to do so in front of the participant. This helps the participant to understand the compliance process and aids in compliance. When determining compliance, always round

fractional capsule quantities to the next highest whole number. Low adherence is considered when the compliance percentage is less than 80%. Participants with high levels of compliance should be commended. If the compliance percentage is below 80%, the RC should counsel the participant for non-compliance.

Counseling for Non-compliance: The RC should remind the participant that compliance with study medication is one of the most important aspects of the study and a part of the commitment s/he made to the study. The RC should point out that the study is designed to look at the effect of taking these medications. If participants do not take the medication as prescribed, they may lose the potential benefits of the medications. In addition, the study results may be inconclusive or misleading.

Part Two: Drug Dispensing

Throughout the study, a record of all medication dispensed (and received) will be recorded on the administrative form, Study Medication Tracking Log (**MEDTRAC**). In addition, labels taken from the bottles will be transferred to Part Two of the Standard Visit Inventory (**STVISIT**) form. Enough medication for an eight weeks' supply of both green and white capsules will be dispensed.

3.5.7 Additional Visits

Additional visits may be required for the participant's normal medical care. However, except for recording Serious Adverse Events, data forms need not be completed for additional visits.

3.6 Continuing on Study Medication After Week 24 - Post Treatment Follow-up Phase

Each participant who continues on study medication through Week 24 is given the option of continuing on masked study medication at the Week 24 visit. This is the only time the participant is given this option. Enough medication will be dispensed for 13 weeks. Participants will return for clinic visits every 12 weeks and the following forms will be administered in the same way as during the follow-up period: Follow-up Symptom measure (**FUSYM**), IC Symptom & Problem Index (**SYMPROB**), University of Wisconsin Symptom Survey (**UNIVWIS**). The participants also will be given the Voiding Diary (**VOID**) to complete at any time before the next clinic visit, when it will be returned. The **PTDIARY** and **DIARYREC** are not completed during post study follow-up phase, but the **MEDTRAC** form is completed at each clinic visit. Please refer to the Visit Schedule (**VTSCH**) for the list of data completion forms and administrative forms completed at each post study follow-up clinic contacts.

3.7 Participant Withdrawal or Transfer

3.7.1 Participant Discontinues Study Medication

When a participant discontinues study medication for the reasons listed below, the following forms should be completed:

- Study Medication Tracking Log (**MEDTRAC**)
- Medication Diary Record (**DIARYREC**)
- Clinical Center Stop Point (**STOP**),

- Patient Close-out (**PTCLOSE**)
- Study Close-out (**STCLOSE**)

Study participation may be discontinued for any of the following reasons:

- The use of unacceptable concomitant medication/s (the inadvertent use of one or two doses of cimetadine is acceptable)
- A positive pregnancy test
- Two consecutive abnormal LFT tests (2.5 times the institution's upper limit of normal)
- Two consecutive blood coagulation tests, outside the institution's limits of normal.
- Discretion of the PI
- Transfer outside the driving distance of the ICCTG network
- Participant choice or noncompliance

If the participant is withdrawn from the study because of laboratory tests or an adverse event, the Lab Results (**LAB**) and the Adverse Event/Serious Adverse Event (**AESAE**) forms should also be completed.

For participants who are withdrawn from the study treatment, the RC should make every attempt to encourage the participant to continue with the study schedule of follow-up visits and administration of symptom questionnaires. This is in line with the "intent to treat" design of the study.

If the participant refuses to come in to the clinic for a final close-out visit, a note on the Study Medication Tracking Log should indicate the disposition of the remaining study medication, if applicable, and the date the participant was last contacted by the Research Coordinator. Participants should be told to return any remaining study medication to the clinic.

3.7.2 Participant Withdraws Consent

If a participant indicates that s/he no longer wants to participate in the study (withdraws consent), the RC will provide a letter on the institution's letterhead for the participant to sign. If this document is mailed to the participant, it must be sent certified mail. The certified mail receipt should be kept with the participant's records. The letter should contain the following information:

- I voluntarily withdraw my consent to participate in this study.
- I no longer wish to be contacted by the clinic regarding this study.
- I understand that my records will be kept confidential.
- I will continue to receive my regular care and treatment at this clinic.

3.7.3 Participant Transfer

It is possible for an ICCTG study participant to transfer to another ICCTG participating randomization site during the course of the study. However, it is preferred, from a scientific as

well as operational point of view that a participant completes the study at the same randomization site in which s/he was enrolled.

3.7.3.1 Transfer of a Participant During the Screening Phase

It is highly recommended that participants not be transferred during the screening process. However, if a participant indicates his/her desire to transfer to another ICCTG participating site during the screening phase (between B1 and B2), then s/he must do the following:

- Complete B1 at the Originating Center.
- Complete B2 at the Receiving Center.
- Maintain this transaction within the time constraints of the screening period, which is no less than 1 week (7 days) or more than 4 weeks (28 days) between B1 and B2.

3.7.3.2 Transfer of a Participant During the Follow-up Phase

It is important that a participant who has been registered at a particular randomization site retain his/her original Patient ID number and ICCTG participant study file throughout the entire study. If a participant indicates his/her desire to transfer to another ICCTG participating randomization site during the follow-up phase (after randomization), the RC must adhere to the guidelines described below.

3.7.3.3 Responsibilities of the Originating Center RC During the Transfer of a Participant

The RC at the Originating Center must complete page 1 of the Participant Transfer (**TRANS**) form. Instructions for completing this are described in the next chapter.

The RC at the Originating Center must provide the participant with contact information about the Receiving Center. Scheduling the first clinic visit at the Receiving Center can be done, either by the participant, or the RC at the Originating Center. The date and contact week number of the first scheduled clinic visit at the Receiving Center is recorded by the RC at the Originating Center on the (**TRANS**) form.

A copy of the Participant Transfer form must accompany the shipment of the participant's study file and remaining study medication to the Receiving Center.

3.7.3.4 Responsibilities of the Receiving Center RC During the Transfer of a Participant

The Receiving Center RC must complete page 2 of the Participant Transfer (**TRANS**) form. The Receiving Center RC must create a new ICCTG participant study file to contain the records that have been shipped from the Originating Center.

It will be the joint responsibility of both the Originating and Receiving Center's RCs to ensure the completeness and accuracy of the participant's ICCTG study file.

The participant should request that a copy of his/her medical records be sent to the Receiving Center. Copies of all transfer forms must be sent to the DCC.

4 DATA AND ADMINISTRATIVE FORMS

4.1 Personnel ID Numbers

Each member of the randomization site staff involved in data collection for the ICCTG RCT #1 will be assigned a unique identification number. This number is used to identify the individual responsible for completing or reviewing a form.

4.2 Acquisition of Forms from the DCC

The Case Report Forms (**CRFs**) are provided to the randomization sites in electronic format as **PDF** (portable document format) files. The randomization site is responsible for printing all data and administrative forms. The forms necessary for each contact are grouped together, in order to streamline the printing process.

4.3 General Instructions for the Completion of Data Forms

There are two types of forms being used for this study: Data Forms (which contain participant data and are entered in the database) and Administrative Forms. The RC should always verify the forms in a packet against the corresponding Contact Checklist to confirm that all forms are available before the participant arrives for the visit, or before a telephone contact is made. For any missing forms, the RC will be able to print a copy from the PDF file. The DCC will make available the current version within the application files.

All CRFs should be completed in ***black*** ink. Pencil, blue ink or red ink is ***not*** to be used. No answers should be left blank. **UNK** should be filled in any space left unanswered. When the participant is not sure of an answer, s/he should use his/her "**best estimate**" rather than leaving the question unanswered. It is important that the RC completes the heading of the CRF ***before*** continuing with the form to insure easy identification in case of separated pages. There are two types of headings for the CRFs. Master headings are on the first page of all CRFs and the abridged heading is found on subsequent pages of multiple-page CRFs. The Patient ID number will come from the Patient Log (**PTLOG**). The RC is responsible for reviewing all the completed forms. All personal identifying information should be removed from lab or procedure reports before forwarding copies to the DCC. All source documentation sent to DCC should have all personal identifying information removed or “blacked out” and the study identifying information (Patient ID and Patient Initials) should be recorded.

4.3.1 Forms Completion

On the left, under the heading is a subheading, which indicates by whom the form is to be completed: Participant completed, Participant Interview completed, Principal Investigator completed, Research Coordinator completed or a combination of these. Instructions for each of these options are described in the next sections.

4.3.2 Participant Completed Forms

Forms with the subheading "Participant completed" are to be completed by the participant. The RC should be readily available in case of any questions. Before the participant leaves the clinic, the RC should review the forms for completeness. If the RC believes that the participant may have trouble reading the forms, the RC may interview the participant to complete the forms.

Since the participant may find some of the information on the forms to be sensitive, whenever possible, the participant should be encouraged to complete the forms alone.

Once the RC reviews the form, the RC should complete the RC ID number in the top right corner of the master heading of the form.

4.3.3 Participant Interview Completed Forms

These forms are NOT to be completed by the participant, but are designed to be administered to the participant by the RC. The forms are completed by interviewing the participant and asking specific questions found on the forms.

The RC is responsible for getting an appropriate answer from the participant if the participant's answer is unclear, incomplete, or irrelevant. If this occurs, the RC should use the "probing" technique used by interviewers to refocus and redirect the participant's attention to the question. The interviewer should get the participant to elaborate or reconsider an incomplete or inappropriate answer without leading the participant or influencing the content of the answer (creating bias in his/her answer).

Some questions addressed in the CRFs are personal and may be very sensitive issues for the participant. When a participant shows reluctance in answering a question, the interviewer should reassure the participant regarding the confidentiality of the response and explain the importance of the question. The RC should review the form for completeness and legibility before the participant leaves, in case additional information or clarification is required.

4.3.4 Research Coordinator Completed and Principal Investigator Completed Forms

Forms indicated as Research Coordinator completed should be completed ***only*** by the RC. PI completed forms should be completed by the PI or the PI's designee. All forms that are to be completed by the RC or the PI should be completed during the contact unless awaiting a necessary lab report.

Upon the completion of all PI completed forms, the RC should review the form for completeness and legibility, and complete the RC ID number in the upper right hand corner of the form. The PI should initial the form, for documentation.

4.3.5 Review of Completed Forms

The RC should review all forms for legibility, accuracy, and completeness ***before*** they are entered into the database. The Data Processing Cover Sheet (**DPCS**) will assist in documenting the review, entry, and verification process. If the RC identifies an error while reviewing the forms, the error should be corrected on the current form by crossing out the error with a single line in **black** ink, entering the correct information, initialing and dating the change. The RC should circle the correct answer for clarification, if necessary.

4.4 Directions for Completing Case Report Forms

This section provides specific instructions on how to complete each CRF. ***The forms are addressed in alphabetical order by form title.*** If, after consulting this section, you are still unsure of how to complete the form, please contact the ICCTG Data Managers at the DCC.

4.4.1 Adverse Event / Serious Adverse Event (AESAE)

Purpose: To collect information concerning any Adverse Event(s) (**AE**) or any Serious Adverse Event(s) (**SAE**) that the participant experiences during the course of the trial, ***except those specified in the protocol as known Adverse Drug Reaction(s) (ADR). ADRs can be tracked by the clinical centers, if they so wish, but are not included on the AESAE form.***

Note: **Any AE/SAE reported by a participant once s/he is randomized (*even if no study drug has been taken*) MUST be recorded whether or not the participant thinks it is significant. *****

Who: RC and PI completed; PI determines the grading.

When: The RC completes a form each time a participant experiences an AE/SAE, either reported during a Phone Contact or during a Clinic Visit, or if the participant contacts the study personnel to report an AE/SAE, between Phone Contacts or Clinic Visits.

A new form is used at each contact/visit.
Multiple AE/SAEs can be reported on the same form during a single Phone Contact or a Clinic Visit.

General Directions:

Questions on the Telephone Contact **(PHONE, Q. #s 3 and 4)** form and the Standard Visit Inventory **(STVISIT, Q. #s 7 and 8)** form can prompt the participant to communicate the occurrence of AE/SAE(s) or other medical conditions since the last contact.

If an AE/SAE warrants a laboratory test, report any clinically significant laboratory result on the Lab Results **(LAB)** form.

For an SAE, a copy of the completed **AESAE** form should be faxed to the DCC **within one (1) working day**.

Contact Week information in the upper right hand corner would be the current contact/visit number in case of a Phone Contact or a Clinic Visit. If a participant contacts the RC between contacts/visits, the ***next*** contact/visit number is entered in the ***Contact Week*** information. For example, if the form is completed between the Clinic Visit at Week 10 and the Phone Contact at Week 14, the ***Contact Week*** is entered as "14".

Adverse Event Number**, "AE __ __ __":* This is a sequential number which begins with "001", "002", "003", etc. These sequential numbers ***DO NOT repeat for the duration of the study, even though the participant may report repeat AE symptoms at different visits.

***Date of Onset**:* Record the date of onset of symptoms that the participant experienced, even if the event lasted one day or less.

***Duration**:* Using the code provided in the column, record whether the episode lasted for minutes, hours or days.

***Frequency**:* Using the available codes in the column, record the frequency of the episodes.

Grade**:* The PI will grade the episode, after evaluating what the participant has reported against the CTC description, using the CTC grade that ***most closely matches the participant's description of the AE/SAE.

- In AESAE version 5.1, dated 9/16/99, the codes range from 0-5, with 1 being mild and 5 being fatal. A code of 9 is used if Grade coding is not applicable to a particular event; a code of 0 implies no grade.
- For ***each*** CTC system organ class category there is a code for "other". Use this if you cannot find an event in that system organ class which matches the participants symptoms.

Relationship to Study medications**:* The RC will record whether the adverse event, ***in the PI's estimation, was related to either of the study medications, by using the codes provided in the column.

Treatment for Adverse Event**:* The RC will code whether the participant received ***any form of treatment from a physician for the event.

- Home remedies or over-the-counter medications taken ***without*** consulting a physician or a pharmacist should be noted on the **PTDIARY** and **DIARYREC** but are ***not*** considered treatment for coding purposes on **AESAE**.
- Recommended treatments or prescribed medications by a physician for the symptoms of AE/SAE(s) are coded as treatments, even though the participant may later choose ***not*** to follow medical advice or take the prescribed medication.
- Medication taken for any AE/SAE must be recorded on the Patient's Daily Medication Diary (**PTDIARY**) and transcribed to the Medication Diary Record (**DIARYREC**) for data entry.

Did Reaction Abate After Stopping Study Medications?: Using the codes in the column, the RC, *in consultation with the PI*, will code his or her observation. This question applies to ***study drugs only*** and not to drugs received for a reported AE/SAE. Appropriate code should be 9 for Not Applicable, if study medications are not stopped.

Did Reaction Reappear After Stopping Study medications?*:** Using the codes in the column, the RC ***in consultation with the PI will code his or her observation. This question applies to ***study drugs only*** and not to drugs received for a reported AE/SAE. Appropriate code should be 9 for Not Applicable, if study medications are not stopped.

Outcome:

- ***Recovered*:** Use this code if a previously recorded or current AE/SAE has been resolved.
- ***No-follow-up*:** This code is used for lost-to-follow-up participants and for conditions still present at study close out.
- ***Ongoing*:** This code is used if a condition is not resolved/on-going. Because this category exists, ***the RC should review all previously reported AESAE forms at every contact/visit.***

To resolve an AE/SAE that was coded as #3 in a previous visit/contact, the RC should do as follows:

> If an AE was originally coded as '3' but at another visit/contact is reported to be resolved, then you will use the next available sequential AE# and record the same CTC event code as the original AE. In this situation you will now use a code of 9 (not applicable) to describe the duration, grade, frequency etc. For outcome you will use a code of 1 (recovered) and in the description box you will write "AE#00X is recovered" along with any other information you believe is critical.

If a **previously reported** AE/SAE still exists at the next visit/contact but has changed in ***grade,*** this changes the previous event to a completely new AE/SAE. To resolve this, the RC should do as follows:

> The RC should "close out" the original AE# the date the change in grade is reported by the participant to the RC. This is done by starting a new AE# (next sequential number available). Record the same CTC event code as the original AE# and using the codes for all the other columns as applicable to the new reported event. In the description box you will write "AE#… is closed" along with the description of the new event.

***<u>Note</u>*:**

Coding 7: **DO NOT USE 7 FOR ANY OUTCOME (see coding 6).**

Event Code: Identify the Event Code number by referring to the coded list of Common Toxicity Criteria (CTC) which has been provided in the Manual of Procedures. (See Appendix D).

Specify Event: This information is linked to the Event Code. When completing the form, write the Event Name specified in the CTC for the event code being used. The same event name is provided ***automatically by the computer*** when the Event Code # is entered by hitting the **TAB** button during data entry/verification.

Description of Event/Comment: The RC describes the condition based on the information provided by the participant. ***Key words*** from the conversation with the participant should be included in the description for monitoring purposes. Anything transcribed directly as the patient explained should be set apart by quotation marks " ".

Was the Event Serious?: If the answer to "Outcome" column is coded *4 through *10, the ***event is serious***. This reported SAE requires a PI signature and date, and a MedWatch form ***must*** be completed.

4.4.2 Baseline Symptoms 1 (BSYM1)

Purpose: To collect information regarding the participant's assessment of his/her general urinary discomfort and/or pain, urgency, frequency, and sexual pain. This form is used when completing the **INCL** form to determine if a participant is eligible to enter the study.

Who: Participant completed.

When: This form is completed at B1.

General Directions: Self-explanatory.

4.4.3 Baseline Symptoms 2 (BSYM2)

Purpose: To collect information regarding the participant's assessment of his/her general urinary discomfort and/or pain, urgency, frequency, and sexual pain. This form is used when completing the **INCL** form to determine if a participant is eligible to enter the study.

Who: Participant completed.

When: This form is completed at the B2.

General Directions: Self-explanatory.

4.4.4 Clinical Center Stop Point (STOP)

Purpose: This form records the date and the primary reason for a participant's termination of study medications.

Who: RC completed.

When: This form is completed at Contact Week 24 for participants who complete the entire study, or when the participant stops taking the study medications, whichever comes first.

General Directions:

The Clinical Center Stop Point form must be completed for every randomized participant when s/he stops taking the study medication.

If this form is completed between scheduled contacts, the RC will specify the next Contact Week and the current date in the upper right hand corner. If the participant elects to continue on study medication beyond Week 24, the RC does not complete Q#2 and Q#3. If a participant continues on study medication after Week 24, this form is also completed when the participant stops participating in the study.

If the participant is discontinuing because of unacceptable concomitant medications, the RC will verify that this medication is properly recorded on the Patient's Daily Medication Diary (**PTDIARY**) and has been recorded on the Medication Diary Record (**DIARYREC**).

If the participant is discontinuing because of a positive pregnancy test, the RC will indicate the date of the test and attach a copy of the test results to the participant's study chart.

If the participant is discontinuing because of out of range LFTs or blood coagulation laboratory results, the RC will indicate the date of the test/s and attach a copy of the test results to the participant's study chart. Also, the RC will complete a Lab Results (**LAB**) form.

If the participant is discontinuing because of an adverse event or serious adverse event as determined by the PI, the RC will indicate the AE number and the date of onset from the **AESAE** form.

If the participant transfers to another randomization site, the RC will complete the Patient Transfer (**TRANS**) form.

4.4.5 Cross Check (CRSCK)

Purpose: This form confirms the participant's age of 18 years or older, by recording his/her birth date and the maximum void during screening visits, which should ***NOT*** exceed 350 ccs.

Who: RC completed.

When: At Baseline Visit 2.

General Directions: This form is completed for every eligible participant at Baseline Visit 2 before the randomization process.

4.4.6 Demographics (DEMO)

Purpose: To collect demographic, IC-related family history, and a brief sexual history assessment.

Who: Participant completed.

When: This form is completed at B2.

General Directions:

Question #1: The year given for the date of birth must be ***four*** digits.

Question #11: "Not applicable" is for participants who answered "No' for question #10.

4.4.7 Eligibility Confirmation and Randomization (ELIG)

Purpose: To ensure that the participant is eligible for entry into the study.

Who: RC and PI completed.

When: This form is completed at B2, at the time of randomization.

General Directions:

The RC will need the following forms to use as reference in answering the questions contained in the Eligibility Confirmation and Randomization form: Inclusion Criteria (**INCL**), Exclusion Criteria (**EXCL**), 1 Criteria (**DEF**), Baseline Symptoms 1 & 2 (**BSYM1** & **BSYM2**), Urine Screening (**URINE**), Lab Results (**LAB**) and Crosscheck (**CRSCK**) forms.

Inclusion Criteria Questions (#2-#4): These questions refer to the **INCL** form.

Exclusion Criteria Questions (#5-#35): These questions refer to the **EXCL** form; questions 10 and 11 have been blacked out due to protocol amendment dated January 2000.

Deferral Criteria Questions (#36-#46): These questions refer to the **DEF** form.

Question #47: Eligibility criteria refers to all entry criteria. These include study criteria defined as inclusion, exclusion, deferral, labs, procedures, scans and includes the time constraints defined in the protocol.

Question #48: The RC will record the registering PI's ID number. The registering PI is the physician who will be primarily responsible for this participant's care while s/he participating in the study.

***Question #49*:** At the completion of computer entry, the system application will allow randomization of the participant and will assign a randomization (drug packet) number.

4.4.8 Follow-up Symptoms (FUSYM)

Purpose: To collect information regarding the participant's assessment of his/her general urinary discomfort and/or pain, urgency, frequency, and sexual pain.

Who: Participant completed.

When: This form is completed at Weeks 3, 10, 17, 24 and during post-treatment follow-up, if applicable.

General Directions: Self-explanatory.

Question #5: A participant may respond "not applicable" if s/he has no partner or does not engage in sexual intercourse for reasons other than his/her IC symptoms.

4.4.9 Health Status Questionnaire (SF-36)

Purpose: To collect information regarding the participant's assessment of his/her general quality of life as related to his/her health, and as measured by various types of activities and emotional problems.

Who: Participant completed.

When: This form is completed at B2 visit and at Week 24.

General Directions: Self-explanatory.

4.4.10 IC Symptom & Problem Index (SYMPROB)

Purpose: To collect information regarding the participant's assessment of his/her IC symptoms and problems related to these symptoms.

Who: Participant completed.

When: This form is completed at B2 and Weeks 3, 10, 17, 24 and during post-treatment follow-up, if applicable.

General Directions: Self-explanatory. The RC should be sure to check the participant's arithmetic when adding the numeric values of the checked entries.

4.4.11 Lab Results (LAB)

Purpose: This form records the results of laboratory tests.

Who: RC completed.

When: This form is completed prior to B2, at Week 24, and when clinically indicated. Note that if these specified laboratory tests are done outside the regular participant contact time frame, this form also will be completed. The "Contact Week" in the upper right hand corner would be the next contact that the participant should have. For example, if the form is completed between the clinic visit at Week 10 and the telephone contact at Week 14, the Contact Week is "14".

Source documentation for **LAB** forms should be kept in the participant binder. All personal identification information should be removed or "blacked out" and

Pt. ID and Contact Week Information should be written in to identify the source documentation is referenced to the participant.

General Directions:

This form is completed when the results of the blood tests are available. The date listed in the upper right hand corner is the date that the form is completed. The RC will list his/her respective institution's lower limits of normal (**LLN**), upper limits of normal (**ULN**) and the actual value for each laboratory test performed. For all follow-up visits, a determination by the PI should be made as to whether the results are clinically significant. If so, this should also be recorded as an AE or SAE and recorded on the AESAE form.

Question #2: To be eligible for entry into the study, the LFT results (AST (SGOT), ALT (SGPT), Gamma GT (Glutamyltransferase), and Alkaline Phosphatase) **should not be** over 1.5 times the ULN. After randomization, if a participant has two consecutive LFT results greater than 2.5 times the institution's ULN, the participant must be taken off the treatment, not the study.

Question #3: To be eligible for entry into the study, the blood coagulation test results (PTT (APTT), PT, Platelets) **must be** within the institution's limits of normal. PTT and PT should be below your institution's upper limits of normal. Platelets should be within the institution's upper (**ULN**) and lower (**LLN**) limits of normal. After randomization, if a participant has two consecutive blood coagulation tests outside the institution's range of normal, the participant must be taken off the treatment, not the study.

4.4.12 Medical History (MED)

Purpose: To collect information regarding the participant's IC and general medical history.

Who: Participant Interview completed.

When: B1.

General Directions:

Question #1: This refers to when the participant's symptoms first appeared, which is not necessarily the same as when the participant was first diagnosed by a physician.

Question #3a: This is not restricted to oral drugs only. This includes drugs taken by any route.

Question #8: This should be a culture positive diagnosis as reported by the potential participant.

Question #30: This does not include biopsies.

4.4.13 *Medication Diary Record (DIARYREC)*

Purpose: To collect information from the Patient's Daily Medication Diary (**PTDIARY**).

***Who*:** RC Completed.

***When*:** Administratively at Screening (B2); every time the **PTDIARY** is collected - at Weeks 3, 10, 17, and 24.

***General Directions*:**

The information for this form is obtained from the **PTDIARY** to track any medications being taken during the study. Beginning with anything the participant is taking at the time of randomization and continuing until contact week 24 (or until study close-out if the participant chooses to continue taking the masked drug after week 24), ***any new medications started, any dosage changes, or any medications stopped*** should be recorded.

Line #: This is a sequential number which begins "001", "002", "003", etc. These sequential numbers do not repeat throughout the study.

Drug Code #: This is the code that has been obtained from the **Medication Reference Tool** in the computer application.

Drug Name: This is the generic name for the medication/treatment which has been generated from the **Medication Reference application**.

Total Daily Dose: From the **PTDIARY**, the RC must multiply the "Total Number of Doses per 24 Hours" by the "Strength" (the individual dose amount).

Unit and route are self-explanatory. Select the **most specific** response possible, based on the information obtained from the **PTDIARY**.

Start Date: Date participant started a new medication or changed a dosing level of a medication s/he is already taking. If the participant is unsure of the start date, have him/her use their "best estimate" in recalling the month and year.

Stop Date: Date participant stopped taking the medication, if applicable.

Was this an exclusionary or restricted medication?: Answer "yes" or "no" based on the Exclusionary and Restricted Medications List. (Appendix B and C)

Was this medication taken by the patient for pain?: This is transcribed directly from the PTDIARY.

Was this medication taken by the patient for his/her IC?: This is transcribed directly from the **PTDIARY**.

4.4.14 MOS Sexual Functioning Scale (MOS)

Purpose: To collect information regarding the participant's assessment of sexual problems related to his/her IC symptoms.

Who: Participant completed.

When: This form is completed at B2 and Week 24.

General Directions: Self-explanatory.

4.4.15 Patient Close-out (PTCLOSE)

Purpose: This form contains the global symptom question, which is the primary study endpoint. In addition, it queries the participant and the RC about the study medication.

Who: Participant and RC completed.

When: This form is completed at Contact Week 24 for participants who complete the entire study, or when the participant stops taking the study medications, whichever comes first.

Note:

If a participant stops taking the study medications prior to Week 24 but continues in the study, this form should ***also*** be completed at Week 24.

General Directions:

The **PTCLOSE** form MUST be completed for every randomized participant when s/he stops participating in the study.

If this form is completed between scheduled contacts, the RC will specify the next Contact Week and the current date in the upper right hand corner. The participant completes the first page of this form.

Question #1: The RC will instruct the participant to try to recall as best as possible his/her symptoms at the time of **study entry**.

Question #5: The RC should complete this question.

4.4.16 Physical Exam (EXAM)

Purpose: To collect information obtained during the participant's routine physical examination.

Who: PI completed or his/her approved designee. This form must be reviewed by the RC prior to data entry.

When: B1 and at Week 24.

General Directions:

Question #1: The RC will record the PI's ID number, even if the examination is performed by his/her approved designee.

Questions #5 - #8: The PI should determine whether the current findings are normal or abnormal.

4.4.17 Run-in Medication Dispensing Log (RUNINMED)

Purpose: To record medication dispensed for the Run-in Phase (Contact Weeks 1-3).

Who: RC completed.

When: This form is completed at B2, after randomization.

General Directions:

Question #1: The RC will indicate the total number of the white capsules dispensed. Include all the capsules dispensed for the entire period (Weeks 1-4). This amount must also be recorded on the **MEDTRAC**. The RC will peel the extra label off the bottle and apply where indicated.

Question #2: The RC will indicate the total number of the green capsules dispensed. Include all the capsules dispensed for the entire period (Weeks 1-4).). This amount must also be recorded on the **MEDTRAC**. The RC will peel the extra label off the blister packs and apply where indicated.

The numbers of green and white pills dispensed should correspond to the numbers on the **MEDTRAC**.

4.4.18 Standard Visit Inventory (STVISIT)

Purpose: To collect information regarding compliance and dispensing, other IC treatments, and any AE's or changes in non-study medications.

Who: RC completed.

When: This form is completed at all clinic visits. Beginning at Week 3 and continuing through Weeks 10, 17, 24 and the post-treatment follow-up period, if applicable.

General Directions:

There are several questions on this form which prompt the participant to communicate changes in adverse experiences or medical conditions and changes in daily medications or treatments.

The RC should have available the following forms when completing the Standard Visit Inventory (**STVISIT**):

- Study Medication Tracking Log (**MEDTRAC**).
- Standard Visit Inventory (**STVISIT**) from the last clinic contact, if applicable.

- Patient's Daily Medication Diary (**PTDIARY**).
- Adverse Event / Serious Adverse Event (**AESAE**).

Question #1: Compliance will not be computed for the Run-in period.

Questions #3 and #4:

- ***COLUMN A, B, C:*** The RC will answer column A, B, and C for each of the green and white capsules. Refer to the **MEDTRAC** or **STVISIT** forms from the last clinic contact (if applicable).

- ***COLUMN D, COLUMN E and COLUMN F*** are self-explanatory. If the percent compliance (column F) is less than 80%, the RC will counsel the participant regarding the importance of taking study medications as prescribed.

Question #5: The RC will indicate the total number of the green capsules dispensed. Include all the capsules dispensed for the entire period, and indicate the week numbers of the dispensing period. This amount must also be recorded on the **MEDTRAC**.

Question #6: The RC will indicate the total number of the white capsules dispensed. Include all the capsules dispensed for the entire period, and indicate the week numbers of the dispensing period. This amount must also be recorded on the **MEDTRAC**.

Question #7: This question prompts the participant to communicate any adverse experiences or any other medical conditions that s/he has experienced since the last contact. If the response is Yes to this question, an AE report must be completed.

Question #8: If the participant responds Yes, the RC will check to make sure the medication has been listed on the **PTDIARY**.

Question #9: These questions refer to the Exclusionary and Restricted Medications table. (Appendix B & C).

Questions A and B refer to ***exclusionary medications***. If the participant answers Yes to either question, s/he must be instructed to discontinue the study medication **immediately**. ***Questions C, D, and E*** refer to ***restricted medications***. If the participant answers Yes to any of these questions, the RC will check to make sure the medication has been listed on the **PTDIARY** and will instruct the participant to alter his/her use of these.

Question #10: If any of the treatments include prescription or over-the-counter medications, the RC will check to make sure the medication has been listed on the **PTDIARY**.

Note:

Only dispense the bottles with the amount of medication participant will need until the next clinic contact, not the whole study.

4.4.19 Study Close-out (STCLOSE)

Purpose: This form requires the RC and the PI to sign-off that all data collected for this participant are correct to the best of their knowledge.

Who: RC and PI completed.

When: This form is completed when participants complete the entire study (at Week 24 or beyond Week 24). It is also completed for participants who withdraw consent or stop taking the study medications, whichever comes first.

General Directions:

The **STCLOSE** form MUST be completed for every randomized participant when s/he stops participating in the study. This form MUST NOT be entered in the database until all other participant data have been entered.

If this form is completed between scheduled contacts, the RC will specify the next Contact Week and the current date in the upper right hand corner.

Question #1: Comments are optional and ***will not*** be entered into the database.

4.4.20 Symptom Ranking Cards (CARDS)

Purpose: To collect information regarding the participant's rating of the distress of five IC symptoms.

Who: Participant Interview and RC completed.

When: This form is completed at B2 and Week 24.

General Directions:

The RC will hand the cards to the participant and read the instructions to him/her. When the participant has ordered the cards, the RC will ask the participant to mark the box that corresponds with his/her response choice. The card that is placed at the top of the pile is “1”, the second card is “2”, etc.

For the card that reads, "Pain with sexual activity, or lack of sexual activity because of pain.": the participant must also respond “yes” or “no” to the question, “Do you have a sexual partner?"

4.4.21 Telephone Contact (PHONE)

Purpose: To collect information on the telephone regarding other IC treatments, AE’s or changes in non-study medications. There are also questions to prompt a discussion of medication compliance, although this information will not be entered in the database.

Who: RC completed.

When: This form is completed between clinic visits. Beginning at the Run-in Phase, it is completed at Weeks 1, 2 and 3. It is also completed at Weeks 6, 14 and 20.

General Directions:

There are several questions on this form which prompt the participant to communicate changes in adverse experiences or medical conditions and changes in daily medications or treatments.

The RC should have available an Adverse Event / Serious Adverse Event (**AESAE**) along with the Telephone Contact (**PHONE**).

4.4.22 University of Wisconsin Symptom Survey (UNIVWIS)

Purpose: To collect information regarding the participant's assessment of his/her general health symptoms.

Who: Participant completed.

When: This form is completed at B2 and at Weeks 3, 10, 17, 24 and during post-treatment follow-up, if applicable.

General Directions: The scale is completed by the participant within the context of reporting the symptoms, as "how much did you experience the following symptoms **today**."

4.4.23 Unmasking (UNMASK)

Purpose: This form documents the unmasking of the treatment assignment because of unforeseen circumstances. This form is enclosed within the unmasking envelope, supplied at the time the run-in period kit is distributed to participants.

Who: RC completed, in collaboration with the PI.

When: This form is completed when the PI deems it necessary to unmask the treatment assignment. Unmasking is only done in the event of a “rescue” situation or at the discretion of the PI, in case of a Serious Adverse Event (**SAE**).

General Directions: The **UNMASK** form is contained within a tamper-evident envelope which is sent with the treatment kit to the randomization site. These envelopes should be kept in a secured location while the participant is taking study medication. It if becomes necessary to unmask the study medication, this form, along with a report explaining in detail the need for unmasking, should be FAXed to the DCC within 24 hours of unmasking, followed by a hard copy. If the participant is not unmasked during the trial, the envelope containing the unmasking form will be returned to the Penn IDS.

PI signature and date must appear on this form before it is FAXed to the DCC.

4.4.24 Urine Screening (URINE)

Purpose: This form records the results of pre-randomization urine ***dipstick and culture*** (all participants) and the residual urine volume (males only).

Who: RC completed.

When: This form is completed ***prior*** to B2.

General Directions:

This form is completed when the urine dipstick and culture results (all participants) and the residual urine volume results (males only) are available.

Source documentation for **URINE** forms should be kept in the participant binder. All personal identification information should be removed or "blacked out" and Patient ID and Contact Week Information should be written in to identify the source documentation is referenced to the participant.

Question #2: If the results are abnormal, the RC will indicate which of the specific tests listed are normal and which are abnormal. These results do **NOT** affect participant eligibility.

Question #3: If the urine colony culture results are greater than $\mathbf{10^5}$ of uropathogens, the potential participant must be deferred.

Question #5**:** A potential male participant is excluded from the study if the results of the residual urine volume are greater than 150cc.

4.4.25 Voiding Diary (VOID)

Purpose: To collect information on a participant's voiding pattern over a 24-hour period throughout the duration of the study.

Who: Participant completed.

When: This form is completed prior to B2 and prior to Weeks 3, 10, 17, 24 and during post-treatment follow-up, if applicable.

General Directions:

The Voiding Diary should be completed during any 24-hour period before the next clinic visit. The participant should bring the diary with him/her to the clinic. The RC should provide several photocopies of the second page of this form and the measuring container in which the participant will measure the void. The RC should complete the top section, which contains Patient ID, Patient Initials, and the Contact Week number. The rest of the master heading information will be completed when the participant returns the voiding diary. When reviewing the form after

completion, ***the RC should pay special attention to the following:*** If the form indicates that a woman of child-bearing potential has skipped one full menstrual cycle (28 days or more), the participant should be instructed to immediately discontinue the study medications, and a serum pregnancy test must be done. The participant should not begin the study medication again until the RC has called the participant with a negative pregnancy test result. If the test is positive, the participant must be withdrawn from the treatment.

Note:

At the screening contact, ***two (2)*** voiding diaries are printed for the participant. One is completed for the screening contact visit. The other is handed out at the end of the B2 for the next clinic contact (week 3).

- **Screening voiding diary**

  - At Baseline Visit 1, the participant gets the Voiding Diary. The only fields completed in the master heading should be Patient ID and Initials and ***Contact Week refers to week 0.***

  - When the participant returns the Voiding Diary at B2, review the diary to make sure the participant has completed it correctly, and then fill in the date and the RC ID.

- **Contact Week 3 voiding diary**

  - At the end of Baseline Visit 2 (screening), give the participant another copy of the voiding diary.

  - Fill in the Patient ID and Initials, and ***Contact Week refers to week 3***. Instruct the participant that this diary is designed to go with the contact week 3 data, and should be completed ***as close to the week 3 clinic contact as possible.***

  - When the voiding diary is returned at contact week 3, review it with the participant, and complete the date and RC ID.

- **FUP voiding diaries**

  - At each clinic contact, distribute the voiding diary for the ***next*** clinic contact.

  - Complete the Patient ID and Initials, and the Contact Week refers to the ***next*** contact.

4.5 Directions for Completing Administrative Forms

Administrative forms are ***not*** optional and must be included in the participant binder as a reminder to be completed at every contact. Administrative forms are sent with the data packets requested by the DCC.

4.5.1 Clinic Visit Contact Checklist (VCHK)

Purpose: This checklist identifies all the procedures and forms to be completed during clinic contact.

Who: RC completed.

When: This checklist should be reviewed before the participant leaves the clinic.

General Directions: This form is attached to the contact packet in the participant's study file and enclosed with the data sent to the DCC.

Note:

At Contact Week 3, Clinic Visit Contact Sheet (**VCHK**) and a Phone Contact Checklist (**PCHK**) is completed.

4.5.2 Data Processing Cover Sheet (DPCS)

Purpose: This form is designed to track any completed packets or forms through the review, data entry and verification process. This form should be included whenever data packets are requested by the DCC.

Who: RC completed.

When: This form should be attached to the packet before data entry, and should be completed at each stage of the entry/verification process at the randomization site.

General Directions: self-explanatory.

Note:

Two Data Processing Cover Sheets are completed for the screening visit:

- The first **DPCS** gets completed at the B1 entry and verification (**BSYM1**, **LAB**, and **URINE**).
- The second **DPCS** gets completed when you do the rest of the screening (B2/CW 0) entry and verification (**MED**, **VOID**, etc.)

4.5.3 Deferral Criteria (DEF)

Purpose: To assess a potential participant's eligibility for the study according to the study deferral criteria.

Who: Participant Interview completed.

When: This form is completed at the B1 after the **INCL** and **EXCL** forms have been completed. For non-deferred participants, this form is reviewed again at B2.

Deferred participants must begin the screening process again (i.e., beginning again with B1) after the deferral period has been met.

General Directions:

If the potential participant has more than one deferral criteria, the RC will note the date for the longest period of time of deferral.

Question #1: The RC will remind the potential participant not to begin any new medications for his/her IC.

Question #3: If Yes, the potential participant must repeat the urine culture. If the second urine culture is negative, the RC will defer for six (6) weeks. If the second urine culture is positive, the RC will repeat again to try for a negative result.

Question #4: Twelve (12) weeks must have elapsed since the conclusion of treatment for an episode of gross hematuria.

Question #5: Twelve (12) weeks must have elapsed since any stage of active genital herpes.

4.5.4 Exclusion Criteria (EXCL)

Purpose: To assess a potential participant's eligibility for the study according to the study exclusion criteria.

Who: Participant Interview completed.

When: This form is completed at B1 after the **INCL** form has been completed, and reviewed again at B2.

General Directions: All criteria should be verified by reviewing the participant's medical records within one week of the participant's visit.

4.5.5 Inclusion Criteria (INCL)

Purpose: This form is used during both B1 and B2 to record whether the participant is eligible to enter the study.

Who: RC completed.

When: B1 and B2, after the **BYSM 1 & 2** forms are completed.

General Directions:

Question #1: The participant's date of birth must be verified in the ***medical record***.

Question #4: See the **BYSM** form, question #1 to answer this question. For the B1, the **BSYM1** is used. For B2, the **BYSM2** form is used.

Question #5: See the **BYSM** form, question #3 to answer this question. For B1, the **BYSM1** form is used. For B2, the **BYSM2** form is used.

Question #6: See the **BYSM1** form, question #4 to answer this question. This question is not asked at B2.

The table is used to tally the scores from the **BYSM** form. Use the first column to record questions #1 and #3 from the **BYSM1** form. Use the second column to record questions #1 and #3 from the **BYSM2** form.

4.5.6 Patient Contact (PTCONT)

Purpose: This form is used to collect participant contact information, and is strictly confidential. This form should ***never*** be forwarded to the DCC.

Who: Participant completed.

When: This form should be completed at B1, immediately following the completion of the informed consent document.

General Directions: If a participant's contact information changes during the course of the study, a new form should be printed, completed and filed with the old one.

4.5.7 Patient's Daily Medication Diary (PTDIARY)

Purpose: This participant-completed diary records medications (both prescription and over-the-counter) that the participant is taking on a daily basis.

Who: Participant completed at home.

When: Every evening while on study, beginning with the day following B1.

General Directions: The RC will provide the participant with one booklet for each week of the study. The RC will have completed the front cover of these booklets. The participant will bring all completed diaries to each clinic visit. It is important that the RC review and correct with the participant any ambiguous entries while the participant is still in the clinic, as the **DIARYREC** is completed from this diary. Instructions to the participant have been provided on the diary as well as a list of restricted and excluded medications. (Appendix B & C).

***Note*:**

The **PTDIARY** should include one "log" page for each day, dated at the top.

- Referring to the photocopy of his/her medications, instruct the patient to record each day all new medications, changes in medications, and all medications s/he has stopped.

- If your patient is recording a medication s/he has stopped taking, there is no column to note this, so she should make a note independently (i.e. Ortho-cyclen – last day)

4.5.8 Patient Log (PTLOG)

Purpose: To record all participants who have signed the informed consent document whether or not they become randomized into the study.

Who: RC completed.

When: Every participant who has signed a consent document will be listed on the **PTLOG** and given a Patient ID number.

General Directions: This is a site-specific form.

4.5.9 Patient Refusal Log (REF)

Purpose: To record the reason a potential participant chooses not to participate in the study.

Who: RC completed.

When: Whenever a potential participant, to whom the study has been fully explained, indicates an unwillingness to participate. Generally, this will occur prior to signing the informed consent.

General Directions: Self-explanatory. Copies of the Refusal Log (**REF**) should be sent to DCC on a regular basis.

4.5.10 Patient Transfer (TRANS)

Purpose: This form is used to notify the DCC and the Receiving Center when a participant transfers from one randomization site to another.

Who: The Receiving Center RC and the Originating Center RC.

When: When a participant transfers to another randomization site.

General Directions: The Originating Center completes page 1 of this form and includes a copy of it with the participant's research record which gets mailed to the Receiving Center along with any available study medications. A copy also should be mailed to the DCC.

The Receiving Center completes page 2 of this form after receiving all the required materials from the Originating Center and the participant has signed the Receiving Center's informed consent document. A copy should also be mailed to the DCC.

4.5.11 Phone Contact Checklist (PCHK)

Purpose: This checklist identifies all the procedures and forms to be completed during phone contacts at Run-In week 3 and Weeks 6, 14 and 20.

Who: RC completed.

When: This checklist should be reviewed before the RC concludes the phone follow-up with the participant. This form is attached to the contact packet in the participant's study file and enclosed with the data sent to DCC.

Please note that at Contact Week 3, Clinic Visit Contact Sheet (**VCHK**) and a Phone Contact Checklist (**PCHK**) is completed.

4.5.12 Run-in Dosage Record (RUNIN)

Purpose: To record weekly telephone conversations between the RC and the participant during the Run-in Phase (weeks 1 through 3); and, to record variation of dosage, if any, of the ***green*** capsules in the blister packet.

Who: RC completed.

When: Weeks 1 through 3.

General Directions: This log is updated at week 1, week 2, and week 3 phone follow-ups. For each day during the 21-day Run-in Phase, the RC should record on the right side of the slash mark, the actual column from which the participant is taking his/her dose of the green pill for that day. In each blank indicate the actual row the participant took the medication from. The bolded box is the maintenance dosage. There is also a place to record the telephone conversations between the RC and the participant. Deviations from the scheduled dose must be approved by the RC during a telephone conversation, and must be documented here.

Note:

If this participant's forms have been requested by the DCC, the DCC should receive:

- a **RUNIN** with the first row completed with week 1 forms.
- a **RUNIN** with the first and second row completed with the week 2 forms.
- a **RUNIN** with rows 1, 2, and 3 completed with the week 3 forms.

4.5.13 Screening Contact Checklist (SCHK)

Purpose: This checklist identifies all the procedures and forms to be completed during phone contacts at Baseline Visits 1 and 2.

Who: RC completed.

When: This checklist should be reviewed before the RC concludes the screening contact with the participant. This form is attached to the contact packet in the participant's study file and enclosed with the data sent to DCC.

If preferred, separate forms can be completed for B1 and B2 visits or one form can be used between the 2 baseline visits, but **at least** one Screening Contact Checklist (**SCHK**) is expected to be completed to record the baseline visits and attached to the screening data sent to DCC.

4.5.14 Study Medication Tracking Log (MEDTRAC)

Purpose: This form is used to record the date the study medication was received from/returned to the Penn IDS, the number of doses of study medication dispensed and returned, the initials of the person dispensing or receiving the medication, and the number of doses wasted.

Who: RC completed.

When: Every time study medication is dispensed or returned.

General Directions: This is an on-going record of the study medication, maintained by the RC, through the course of the participant's involvement in the study, and updated at each clinic visit. The **MEDTRAC** is completed if the participant chooses to continue on the study medication past week 24. When study medication is received from the Penn IDS, the RC should record the week numbers of the medication supply (e.g., Weeks 4 – 11, 11 – 18, 18 – 24) and date the study medication was received from the IDS. When study medication is dispensed, the RC will record the week number/s (contact week), the date, the number of individual doses dispensed, and the initials of the RC. When study medications is returned, the RC will record the Week number (contact week), the bottle number (or blister pack number for the first three weeks of the green medication), the date, the number of individual doses returned, the initials of the RC, and the number of doses wasted. A separate form is maintained for each medication (green and white). The RC should make as many copies of this form as necessary. When the participant discontinues drug permanently, a tally should be made and the total page count recorded in the page notation. Whenever study medication is returned to the Penn IDS, a copy of the **MEDTRAC** form should accompany the shipment. A copy of the updated **MEDTRAC** form corresponding to the Contact Week should be attached to the data requested by DCC.

Note:

- **MEDTRAC** is updated at each clinic contact. At B2, the run-in study medications dispensed for weeks 1-3 should be documented; at contact week 3, study medications

returned from weeks 1 to 3 and study medications dispensed for weeks 4 to 10 should be documented. This process is followed for each subsequent clinic visit and **MEDTRAC** form is thus be part of each contact packet.

- Separate sheets are provided for documentation of **WHITE** and **GREEN** pills.
- ***Week Numbers*** should correspond to contact week numbers.
- ***Date Received*** From/Returned to IDS refer to the date drugs were received in the mail.
- ***Caspules Dispensed*** – Date of contact when study medication was given to the participant (i.e. in row two, week 4)
- ***Capsules Returned*** – Date of contact when study medication was returned to the RC (i.e. in row two, week 10)
- ***Number Of Capsules Dispensed/Returned*** – capsules must be counted each time in the participant's presence.
- ***Number of Capsules lost/destroyed*** are total unaccounted capsules, based on the number taken (**PTDIARY**) minus number returned.

4.5.15 Urine Sample Tracking (UTRAC)

Purpose: To log information about the urine sample's processing and shipment.

Who: RC completed.

When: Urine is collected at B2 and the Week 24 visit.

General Directions: Photocopies of this form with signature by either the PI or the RC must accompany the shipped sample and be sent to the University of Pennsylvania. The address is provided in the section 5.1.3 Urine Specimen for Banking.

4.5.16 Urine Sample Tracking Log (ULOG)

Purpose: To log information on one form that records each participant's urine sample shipment in order and by date.

Who: RC completed.

When: When the frozen urine is batched and shipped.

General Directions: This form is enclosed with the data requested by DCC.

4.6 Entering Data in the Database

Participants who meet the Baseline Visit 1 screening criteria are registered into the database. Registered participants who fail the eligibility criteria at Baseline Visit 2 are deleted from the database. Completely screened and eligible participants are randomized into the study. Participants once randomized cannot be deleted from the database. For randomized participants, all contact packets and single forms should be entered in the database and verified. ***Forms for a contact should not be entered or verified in the database until all forms in that packet are completed except for AESAE forms, which should be entered as soon as possible.*** Entry and

verification must be done by two, separate individuals. Specific instructions for updating the database are found in Chapter 8.

4.6.1 Entry

First data entry should only be done by designated data entry personnel. It is recommended that the RC complete the second entry (verification). The forms for a particular "Contact" (packet entry) will appear in sequential order to be entered. Any "single" form (**AESAE**, **PTCLOSE**, **STCLOSE**, **LAB**, **STOP**) will need to be entered in a separate entry process. Any form that was not completed, for whatever reason, should be noted by clicking the "Missing Form" button. If the entire contact has been missed then, during entry, the "Missing Contact" button should be clicked.

4.6.2 Verification

It is recommended that the RC complete verification, since any discrepancies that arise would best be resolved immediately. During verification, any field that is different from the first data entry will appear as an error. The first entry response will be presented along with the verification response, and the option for choosing the first entry response, the verification response, or entering another response.

4.7 Submission of Forms to the DCC

The DCC may request a copy of any forms or contact packets for study participants at any time during the course of the study. Copies of forms could be requested for several reasons, including data auditing and form completion review. If a request is made, the randomization site is responsible for making photocopies of all forms requested. The original should remain in the participant's study file and the photocopies sent to the DCC. All personal identifiers should be removed from the copies sent to DCC. All multi-page forms should be stapled and an entire packet should be paper-clipped. It is preferred that copies be sent to the DCC via overnight mail. To ensure data quality, it is very important that requests are responded to as quickly as possible.

All forms and correspondence to the DCC regarding forms should be addressed as follows:

University of Pennsylvania
Clinical Research Computing Unit
ICCTG Data Manager
501 Blockley Hall
423 Guardian Drive
Philadelphia, PA 19104 - 6021

5 LABORATORY TESTS AND GENERAL PROCEDURES

The following sections outline the details of procedures to be followed for urine collections, blood draws and physical exam.

5.1 Urine Testing

5.1.1 Urine Analysis and Culture

This test is performed at B1. The results should be recorded on the Urine Screening form (**URINE**).

The participant is instructed to wipe his/her urethral area with an antiseptic towelette. A midstream urine sample is collected in a sterile cup. A sample of the urine is sent in a sterile container to the laboratory for a culture and antibiotic sensitivity. The remaining urine is gently swirled. A Chem-strip 9 reagent strip is completely immersed in the urine and immediately removed. The strip is held in the horizontal position and compared to the standardized color chart at the appropriate time interval for each test. The specific tests to be recorded on CRF's include Nitrite, Blood, Hemoglobin and Leukocytes.

Materials needed:

- Antiseptic towelette
- Sterile specimen cup
- Chemstrip-9 reagent strips

5.1.2 Residual Urine Volume

This test is performed at B1. The results should be recorded on the Urine Screening form (**URINE**).

A determination of the residual urine volume after voiding will be performed in men entering the study in order to exclude bladder outlet obstruction as a cause of their symptoms. The determination will be performed utilizing the technique of ultrasound imaging. After the participant empties his bladder, the ultrasound scan is done by scanning the suprapubic area after ultrasound scanning gel is applied to the area. The ultrasound machine scans in two planes and calculates the post-void residual urine volume in ml.

The equipment needed:

- Bladder ultrasound scanning machine
- Ultrasound scanning gel.

5.1.3 Urine Specimen for Banking

1. Tracking of this sample should be recorded on the Urine Sample Tracking Log (**UTRAC**). Collect urine sample at the visit immediately preceding treatment. ***Baseline 2 visit is preferred; Baseline 1 Visit is permitted.*** Collect another sample at the last visit (following treatment). Instruct the participant in the clean catch/midstream method as described at your

institution. Collect a midstream urine sample in a standard sterile container. Label the specimen with the patient ID number and date. Store at 4^0C or on ice until transported to a laboratory, (within one hour of collection is desirable). If unable to spin within one hour, ***refrigerate*** the specimen until it is spun. **DO NOT ALLOW** the specimen to stand at room temperature.

2. Put urine specimens into 15ml sterile centrifuge tubes. Fill (2) – 15ml rubes to the 12 ml level. Separate cellular debris by low speed centrifugation (1900 x g for 10 minutes at room temperature).

3. Remove urine supernatants; aliquot urine into (10) – 2ml aliquots in polypropylene freezer tubes. Transfer the remainder to a clean 15ml tube. Freeze specimen as quickly as possible at –700C to –800C. (Label each tube with patient's ID number and date of collection). Also, send tube with cellular debris.

Specimens may be sent to the University of Pennsylvania as needed, depending on available freezer storage space. Specimens may be frozen at 20˚ C ONLY IF they are being sent overnight on the day of collection.

4. Every six months, all banked urine from patients who have completed the study should be shipped in styrofoam lined boxes on dry ice by an overnight carrier (e.g. Federal Express or other), to the addresses below. Please note that dry ice is essential. Freezer packs cannot be used.

Dr. John Tomaszewski/Li-Ping Wang
University of Pennsylvania
Department of Pathology, 6-024 Founders Building
3400 Spruce Street
Philadelphia, PA 19104

5.2 Blood Draw Procedures.

Each clinical site will utilize its respective on-site clinical laboratory for serum pregnancy test. This test will be performed at B1 and when a participant has missed one full menstrual cycle (>28 days as indicated on her Voiding Diary). In addition, liver function tests (AST, ALT, Glutamyltransferase and Alkaline Phosphatase), and blood coagulation tests (PT, PTT and platelet count) will be performed at B1 and Week 24 of the study, or when requested by the PI. The reference ranges at each site will determine clinical decision regarding exclusion or withdrawal from the study. Results of tests should be recorded on the Lab Results form (**LAB**).

Supplies for venipuncture for serum pregnancy test:

Tourniquet	Alcohol Sponges
Red Top Tube	Bandage
Gloves	Dry 2X2 Sponges
Vacutainer	Vacutainer needle

5.3 Physical Examination

The results of the Physical Examination should be recorded in the participant's medical chart as well as on the Physical Examination form (**EXAM**). The Physical Exam will be performed during B1, (or before the B2 visit) and Week 24 of the study.

1) Inspect and palpate the abdomen for masses, tenderness or presence of a hernia and record findings.

2) For Women:
   a) With the participant in the dorsal lithotomy position, inspect for:
      i) Urethral caruncle
      ii) Cutaneous lesions
      iii) Vaginal discharge (if suspicious for vaginitis, perform a wet prep)
      iv) Atrophic vaginitis
   b) Palpate the urethra to check for masses, to observe if pus can be expressed, and to check for tenderness.
   c) Palpate the perineum to check for masses and tenderness.
   d) Palpate the urethra, bladder base, posterior vaginal wall, and right and left vaginal wall (levator muscles) for tenderness.
   e) Inspect for cystocele and rectocele at rest and during valsalva.
   f) Inspect for enterocele and prolapsed uterus.
   g) Inspect for redness and tenderness of introitus.
   h) Check for clinical diagnosis of vulvodynia

3) For Men:
   a) Inspect the urethral meatus for discharge, size, and tenderness; palpate the urethral course, including the perineum.
   b) Inspect and palpate the scrotal contents.
   c) Check for circumcision
   d) Inspect the genital skin for lesions.
   e) Examine the prostate for size, nodules and tenderness.
   f) Check the rectum for abnormalities or masses.
   g) If a neurologic exam is indicated by the participant's symptoms, then assess rectal sphincter tone, voluntary contraction, and bulbocavernosus reflex and perianal sensation.

6 TREATMENT PROCEDURES

Once it has been determined during B2 that the participant meets all inclusion criteria, the RC will distribute to the participant the appropriate kit from their stock. Each kit contains the following: a four (4) 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), unmasking envelope and a Drug Request FAX sheet for ordering the maintenance dose. After carefully reviewing the number assigned to the individual participant during randomization, the RC will record all medications given to participant on the Study Medication Tracking Log (**MEDTRAC**). The RC will remove the peel-off labels from all blister packs and bottles distributed that day and affix the labels to the Run-in Medication Dispensing Log (**RUNINMED**).

6.1 Run-In Dosing Procedures

The participant should be instructed to take the **WHITE** capsules as follows:

- Begin your medication tomorrow.
- Take three (3) WHITE capsules per day.
- Take eight (8) hours apart (depending on schedule)
- Take on an empty stomach, either one (1) hour before or two (2) hours after a meal.
- Continue to take medication until next clinic visit.
- If you miss a dose, do not double up. Skip that capsule and continue as usual.
- Return bottles whether empty or full at next clinic visit.
- If there are any problems, contact the RC immediately.

During the Run-in phase (Weeks 1-3), the participant will continue to take three (3) WHITE capsules per day from the same bottle each day.

The participant should be instructed to take the **GREEN** capsules as follows:

- Begin your medication tomorrow.
- Take one (1) GREEN capsule per day.
- Take at bedtime (this may be taken with final daily dose of WHITE capsules, it is not a requirement).
- Continue to take medication until next clinic visit.
- If you miss a dose, do not double up. Skip that capsule and continue as usual.
- Return all blister packs whether empty or full at next clinic visit.
- If there are any problems, contact the RC immediately.

During **Week 1**, the participant will take one (1) GREEN capsule per day from the blister pack marked Week 1/"Dose 1". The participant will be contacted at the end of this week to determine treatment tolerability.

During **Week 2**, the participant will take one (1) GREEN capsule per day from the blister pack marked Week 2. This pack will contain "Dose 1" and "Dose 2". The participant should take one (1) green capsule per day from the "Dose 2" column only. If for any reason the participant cannot tolerate "Dose 2", the RC will instruct the participant to take "Dose 1" for three (3) to

five (5) days then begin taking "Dose 2" for the remainder of the week, if tolerated. The participant will be contacted at the end of this week to determine treatment tolerability.

During **Week 3**, the participant will take two (2) GREEN capsules per day from the blister pack marked Week 3. This pack will contain "Dose 1, 2 and 3". For participants who successfully completed Week 2 on "Dose 2", they will take capsules from the columns marked "Dose "2 and Dose 3". If the participant cannot tolerate "Dose 3", s/he will be instructed to switch back to "Dose 2" for two (2) days then increase to "Dose 3". If the same reactions occur, the participant will be instructed to stay at "Dose 2". For participants who were unable to tolerate "Dose 2" during Week 2, they will attempt "Dose 2" during Week 3. The participant will be contacted at the end of this week (21 days) to determine the maximum tolerable dose (either "1, 2 or 3') for the green capsules. This is the dose that will be used for the participant throughout the remainder of the study. The RC will immediately contact the Penn Investigational Drug Service (**IDS**) with the dose. The Penn IDS will ship one sealed bottle of green capsules to the randomization site via overnight mail on time for the three (3) week follow-up visit.

The participant will be provided an extra Week 3 blister card for use in the event that s/he cannot schedule the Week 3 follow-up clinic visit within exactly 22 days.

6.1.1 Run-In Dosing Changes

The participant will be instructed to contact the RC immediately before making any changes to the dosing of the study medications. S/he will be encouraged to reduce his/her dose only by one (1) level. No adjustments to the WHITE capsules can be made. All doses should be stabilized by the end of 3 weeks. All changes must be recorded on the Run-in Dosage Record (**RUNIN**).

6.1.2 Maintenance Dosing Procedure

At the Week 3 clinic visit, the RC will distribute one (1) bottle of white capsules and one (1) bottle of green capsules to the participant based on the number assigned to the participant during randomization. These will supply the participant with adequate medication until the next clinic visit. This will repeat for Weeks 10 and 17. All information is recorded on the Medication Tracking Log (**MEDTRAC**). Unused medication and/or empty bottles will be returned to the study RC at each clinic visit. If the participant forgets to bring the bottle remind him/her to do so at the next visit or provide a self-addressed stamped envelope for the participant to return the bottle.

6.2 Post-Study Dosing Procedure

If the participant chooses to continue study medication after all of his/her follow-up visits are complete, study drug will be dispensed until the study officially closes. The study will close when the last participant has completed Week #24. At Week 23, the RC will call the participant to determine whether s/he wants to remain on the study drugs after Week 24. If the participant chooses to continue at the Week 24 visit, the RC will order the study drug from the Penn IDS. The participant will be required to pick up his/her medication at the randomization site.

6.3 Compliance

The participant will be instructed to return all bottles/blister packs to the RC at each clinic visit even if they are empty. The RC will record the information on the Standard Visit Inventory form

(**STVISIT**). If the participant does not return the packaging at the clinic visit, the RC will provide a self-addressed stamped envelope to the participant in which the packaging can be returned. This will assist the study in compliance monitoring.

6.4 Changes in Dosage

The participant will be instructed to contact the RC immediately before making any changes to the dosing of the study medications. No adjustments to the WHITE capsules can be made. The RC will record all changes on either the (**RUNIN**) or (**STVISIT**) forms. Participants will be encouraged to take the highest dose of medication tolerated.

6.5 Medication Diary

The RC will distribute to the participant at each clinic visit eight (8) weeks worth of Patient's Daily Medication Diaries. Using his/her copy of the original list of daily medications completed at the B1 visit, the participant should list changes in medications or any new (not just study) medications taken each day, every week, between clinic visits. The RC should review this with the participant while s/he is still in the clinic to clarify inconsistencies, ambiguities, etc. This information will be transcribed onto the **DIARYREC** by the RC.

6.6 In Case of Problems

The participant will be instructed to contact the RC immediately with any problems. These can include but are not limited to missing a dose, losing medication, not understanding the dose changes, confusion about medication diary, not able to keep scheduled appointment, hospitalization/illnesses and adverse experiences. The RC will notify the PI immediately if the problem is one of the latter.

6.6.1 Reported Problems

Although all participants are expected to develop some initial adverse events from the GREEN medication, predominately sedation, it has been shown that participants tend to become tolerant to these events if a slow titration is used. The entire dose of GREEN medication should be taken before bedtime to minimize the sedation effects during waking hours the following day. The following applies to the GREEN study medication:

- 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 adverse events, s/he will be encouraged to reduce his/her dose by one (1) level, but continue on the medication. This information should be recorded on the **AESAE** form.
- If the participant reports discontinuing the study medication due to illness/adverse events, etc., the following criteria will determine whether or not the participant can continue taking the study medication:

    - If the participant has been off study drug for < three (3) days s/he can start back at the same dose s/he was on prior to discontinuation.

- If the participant was taking "Dose 2" and has been off study drug for > three (3) but < seven (7) days, s/he can start again at the same dose.

- If the dose the participant was taking was "Dose 3", and has been off the study drug for > three (3) but, <seven (7) days, s/he must start at "Dose 2" for two (2) days then increase to "Dose 3" for the remainder.

- If the participant has been off study drug for seven (7) consecutive days, s/he ***cannot*** re-initiate study drug. The participant will continue to follow the remainder of the study guidelines.

- Participant complaints will be reported to the PI immediately.

6.7 Concomitant Medications

The RC will distribute to the participant at each clinic visit an eight (8) week supply of Patient's Daily Medication Diaries on which the participant will record **ALL** medications taken. The participant will return this at the next clinic visit. The RC should review the diaries at that time to ensure that the participant is not taking any of the following ***exclusionary*** medications:

- Histamine-2 receptor antagonists (e.g. cimetidine/Tagamet)
- Intravesical Heparin.

If it is found that the participant is taking any of the above exclusionary medications, the RC should instruct the participant to discontinue study medications immediately and the RC should continue to follow the participant for the duration of the study of until the participant withdraws consent.

Note: the inadvertent use of one or two doses of Cimetidine is acceptable. The DCC must be contacted within 24 hours.

The RC will also review to ensure that the participant is not **CHRONICALLY** (more than three (3) days within a seven (7) day week) taking any of the following ***restricted*** medications:

- Histamine-1 receptor antagonists containing diphenhydramine, brompheniramine or chlorpheniramine (e.g. Contact, Excedrin PM, Unisom etc.)
- More than one (1) gram of aspirin products (e.g. Anacin, Bufferin etc.)
- More than the maximum single dose allowed by the PDR for prescription use within a 24-hour period of NSAIDs.

If it is found that the participant is taking any of the above listed restricted medications outside of the acceptable levels described above, the RC should advise the participant to stop taking the concomitant medication immediately. The participant may continue on the study as long as the concomitant medication is stopped. (Appendix B & C).

7 RISKS AND BENEFITS TO PARTICIPANTS

7.1 Risks

Potential risks to the participant are limited to the risks related to venipuncture and the use of the study drugs. The RC should be sure to clearly explain these risks to the participant.

7.2 Benefits

Based on previous Elmiron® and hydroxyzine studies, it is anticipated that there will be a direct benefit to the participants, however, direct benefits are not guaranteed and SHOULD NOT be promised.

7.3 Adverse Drug Reactions

Events known to be associated with the use of the drug are called Adverse Drug Reactions (**ADR**). These **DO NOT NEED** to be reported unless they fall into the SAE category, which is determined on the AESAE form.

7.3.1 Elmiron® ADRs

Known reactions to Elmiron® are:

- Diarrhea
- Nausea
- Alopecia
- Headache
- Rash
- Dyspepsia
- Abdominal pain
- Liver function abnormalities
- Dizziness

7.3.2 Hydroxyzine ADRs

Known reactions to hydroxyzine at the study dose level are:

- Temporary drowsiness
- Dry mouth

Known reactions to hydroxyzine dosages considerably higher than the study dose level are:

- Urinary retention
- Nightmares
- Weight gain
- Shakiness of hands

If the grade, frequency or duration of the adverse drug reaction deviates from those known for that drug, the ADR is now an AE or SAE as indicated on the **AESAE** form and must be recorded and reported. Information about grade, frequency, or duration can be found in the Physician's

Desk Reference **(PDR),** Investigator's Brochure, Common Toxicity Criteria **(CTC),** Drug Facts and Comparisons, or other reputable resources.

7.4 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. If the event is **THOUGHT** to be associated with the drug, but not **KNOWN** to be associated with the drug, then it will be reported as an AE or SAE as appropriate, on the **AESAE** form. 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.
- Recording AEs

All AEs, not already defined as **ADRs**, will be recorded on the **AESAE** form according to the specifications outlined earlier in this MOP. AEs will be addressed at each participant visit. The **AESAE** forms will be reviewed by the DCC regularly.

7.4.1 Reporting AEs

ANY AE reported by the participant will be immediately reported to the PI.

7.5 Serious Adverse Events (SAE)

An 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, a persistent or significant disability/incapacity, requires in-patient hospitalization or prolongation of inpatient hospitalization or is a congenital anomaly/birth defect. Important medical events that are not any of the above, may be considered an SAE when, based upon appropriate medical judgement, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.5.1 Recording SAEs

All SAEs will be recorded on the **AESAE** form according to the specifications outlined earlier in this MOP. A **MedWatch** form will be used to record SAEs for reporting purposes.

7.5.2 Reporting SAEs

All SAEs will ***IMMEDIATELY*** be reported to the PI. The clinical site IRB and the DCC must be notified via telephone within one (1) working day following the reporting. A **MedWatch** form, along with a copy of the **AESAE** form, must be faxed and hard copies mailed to the same within one (1) working day.

Deaths must be reported for a period of thirty (30) days following cessation of study medication.

7.5.3 Following SAEs

All SAEs must be followed with appropriate medical management until resolved.

7.6 Unmasking the Drug

Each randomization site will keep in a secured area, blinded envelopes, which will contain the treatment to which each participant is randomized. These envelopes will be contained in each treatment kit provided by Penn IDS.

It is anticipated that unmasking will be a ***very rare occurrence*** and will only happen under the most critical of situations. Unmasking process should be initiated very carefully and selectively, in a serious or life-threatening situation for the participant only. If the need does arise, however, the RC should instruct the participant to call the RCs pager with unmasking concerns. The RC will discuss with the PI whether unmasking should occur. The RC cannot make the decision on his/her own. The PI or his/her designee will decide whether or not to unmask the drug. It is advised that the PI or designee also consult with Sponsor Physician, Leroy Nyberg, if the situation allows. If the PI determines that the treatment should be unmasked, s/he will instruct the RC to travel to the randomization site, break the seal for the participant's secured envelope and notify the PI of the treatment assignment. In the event the RC can not travel to the randomization site to retrieve the envelope, s/he will call the pager of Judy Stover **(215 308-0627)**, QA Director of the DCC, any time, day or night, who will be able to unmask the treatment. A detailed report explaining the need for unmasking along with the unmasking CRF should be faxed with a hard copy to ***follow within 24 hours to the DCC.*** The DCC will be responsible for contacting NIH.

7.6.1 Storage of Unmasking Envelopes

Envelopes must be kept in a locked drawer at the randomization site. Only the PI and RC should have the key to access the drawer.

7.6.2 Return of Unmasking Envelopes

At study termination the envelopes will be returned to the Penn IDS via certified mail for inspection.

8 DATA MANAGEMENT SYSTEM USER GUIDE

This chapter provides specific instructions on the use of the software application used to enter data into the ICCTG RCT #1 database. **Note:** the terms used in the software application are identical to those used in the Case Report Forms.

8.1 System Support Plan

The DCC will provide technical and managerial support for certain aspects of the ICCTG RCT #1. Computing support specifically related to the ICCTG RCT #1 application and database will be provided to the randomization site by the Data Coordinating Center help desk. In addition, as a back up to the network system, the DCC has established an external Internet Service Provider (ISP) for randomization sites in the event of a network failure. Requests for DCC support will generally fall into the following three areas:

Computer Systems:
For problems involving:

1) ICCTG email problems
2) ICCTG RCT #1 application
3) Internet network connection problems involving the ICCTG RCT #1 application, or
4) Problems accessing study CRFs and the ICCTG application contact the ICCTG DCC helpdesk.

Note: General computer system support is **not** provided by the ICCTG DCC helpdesk.

Clinical Data Management:
Questions related to the administration of case report forms, administrative forms, patient enrollment, and visit scheduling and administration should be directed to the DCC Clinical Data Manager.

Project Management:
Questions related to the study protocol, organization, general policies regarding publication and ancillary studies, and internal and external communication should be directed to the DCC Project Manager.

8.2 ICCTG Application Menu

Purpose: To allow access to ICCTG RCT #1 database system applications. These applications allow entry of patient contact data into the database located at the DCC and viewing of randomized patient status.

Users: Randomization site personnel:

1. Data Management/Data Entry Personnel
2. Research Coordinator

User Actions:

Start the application by connecting to the "ICCTG CC Menu" using the Web browser from the Windows Workstation desktop or from the Windows Menu. Initially, a loading Web page will appear. There are instructions presented on this initial screen, read and follow those instructions. Next, the database login dialog box will appear.

8.2.1. Log on the database:

- Enter User ID
- Enter User Password
- Enter database name
- Press "Connect" button

8.2.2. Acknowledge User Identification:

- Dialog box displays username and role
- Press OK button

8.2.3. Acknowledge Notice for Exiting Program:

- Dialog box displays message describing how to exit the program
- Press OK button

8.2.4. The CC Menu appears with the following options:

- Register Patient
  - Allows registration of a patient into the database
  - Requires:
    - Patient ID,
    - Patient Initials
- Eligibility Entry
  - Starts Entry Program for Baseline Visit Information
  - Requires:
    - Patient ID
    - Patient Initials
    - Clinical Center Number
    - Baseline Visit Number
- Eligibility Verification
  - Start the Baseline Visit Information Verification Program
  - Requires:
    - Patient ID
    - Patient Initials
    - Clinical Center Number
    - Baseline Visit Number
- Delete Ineligible Patient
  - Allows Removal of Patient Information for Ineligible Patients
  - Requires:
    - Patient ID
    - Patient Initials

        - Clinical Center Number
- Packet Entry
  - Start the Packet Entry Program
  - Requires:
    - Patient ID,
    - Patient Initials,
    - Clinical Center Number,
    - Contact Week, and the packet of completed contact forms that are to be entered.
- Single Form Entry
  - Start the Single Form Entry Program
  - Requires:
    - Patient ID,
    - Patient Initials,
    - Clinical Center Number,
    - Form Date,
    - Contact Week, and the completed single form to be entered.
- Packet Verification
  - Start the Packet Verification Program
  - Requires:
    - Patient ID,
    - Patient Initials,
    - Clinical Center Number,
    - Contact Week, and the packet of previously entered contact forms that are to be verified.
- Single Form Verification
  - Start the Single Form Verification Program
  - Requires:
    - Patient ID,
    - Patient Initials,
    - Clinical Center Number,
    - Form Date,
    - Contact Week, and the previously entered single form to be verified.
- Entry Status
  - Starts the Entry Status Program
  - Requires
    - Patient ID to view a specific patient contact form status.
    - Presents the randomized patient status and contact forms status.
- Randomize Patient
  - Starts the Patient Randomization Program
  - Requires:
    - Patient ID,
    - Patient Initials, and
    - Completed Baseline Visit #1 and Baseline Visit #2.
    - Completed Eligibility Confirmation Randomization Form
- Medication Reference

- Starts the Medication Reference Program that is used to cross-reference drug brand name with their generic equivalents.

- Reports: Opens the Reports Menu
- Cancel: Exits the ICCTG CC Menu

8.2.5. The User chooses the desired program (Register Patient, Eligibility Entry, Eligibility Verification, Delete Ineligible Patient, Randomize Patient, Enter Packet or Single Forms, Verify Packet or Single Forms, Entry Status, Reports Menu) or chooses Cancel to exit the application.

8.3 Register Patient

Purpose: To make the data management system aware of a new patient.

This is required prior to entering patient contact forms.

Users: Randomization site personnel:

- Research Coordinator or Data Management/Data Entry Personnel

User Actions:

8.3.1. Enter Patient Identification Information:

- Enter the Patient ID:
- Patient ID must be exactly 5 numeric characters.
- The first digit must be a “1" to represent the first protocol.
- The last three digits will represent the sequence of patient enrollment using the randomization site number for the first digit (1001..1999 for site one, 2001..2999 for site two, ... , 7001..7999 for site seven).
- An error will occur if fewer than or more than 5 digits are entered or any non-numeric characters are entered.
- An error message is given for duplicate Patient IDs.

8.3.2. Enter the Patient Initials:

- Patient Initials must be 2 to 3 uppercase letters.
- Error message is given if less than 2 or more than 3 letters are entered or any character that is not a letter is entered.
- Warning message given for duplicate initials.

8.3.3. Patient ID and Patient Initials are mandatory fields; neither may be left blank.

8.3.4. The entered Patient ID and Patient Initials must be confirmed by re-entering both fields:
- If either field differs from the first entry, an error message is given and the both fields must be re-entered for confirmation.
- Each field has the same constraints as indicated above.

8.3.5. The application enters the Patient ID and Patient Initials into the database.

8.3.6. Patient Registration Screen is cleared and ready for registration of another patient

8.3.7. Press Cancel button to return to ICCTG CC Menu

8.4 Eligibility Entry

Purpose:

Logs the patient baseline contact forms into the DCC database system.
Allows entry of the patient baseline contact form data into the DCC database system.

Users: Randomization site personnel:
- Data Management/Data Entry Personnel

User Actions:

- Enter the Patient ID.
- Patient ID has the same requirements as in the Registration Application.
- The Patient ID will be checked against the registration table to verify that the patient does exist.
- If the Patient ID is not registered in the database, an error message will be generated and the user will not be allowed to proceed unless a Patient ID registered with the randomization site is entered.

8.4.1. Enter patient initials
- The patient initials will be cross checked with the patient initials for the corresponding Patient ID in the registration table.
- If initials do not match, then an error message will be generated and user will not be able to proceed until the correct initials are entered.

8.4.2. Enter Clinical Center Number
- This number must be the number assigned to the randomization site for the study.
- If the CC number entered is not the same as that assigned to the center, an error message is given.

8.4.3. Enter Baseline Visit Number
- The baseline visit number must be 1 or 2.

- An error will occur if baseline visit number is not valid or if you try to enter any other character that is not a number.
- If the baseline visit has already been entered, an error should appear.
- If any previous baseline contacts have not yet been entered, an error is given, and will prevent entry of contact forms.

8.4.4. All four fields (Patient ID, Patient Initials, Clinical Center Number, and Baseline Visit Number) are mandatory.

8.4.5. After entering the mandatory fields, choose:
- Proceed to enter the packet , or
- Cancel to exit the Entry Application.

8.4.6. After choosing to proceed to packet entry:
- The system will open the entry screens for each form in the appropriate order.
- If a form has been previously entered, a message will be issued indicating the form status. After acknowledging any form status messages, the next form is presented.
- The form entry screens will look like the case report forms.
- For all forms, the heading in the upper right hand corner will display the Patient ID, patient initials, clinical center number, and the contact week automatically as a standard heading.
- Proceed by entering the visit date in the upper right hand corner. This date is the date the form was completed, and it must be entered. The range for the date must be between the study start date, and the current date.
- Enter the Research Coordinator ID in the upper right hand corner.
- Enter all data on the forms into the appropriate fields.
- The data fields fall into the following categories: alphabetic letter, alphanumeric, categorical, date, numeric, time, and free text. Specifications for these fields are described in the Data Field Specifications. If the entry does not meet the required range or specification, then an error message is given in the message area at the lower left-hand corner of the application window.
- For case report forms with multiple pages, the option to either proceed and move forward to next page of the form or move back to the preceding page is available.
- Upon completing data entry for each case report form a Commit button will allow the entries for that form to be saved and move onto the next.
- The data cannot be changed after it has been saved.
- After the last form has been entered, the entry process can be repeated for the next patient.
- You will have the option of exiting the entry process at any time. The data entered on any unsaved forms will be lost.

8.5 Eligibility Verification

Purpose: Allow second entry verification of all entered forms for a patient baseline visit.

Users: Randomization site personnel:
- Research Coordinator

User Actions:

8.5.1 The user action items 8.4.1 through 8.4.6 in the Eligibility Entry Application apply.

8.5.2 The data entered for each form field are compared to the data from first entry.

8.5.3 If it is different, a message is given (indicating first entry value, verification entry value, and something else), you must choose which entry is correct. If "Something Else" is chosen, you must enter the new value.

8.5.4 You are not allowed to proceed to the next field without choosing the correct value.

8.6 Delete Ineligible Patient

Purpose:

- Removes all information for an ineligible from the DCC database system.
- Patients who have been randomized can not be deleted.

Users: Randomization site personnel:
- Research Coordinator

User Actions:

8.6.1. Enter the Patient ID
- Patient ID has the same requirements as in the Registration Application.
- The Patient ID will be checked against the registration table to verify that the patient does exist.
- If the Patient ID is not registered in the database, an error message will be generated and the user will not be allowed to proceed unless a Patient ID registered with the randomization site is entered.

8.6.2. Enter patient initials
- The patient initials will be cross checked with the patient initials for the corresponding Patient ID in the registration table.
- If initials do not match, then an error message will be generated and user will not be able to proceed until the correct initials are entered.

8.6.3. Enter Clinical Center Number
- This number must be the number assigned to the randomization site for the study.
- If the CC number entered is not the same as that assigned to the center, an error message is given.

8.6.4. All three fields (Patient ID, Patient Initials, and Clinical Center Number) are mandatory.

8.6.5. After entering the mandatory fields, choose:
- Proceed to delete the patient, or
- Cancel to exit the Entry Application.

8.6.6. Acknowledge intent to delete patient
- Dialog Box displays patient identifying information and requests confirmation of intent to delete patient.
- Press OK button to delete patient or Cancel button to return to previous screen.

8.7 Randomize Patient

Purpose:

- To allow entry of patient eligibility information,
- To randomize a new patient into the ICCTG study, and
- To make the data management system aware of the randomized patient.

This is required prior to entering patient contact forms.

Users: Randomization site personnel:
- Research Coordinator

User Actions:

8.7.1. Enter Patient Identification Information:
- Enter the Patient ID.
- Patient ID must be exactly 5 numeric characters.
- The first digit must be a "1" to represent the first protocol.
- The last three digits will represent the sequence of patient enrollment using the randomization site number for the first digit (1001..1999 for site one, 2001..2999 for site two, ... , 7001..7999 for site seven).
- An error will occur if fewer than or more than 5 digits are entered or any non-numeric characters are entered.
- An error message is given for duplicate Patient IDs.

8.7.2. Enter the Patient Initials:
- Patient Initials must be 2 to 3 uppercase letters.
- Error message is given if less than 2 or more than 3 letters are entered or any character that is not a letter is entered.
- Warning message given for duplicate initials.

8.7.3. Patient ID and Patient Initials are mandatory fields, neither may be left blank.

8.7.4. The entered Patient ID and Patient Initials must be confirmed by re-entering both fields:
- If either field differs from the first entry, an error message is given and the both fields must be re-entered for confirmation.

8.7.5. Each field has the same constraints as indicated above.

8.7.6. Enter the Eligibility Confirmation and Randomization **(ELIG**).

8.7.7. The only allowed data entry is that leading to an eligible patient.

8.7.8. All inclusion questions must be answered with a "yes".

8.7.9. All exclusion questions must be answered with a "no".

8.7.10. All deferral questions are checked for eligibility.

8.7.11. All skip patterns are enforced.

8.7.12. Gender questions:
- If earlier question responses indicate that a patient is female, questions pertaining to females must be answered and questions pertaining to males must be skipped or marked "not applicable".
- If earlier question responses indicate that a patient is not female, questions pertaining to females must be skipped or marked "not applicable" and question pertaining to males must be answered.

8.7.13. Date entry is required for "yes" responses to deferral criteria. Otherwise, the date fields will be skipped.

8.7.14. All questions require a response, except for the deferral criteria dates for "no" responses to deferral criteria (and question #49 described below).

8.7.15. Question #49: "Perform computer randomization and record randomization number:" will not be entered.

8.7.16. The randomization number will be issued by the application in the controlled process described below.
- Instead of being provided an entry field, the user is provided a button that causes the application to proceed to the randomization process.
- After the **ELIG** form information has been entered the user presses the "Randomize Patient" button for ELIG form question #49.
- The application enters the Patient ID, Patient Initials, and the **ELIG** form data into the database.
- The application issues the Randomization Number and records this event in the database.

- The user is requested to record this number for ELIG form question #49 and acknowledge this by pressing the "Continue" button.
- The application requests that the user re-enter the number for verification.
  - If the number is not entered correctly, the application displays the correct Randomization Number and requests that it be recorded for ELIG Form question #49.
  - The verification process is repeated until the user enters the correct Randomization Number.
    - After the Randomization Number has been properly verified, the application records the verification in the database and proceeds to the Randomization Confirmation Screen.
    - The application displays the Randomization Confirmation Screen.
  - This screen requests that the user acknowledge that the randomization process has been completed successfully, by pressing the "Continue" button.
  - After the user acknowledges this fact, the application records the acknowledgement in the database.
  - After completing the randomization process, the application returns to the ICCTG CC Menu.

8.8 Medication Reference

Purpose: Provide the randomization sites with a standard cross-reference to convert brand name medications to their generic equivalent and provide a standard medication code.

Users: Randomization site Personnel:
1. Data Management/Data Entry Personnel
2. Research Coordinator

User Actions:

8.8.1. The Medication Reference appears with the following options:
- Brand Name
- Generic Name
- Cancel

8.8.2. Enter Query Criteria:
- Select "Brand Name" or the "Generic Name" then enter the drug name in the appropriate box.
- If you are unsure of the spelling, just enter the first few letters.

8.8.3. After entering the drug name, press enter (the enter key on the keyboard). The list of matching medication names along with the medication code and the cross-reference medication name appears in the "Drug Names and Codes" block.

8.8.4. You can then review the list and choose the appropriate medication code.

8.8.5. Choose "Cancel" when finished, in order to return to the main menu.

8.9 Packet Entry

Purpose:

- Logs the patient contact and patient contact forms into the DCC database system.
- Allows entry of the patient contact form data into the DCC database system.

Users: Randomization site personnel:
- Data Management/Data Entry Personnel

User Actions:

8.9.1. Enter the Patient ID
- Patient ID has the same requirements as in the Registration Application
- The Patient ID will be checked against the registration table to verify that the patient does exist.
- If the Patient ID is not registered in the database, an error message will be generated and the user will not be allowed to proceed unless a Patient ID registered with the randomization site is entered.

8.9.2. Enter patient initials
- The patient initials will be cross checked with the patient initials for the corresponding Patient ID in the registration table.
- If initials do not match, then an error message will be generated and user will not be able to proceed until the correct initials are entered.

8.9.3. Enter Clinical Center Number
- This number must be the number assigned to the randomization site for the study.
- If the CC number entered is not the same as that assigned to the center, an error message is given.

8.9.4. Enter Contact Week
- The contact week must be 1 to 2 numeric characters.
- An error will occur if contact week is not a valid contact or if you try to enter any other character that is not a number.
- If the contact has already been entered, an error should appear.
- If any previous contacts have not yet been entered, an error is given, and will prevent entry of contact forms.

8.9.5. All four fields (Patient ID, Patient Initials, Clinical Center Number, and Contact Week) are mandatory.

8.9.6. After entering the mandatory fields, choose:
- Proceed to enter the packet ,
- Packet Missing to mark the packet as missing, or
- Cancel to exit the Entry Application.

8.9.7. After choosing to proceed to packet entry:

- The system will open the entry screens for each form in the appropriate order.
- If a form has been previously entered or marked as missing, a message will be issued indicating the form status. After acknowledging any form status messages, the next form is presented.
- The form entry screens will look like the Case Report Forms.
- If the form is missing from the packet, mark the form as missing and proceed to the next form in the packet. Forms marked as missing cannot be entered.
- For all forms, the heading in the upper right hand corner will display the Patient ID, patient initials, clinical center number, and the contact week automatically as a standard heading.
- Proceed by entering the visit date in the upper right hand corner. This date is the date the form was completed, and it must be entered. The range for the date must be between the study start date, and the current date.
- Enter the Research Coordinator ID in the upper right hand corner.
- Enter all data on the forms into the appropriate fields.
- The data fields fall into the following categories: alphabetic letter, alphanumeric, categorical, date, numeric, time, and free text. Specifications for these fields are described in the Data Field Specifications. If the entry does not meet the required range or specification, then an error message is given in the message area at the lower left-hand corner of the application window.
- For case report forms with multiple pages, the option to either proceed and move forward to next page of the form or move back to the preceding page is available.
- Upon completing data entry for each case report form a Commit button will allow the entries for that form to be saved and move onto the next.
- The data cannot be changed after it has been saved.
- After the last form has been entered, the entry process can be repeated for the next patient.
- You will have the option of exiting the entry process at any time. The data entered on any unsaved forms will be lost.
- Special Form Requirements for **VOID** and **DIARYREC**: The number of voids or medications on the form must be entered.
- If the number of records is changed, the user will be warned that this will result in the loss of all entered records.
- Extra records can only be deleted by changing the number of records entered in 8.1. and reentering the correct records.
- Incorrect records can be changed/edited prior to committing the form data.

8.10 Single Form Entry

Purpose:

- Logs the patient single forms into the DCC database system.
- Allows entry of the patient single form data into the DCC database system.

Users: Randomization site personnel:

- Data Management/Data Entry Personnel

User Actions:

8.10.1. Enter the Patient ID

- Patient ID has the same requirements as in the Registration Application.
- The Patient ID will be checked against the registration table to verify that the patient does exist.
- If the Patient ID is not registered in the database, an error message will be generated and the user will not be allowed to proceed unless a Patient ID registered with the randomization site is entered.

8.10.2. Enter patient initials

- The patient initials will be cross checked with the patient initials for the corresponding Patient ID in the registration table
- If initials do not match, an error message will be generated and user will not be able to proceed until the correct initials are entered.

8.10.3. Enter Clinical Center Number

- This number must be the number assigned to the randomization site for the study.
- If the CC number entered is not the same as that assigned to the center, an error message is given.

8.10.4. Enter Contact Week

- The contact week must be 1 to 2 numeric characters.
- An error will occur if contact week is not a valid contact or if you try to enter any other character that is not a number.
- If the contact has already been entered, an error should appear.
- If any previous contacts have not yet been entered, an error is given, and will prevent entry of contact forms.

8.10.5. All four fields (Patient ID, Patient Initials, Clinical Center Number, and Contact Week) are mandatory.

8.10.6. After entering the mandatory fields, choose the single form to enter.

8.10.7. After choosing the form:

- select Proceed to enter the form
- or select Cancel to exit the Single Form Entry Application.

8.10.8. Form Entry:

- The system will open the entry screens for the single form selected.
- If a form has been entered, a message will be issued indicating the form status.
- The form entry screen will look like the case report form.

- The single forms can not be marked as missing.
- For all forms, the heading in the upper right hand corner will display the Patient ID, patient initials, clinical center number, and the contact week automatically as a standard heading.
- Proceed by entering the visit date in the upper right hand corner. This date is the date the form was completed, and it must be entered. The range for the date must be between the study start date, and the current date.
- Enter the Research Coordinator ID in the upper right hand corner.
- Enter all data on the forms into the appropriate fields.
- The data fields fall into the following categories: alphabetic letter, categorical, date, numeric, time, and free text. Specifications for these fields are described in the Data Field Specifications.
- Upon completing data entry for the form a Commit button will allow the entries for that form to be saved and return the user to single form entry screen.
- The data cannot be changed after it has been saved.
- This entry process can be repeated for the single form.
- You will have the option of exiting the entry process at any time. The data entered on any unsaved forms will be lost.

8.10.9. Special Form Requirements for **AESAE**:

- The number of event records on the form must be entered.
- If the number of records is changed, the user will be warned that this will result in the loss of all entered records.
- Extra records can only be deleted by changing the number of records entered in 9.1. and re-entering the correct records.
- Incorrect records can be changed/edited prior to committing the form data.

8.11 Packet Verification

Purpose: Allow second entry verification of all entered forms for a patient contact.

Users: Randomization site personnel:

- Research Coordinator

User Actions:

8.11.1. The user action items 1-7 in the Packet Entry Application apply.

8.11.2. The data entered for each form field are compared to the data from first entry.

8.11.3. If it is different, a message is given (indicating first entry value, verification entry value, and something else), you must choose which entry is correct. If “Something Else” is chosen, you must enter the new value.

8.11.4. You are not allowed to proceed to the next field without choosing the correct value.

8.11.5. Special Form Requirements for **VOID** and **DIARYREC**:

- You are required to enter the number of void or medication entries.
- If this is different from the number of records entered in first entry a message is given (indicating first entry value, verification entry value, and something else), you must choose which entry is correct. If "Something Else" is chosen, you must enter the new value.
- You are not allowed to enter a different number of records than indicated in the first bullet.
- All verification entries are compared with 1st entry as described above (under 2.).

8.12 Single Form Verification

Purpose: Allow second entry verification of single forms for a patient contact.

Users: Randomization site personnel:

- Research Coordinator

User Actions:

8.12.1. The user action items 1-8 in the Single Form Entry Application apply.

8.12.2. The data entered for each form field are compared to the data from first entry.

8.12.3. If it is different a message is given (indicating first entry value, verification entry value, and other "something else" value), you must choose which entry is correct. If other is chosen, you must enter the new value.

8.12.4. You are not allowed to proceed to the next field without choosing the correct value.

8.12.5. Special Form Requirements for **AESAE**:

- You are required to enter the number of event records.
- If this is different from the number of records entered in first entry a message is given (indicating first entry value, verification entry value, and something else), you must choose which entry is correct. If "Something Else" is chosen, you must enter the new value.
- You are not allowed to enter different amount of records than initially indicated in above.
- All verification entries are compared with first entry as described above.

8.13 Entry Status

Purpose: Allow viewing the list of randomized patients and the entry status of patient contact forms.

Users: Randomization site Personnel:

- Data Management/Data Entry Personnel
- Research Coordinator

User Actions:

8.13.1. Select status type (Patient or Forms) to view and enter Patient ID if Forms Status for a specific Patient is desired, then select Proceed to view the list or select Cancel to exit and return to the ICCTG CC Menu.

8.13.2. Randomized Patient List is presented with the:

- randomization number,
- registration dates and the user codes of the registering application users,
- randomization number issued dates and the user codes of the application users receiving the randomization number,
- randomization number verification dates and the user codes of the application users verifying the randomization number,
- randomization number confirmation dates and the user codes of the application users confirming the randomization number.

8.13.3. Contact Forms List is presented with the:

- registration dates and the codes of the registering application users,
- entry dates and the codes of the entry application users,
- verification dates and the codes of the verification application users.

8.14 Reports

Purpose: To allow the generation of monitoring reports.

Users: Randomization site Personnel:

- Data Management/Data Entry Personnel
- Research Coordinator

User Actions:

8.14.1. The Report Menu appears with the following options:

- Patient Randomized With No Contacts
- Patient Randomized With Outstanding Contacts
- Patient Contact Not Completely Entered
- Patient Contact Entered But Not Completely Verified
- Patient Follow-up Contact Schedule
- Clinical Center Patient Contact Schedule
- Cancel

8.14.2. Choose the desired report or choose Cancel to exit the application and return to the ICCTG CC Menu.

8.15 Data Field Specifications

Alphabetic Letter Fields: The patient initials is the only alphabetic letter field in the Case Report Forms. Patient initials must be 2 to 3 uppercase letters. Errors will occur if you try to enter fewer than 2 or more than 3 letters or any characters that is not a letter.

Categorical Fields: A categorical field is a set of numeric choices as indicated in the Case Report Forms. The user must enter a number, and it must be contained within the range specified on the annotated case report forms. If user enters an out of range number, then the system should make user aware that an illegal number has been entered and needs correction before proceeding to next question.

Date Fields: There are two types of date fields: MM/DD/YY and MM/DD/YYYY. For the MM/DD/YY fields, the user may enter 5 or 6 digits. The month may be represented by one digit, but the day and the year must be represented by two digits. For the MM/DD/YYYY fields (only one—the birth date on the **DEMO** and **CRSCK**), the user may enter 9 or 10 digits. The month may be represented by one digit, the day by four digits and the year must be represented by four digits. A slash (/) is not needed to separate the month, day, or year, however, a slash (not at dash) is allowed in entry. The range for each date field is indicated on the annotated forms.

Numeric Field: Numeric fields must contain numbers only, and an error should prevent the user from entering any value other than a number. The size of the field should correspond to the size indicated on the case report form. The ranges for each field are indicated on the annotated forms.

Time Field: The user may enter 3 or 4 digits for the time field. The hour may be represented by one or two digits, and the minutes must be represented by two digits. The user is not required to enter the semicolon (:) between the hour and the minutes, but the system should accept it. All time fields are in the 24 hour format.

Free text fields: There are several places where a free text answer is requested. The only text field that will be entered on the database is AESAE.

9 DATA COORDINATING CENTER RESPONSIBILITIES

9.1 Data Coordinating Center (DCC)

The 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:

- Overall leadership regarding study design and conduct of the clinical trial.
- Preparation and distribution of the study protocol and Manual of Procedures, based on collaboration with the Steering and Planning Committee and NIDDK Project Scientists.
- Collaboration with other study investigators in the development, testing, and use of all CRFs and study procedures.
- 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.
- Development and application of quality assurance procedures including data tracking and validation, query processes, and maintenance of related documentation.
- Development of tracking and storage procedures for laboratory samples.
- Training of clinical site staff and coordination of the site monitoring.
- Coordination of Steering and Planning Committee and External Advisory Committee meetings.
- Preparation of detailed reports regarding participant recruitment and retention, data collection activities, and interim results to the External Advisory Committee.
- Collaboration with study investigators in the analysis and publication of study results.

9.2 Clinical Site Monitoring

The ICCTG is a cooperative agreement study in which all investigators and the NIDDK have a shared responsibility for the overall quantity and quality of the data collection.

While it is the responsibility of the DCC to monitor the quantity and quality of data being collected throughout the course of the study, the NIDDK Project Officer has authorized a sub-contract with a site monitoring firm that will operate under the guidance of the DCC.

The site visits will help the DCC identify concerns that had not been identified through database queries and will assist the randomization sites in improving their overall compliance with protocol and regulatory requirements and with data collection procedures.

This firm is expected to conduct three (3) monitoring visits to each randomization site during the course of the study as follows:

- the first site visit after 3 – 5 patients have been accrued;
- the second, at a mid-way point during participant accrual;
- the third, at the close of the study.

A letter describing the requirements and expectations of the site visit monitor will be sent to the PI, with a copy to the RC, at least four weeks before the scheduled visit.

9.3 Clinical Site Visit Activities

9.3.1 Clinical Site Assessment Parameters

At a minimum, the following areas will be assessed at each site visit:

- Adequacy of participant accrual environment and support systems
- Adequacy of regulatory compliance documents
- Adherence to the protocol
- Data processing procedures
- Validation of all participants randomized
- Verification of medical records and other source documents
- Completeness and accuracy or CRFs
- Inspection of drug storage and accountability records
- Security of confidential documents and drug storage system.

Participant confidentiality will be maintained at all stages of the review process. In the event that conflicts exist between the source documents and the study documents, the site visit monitor will have the RC make a notation to this effect on the study document and have him/her initial and date the notation. Confidential participant records will not be copied.

9.3.2 Clinical Site Assessment Review

At the completion of the site evaluation the site monitor will meet with the RC and the PI if possible, to provide an overview of the visit. The site monitor may also meet with the RC to discuss solutions to or improvements of any data collection and/or participant record organizational problems. At this time the site monitor will prepare an itemized list of issues outstanding on each CRF reviewed during the visit that the RC must correct or clarify prior to the next site visit.

Note: the Site Visit Report should not include issues, which have not been verbally discussed with the RC or PI prior to termination of the visit.

At the close of the site visit, the site monitor will complete the SiteVisit Close-Out Form. This form should be signed by the site monitor and either the randomization site PI or the RC. A copy of this form should be made for the randomization site and the original returned to the DCC for filing. It is the responsibility of the DCC to review these reports in a timely fashion and take any and all necessary actions.

9.4 Clinical Site Visit Reports

The site monitor will be responsible for writing and submitting an official Site Visit Report to the DCC. These reports will be marked CONFIDENTIAL and will be released only to the individuals and organizations listed in this section. A Site Visit Report, following a general,

standardized outline, will be submitted to the DCC, the PI and the RC at the respective randomization site within one (1) week of completing the site visit.

At a minimum, the Site Visit Report will include the following sections:

- A general overview of the purpose of the site visit
- A detailed description of the findings which may include but are not limited to, assessment of protocol adherence and compliance with regulatory requirements
- Data collection process
- Randomization site organization and environment
- Recommendations, including a time frame for their implementation

9.5 Clinical Site Grievance Process

If the randomization site PI does not agree with the recommendations outlined in the Site Visit Report, a formal letter of grievance should be sent to the NIDDK Project Officer, with copies to the Chair of the Steering and Planning Committee and the DCC PI, within three (3) weeks of the submission of the Site Visit Report. The NIDDK Project Officer should provide a formal response to the grievance within two weeks, with copies to the Chair of the Steering and Planning Committee and the DCC Principal Investigator.

9.6 Clinical Site Follow-up Site Visits

A follow-up site visit may be performed in an appropriate time frame that allows for implementation of the Site Visit Report recommendations. The scope of this visit will be to verify that the site monitor's recommendations from the previous site visit have been implemented. The follow-up visit should be completed within three (3) months of the submission of the Site Visit Report.

9.7 DCC Site Visit Activities

The DCC site visit activities will be determined by the NIDDK Project Officer.

The primary purpose of the DCC site visit is to ensure to the Steering and Planning Committee the accuracy and quality of data once they have been submitted to and processed by the DCC.

9.7.1 DCC Site Assessment Parameters

At a minimum, the following issues will be assessed at each site visit:

- Infrastructure and organization
- Project management
- Data management, including quality assurance (QA) monitoring
- Database management systems
- Statistical analysis plans
- Administration and budget issues

The NIDDK Project Officer will be responsible for assembling the site visit team. The DCC will have at least four weeks' written advance notice. The major determinant of scheduling will be the availability of the DCC's Principal Investigator. The absence of other DCC personnel will not necessarily preclude a site visit. A letter describing the requirements and expectations of the site visit team will be sent to the DCC Principal Investigator, with a copy to the Project Manager, at least four weeks before the scheduled visit. A Site Visit Report will be submitted to the Principal Investigator, with copies to the site visit team and the DCC Project Manager, within two weeks of completing the site visit. The DCC will be visited for quality assurance purposes at least once a year, pending NIDDK funding, or as determined by the NIDDK Project Officer. The NIDDK Project Officer will work with the DCC's Project Manager to coordinate the visit dates.

9.7.2 DCC Site Assessment Review

The site visit team will meet with the DCC's PI at the end of the visit to provide verbal feedback. All major issues will be discussed at that time. ***Note:*** The Site Visit Report should not include issues which have not been verbally discussed with the DCC PI prior to termination of the visit. This allows the DCC's PI an opportunity to clarify any issues.

At the close of the site visit, the NIDDK Project Officer or his designee will complete the Site Visit Close-Out form. This form should be signed by the NIDDK Project Officer or his designee, and either the DCC's PI or Project Manager. A copy of this form should be made for the DCC and the original kept by the NIDDK Project Officer for filing.

9.7.3 DCC Site Visit Reports

The NIDDK Project Officer or his designee will be responsible for writing and submitting an official Site Visit Report to the DCC's PI and Project Manager within two (2) weeks of the completed site visit. These reports will be marked ***CONFIDENTIAL*** and will be released only to the DCC's PI and Project Manager.

At a minimum, the Site Visit Report should cover the following areas:

- A general overview of the purpose of the site visit
- Assessment of infrastructure, organization, and project management
- Evaluation of data management and quality assurance (QA) procedures
- Evaluation of computing systems and network support, and backup and security procedures
- Determination of adequacy of staff and budget
- Recommendations, including a time frame for their implementation

9.8 DCC Grievance Procedures

If the DCC PI does not agree with the recommendations outlined in the Site Visit Report, a letter of grievance should be sent to the NIDDK Project Officer, with copies to the Chair of the Steering and Planning Committee, within three (3) weeks of the submission of the Site Visit Report. The grievance will be reviewed by the NIDDK Project Officer and the Chair of the Steering and Planning Committee. The NIDDK Project Officer should provide a response to the grievance within two weeks, with a copy to the Chair of the Steering and Planning Committee.

9.9 DCC Follow-up Site Visit

A follow-up visit may be performed in an appropriate time frame that allows for implementation of the Site Visit Report recommendations. The scope of the visit will be to ensure all recommendations made at the previous site visit have been implemented. The follow-up visit should be completed within three (3) months of the submission of the initial report.

9.10 Maintenance and Disposition of Study Documents, Data and Materials

This section describes the procedures that will be employed for maintenance and disposition of study documents, data forms, tapes, results of analysis and materials during and at the conclusion of the ICCTG RCT #1.

9.10.1 Internal Distribution of Study Documents

The DCC is responsible for maintaining a record of all documents, reports and meeting minutes pertaining to ICCTG RCT #1. During the conduct of this protocol, the DCC will be responsible for the distribution of the Protocol, Manual of Operations and Procedures, and study reports to the ICCTG randomization sites. At the end of the study, these documents will be archived by the DCC and forwarded to the National Technical Information Service (**NTIS**). Minutes of all appropriate committee meetings will be maintained in the files at the DCC. At the conclusion of the study, these minutes will be archived and forwarded to the NIDDK.

9.10.2 External Distribution of Study Documents

The NIDDK will be responsible for the distribution of study documents and manuscripts requested by individuals not associated with ICCTG RCT #1.

9.10.3 Case Report Forms (Data Collection Forms)

At the close of the study, all CRFs on file at the DCC, without personal identifiers, will be archived and stored at the DCC. The clinical sites will maintain a file on each participant, which will become part of the participant's medical record.

9.10.4 Data Tapes and Analysis of Results

The DCC will prepare a computer tape of the study data, results, and analyses at the conclusion of the study. This tape will be accompanied by appropriate documentation. One copy will be forwarded to NIDDK and one to the NTIS, U.S. Department of Commerce, Springfield, Virginia so that the information may be generally available, at a small charge, to the scientific community. The DCC will prepare a data tape of analysis pertaining to each major study paper. At the end of the analysis phase, all of these tapes with appropriate accompanying documentation will also be submitted to NIDDK and NTIS. The DCC will provide documentation of all formulas and statistical analyses used in the study or referred to in the study documents. This information will also be made available to NIDDK and NTIS.

9.10.5 Laboratory Specimens and Materials

Specimens collected by the randomization sites will be kept for long-term storage until the end of ICCTG RCT #1. At that time, the Steering and Planning Committee will decide as to the

disposition of these specimens. All specimens and materials not claimed or designated by the Steering and Planning Committee will be destroyed.

9.11 Record Retention

The DCC must maintain all trial records for a period of seven (7) years.

References

1. Slade, D., V. Ratner, and R. Chalker. 1997. A collaborative approach to managing interstitial cystitis. Urology 49:10-13.

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4. Held, P.J., P.M. Hanno, A.J. Wein, M.V. Paul, and M.A. Cahn. 1990. Epidemiology of interstitial cystitis. In Interstitial Cystitis. P.M. Hanno, editor. Springer-Verlag, London. 29-48.

5. ICDB Data Coordinating Center. Interstitial Cystitis Data Base (ICDB) Study Manual of Operations. Version 4.1. 6-14-1995. Milton S. Hershey medical Center, Hershey, Pa. (GENERIC)
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6. Anonymous. Code of Federal Regulations: Title 21, Volume 5, Parts 310.305, 312.32, and 314.80, Parts 310.305; Final Rule in the Federal Register as of April 6, 1998. DC. U.S. Government Printing Office.

Glossary

Abdomen: The portion of the trunk located between the pelvis and the thorax. It contains the stomach, lower part of the esophagus, small and large intestines, liver, gallbladder, spleen, pancreas, and bladder.

Abortion: Forced ending of a pregnancy before the embryo or fetus is capable of surviving outside of the uterus.

Acupuncture: A traditional Chinese technique for treating certain painful conditions by passing long thin needles through the skin to specific points.

Acetylsalicylic acid: Aspirin.

Active genital herpes: Symptomatic (urinary discomfort which may be accompanied by retention) infection of recurrent (not first) episode of genital herpes.

Active urethral calculi: Painful episode of calculi (stone) lodged in the urethra that may have no other urinary symptoms. Treatment depends on the size, shape and position of the stone.

Adverse Event (AE): An 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.

Allergic rhinitis: Also known as hay fever.

Allergy: An abnormally sensitive bodily reaction to environmental factors or substances.

Analgesic: A drug that relieves pain. Analgesic drugs include nonprescription drugs such as aspirin and other nonsteriodal antiflammatory drugs (NSAIDs), and those classified as controlled substances and available only by prescription.

Anesthesia: Drugs which cause total or partial loss of physical sensation with or without loss of consciousness.

Antibiotics: Drugs that stop the growth of or destroy microorganisms (germs). Used to treat and prevent infectious diseases.

Anticholinergics: A type of drug which relaxes the bladder muscle to ease bladder spasms. Other possible effects include relaxing the bowel muscle (to ease cramps), dry mouth, difficulty in focusing the eyes to read, or decreased sweating.

Antigen: A substance that induces the formation of antibodies which interact specifically with it.

Antihistamines: Drugs used to counteract the effects of histamine production in allergies and colds. These effects include a stuffy nose, runny eyes, itching or rash.

Anti-inflammatories: Drugs that reduce inflammation.

Anxiolytic: A drug that relieves anxiety.

APTT: Activated Partial Thromboplastin Time

Arthritis (not rheumatoid): Inflammation of one or more joints in which the connecting tissue surrounding the joint gradually wears away.

Arthritis (rheumatoid): A type of arthritis in which the patient's body makes antibodies which attacks his/her own joints.

Asthma: A condition of the lungs in which the airways become narrow, the chest feels tight, and breathing is difficult.

Atopic dermatitis: An inflammation of skin evidenced by itching, redness, and various skin lesions. This type of dermatitis is of unknown etiology.

Augmentation cystoplasty: An operation which enlarges the bladder by attaching a patch of bowel onto the bladder.

Autoimmune Disorder: A disorder produced when the body's normal tolerance of its own antigenic markers on cells disappears.

Bacteria: A group of single cell microorganisms, some of which cause diseases.

Bacterial cystitis: Bacterial infection of the bladder.

Bacterial prostatitis: Inflammation of the prostate due to bacterial infection.

Balloon dilation of the prostate: An interventional radiologic procedure whereby a balloon is passed through the urethra and inflated in the region of the prostate thereby compressing the prostate.

Barbiturate: A group of organic compounds that depress the central nervous system, depress respiration, affect heart rate, and decrease blood pressure and temperature. These drugs are habit forming.

Baseline Visit 1(B1): Conducted sometime between days –28 to –7.

Baseline Visit 2 (B2, Day 0): If the patient is eligible, the day/visit in which he/she is randomized and given study drug.

BCG (Bacillus Calmette-Guerin): Medication for the treatment of Interstitial Cystitis.

Benign: Not recurrent or progressive; nonmalignant.

Benign Prostatic Hypertrophy (BPH): A nonmalignant enlargement of the prostate due to excessive growth of prostatic tissue.

Benzodiazepine: Any of a group of chemically similar psychotropic drugs with potent hypnotic and sedative action; used predominantly as anti-anxiety and sleep-inducing drugs.

BID: 2 times a day

Biofeedback: Transvaginal/transrectal probe placed to contract/relax pelvic floor muscles appropriately.

Birth control: Temporary and permanent methods which prevent fertilization of an egg or the implantation of a fertilized egg.

Bladder: A sac that lies in the bottom part of the pelvic cavity and holds urine before urination.

Bladder biopsy: The removal of bladder tissue to examine under a microscope.

Bladder calculus: An abnormal concretion, commonly called a stone, located within the bladder.

Bladder capacity: Amount the bladder will hold or store.

Bladder distention: See " bladder hydrodistention".

Bladder holding/retraining therapy: Once pain is under control, delay voiding 5-10 minutes over a 12 week period to increase voiding interval. 5-10 quick pelvic floor muscle contractions with urgency may be helpful.

Bladder hydrodistention: Stretching of the bladder by filling it with water.

Bladder instillation: Placing a medication into the bladder through a catheter.

Bladder ulcers: A hole or crater in the bladder wall.

Blood coagulation: The process of clumping together of blood cells to form a clot.

Blood coagulation tests: Used for testing clotting of the blood.

Brompheniramine: An antihistamine.

Caesarian section (C-section): An operation to remove a baby through a surgical incision made in the mother's abdominal wall.

Carcinoma: A new growth or malignant tumor that occurs in epithelial tissue.

Catheter: A tube passed through the body for evacuating fluids or injecting them into body cavities.

Central (sacral nerve root) electrical stimulation: Electrode placed next to third sacral nerve root to inhibit an overactive bladder.

Cervix: The narrow outer end of the uterus.

Chiropractic treatment: The use of massage/manual therapy/spinal manipulation for lumbosacral/pelvic floor asymmetry/hypo and hypertonic states.

Chlorpheniramine: An antihistamine.

Chronic bacterial prostatitis: Inflammation of the prostate due to long-standing bacterial infection.

Chronic Fatigue Syndrome (CFS) (Epstein-Barr Virus): A virus believed to cause infectious mononucleosis, a disease characterized by swollen lymph glands, high fevers, headache, sore throat, and a general felling of illness and weakness.

Cimetidine (Tagamet): A histamine H_2 receptor antagonist. It inhibits gastric secretions and is indicated for treatment of gastric and duodenal ulcers.

Clinical Trial: A carefully designed and executed investigation of the effects of a drug administered to human subjects.

Clorpactin: A drug that decreases IC symptoms in some patients when placed directly into the bladder.

Connective tissue mast cell (CTMC): A connective tissue cell that contains heparin and histamine in its granules.

Contact Dermatitis: Inflammation and irritation of the skin due to contact with an irritating substance.

Cyclophosphamide: A drug used in certain types of cancer chemotherapy, or to treat certain auto-immune disease, or (in some cases) to prevent rejection after organ transplant. Marketed under the name Cytoxan.

Cystectomy: Removal of all or part of the bladder.

Cystocele: A bulge which occurs when the bladder descends (“falls”) into the vagina.

Cystolysis: Cutting the nerves which surround the bladder in an attempt to stop bladder pain or spasms.

Cystometrogram (CMG): A recording of urinary bladder pressure at various stages of filling.

Cystoscopy: Looking into the bladder through a lighted tube so the inside of the bladder can be seen.

Cytoxan: A drug used in certain types of cancer chemotherapy , or to treat certain auto-immune disease, or (in some cases) to prevent rejection after organ transplant. The brand name of cyclophosphamide.

Day 0 (Baseline Visit 2): If the patient is eligible, the day/visit in which he/she is randomized and given study drug.

D&C: Abbreviation for dilation and curettage – a gynecological procedure which involves dilating the cervix and scraping the uterine lining. Sometimes used as a 1st trimester abortion procedure.

D&E: Abbreviation for dilation and evacuation – a 2nd trimester abortion procedure that uses suction and forceps.

Detrusor: External longitudinal layer of the muscular coat of the bladder.

Diabetes: A disease characterized by excessive urination, In sugar diabetes (diabetes mellitus), the body tissues do not use sugars normally and excess sugar is found in the urine. In water diabetes (diabetes insipidus), the kidneys are unable to hold water in the body, and the lost water appears as excess urine.

Diabetic cystopathy: Bladder dysfunction caused by diabetes.

Diagnostic tests: Medical tests performed to assist the doctor in determining the cause and nature of the illness.

Diaphragm: A soft rubber or plastic cup that fits over the uterine cervix for birth control purposes.

Diphenhydramine: An antihistamine.

DMSO: Dimethyl sulfoxide. A medication instilled directly into the bladder that acts as an anti-inflammatory agent.

Diverticulectomy: A transvaginal surgical excision of a mulcosalized sac adjacent to the urethra (see the urethral diverticulum).

Diverticulitis: Inflammation of the diverticulum, which is an abnormal pouch or sac opening from a hollow organ (as the intestine or bladder).

Double-blind: A method of scientific investigation in which neither the subject nor the investigator knows what treatment, if any, the subject is receiving.

Dysuria: Painful or difficult urination.

Elmiron® pentosan polysulfate): An oral medication believed to coat the bladder wall and protect it from irritants in the urine.

Endometriosis: A condition which occurs when tissue that normally lines the uterus grows in other parts of the body. Since this tissue cannot leave the body, it grows with every menstrual cycle and may become painful.

Enterocele: A bulge seen when part of the intestines "fall" into the vagina.

Epithelium: The layer of cells forming the epidermis of the skin and the surface layer of mucous and serous membranes.

Epstein-Barr Virus (Chronic Fatigue Syndrome): A virus believed to cause infectious mononucleosis, a disease characterized by swollen lymph glands, high fevers, headache, sore throat, and a general felling of illness and weakness.

Erection: The state of swelling, hardness, and stiffness observed in the penis and to a lesser extent in the clitoris, generally due to sexual excitement.

Etiology: All of the causes of a disease.

Exocytosis: The discharge of particles from a cell. They are too large to pass through the cell membrane by diffusion.

Fibromyalgia or Fibromyositis: Chronic pain in the muscles and soft tissues surrounding the joints.

Flare: A period of time in which the symptoms of a disease become more severe.

General anesthesia: Anesthesia that is complete and affects the entire body with loss of consciousness when the anesthetic acts on the brain.

Genital herpes, active: Symptomatic (urinary discomfort which may be accompanied by retention) infection of recurrent (not first) episode of genital herpes.

Genitalia: Organs of generation; reproductive organs.

Glomerulations (Hunner's ulcer): A painful, slow-to-heal ulcer of the urinary bladder.

Glycosaminoglycans (GAGs): GAGs exist as a continuous layer on the bladder urothelium. The GAG layer functions as a permeability and antiadherence barrier

Gross hematuria: Visible blood in the urine.

H1 receptor antagonist: Antihistamine: Neutralizes histamine; works by blocking the action of histamine.

H2 receptor antagonist: Group of ulcer healing drugs related to antihistamines related to specific preventing release of acid in stomach.

Half-life: In biology and pharmacology, the time required by the body, tissue, or organ to metabolize or inactivate half the amount of a substance taken in.

Hay fever: Popular name for allergic rhinitis, maybe seasonal due to pollens or year round due to house dust, molds or pets. It is an inflammation of the mucous lining of the nose.

Hemoglobin: The iron-containing pigment of the red blood cells which carries oxygen from the lungs to the tissues.

Hemostasis: An arrest of bleeding or of circulation.

Heparin: A drug placed directly into the bladder for the treatment of IC. It is also used to prevent or treat blood clots.

Histology: The study of the microscopic structure of tissue.

Homeopathy: Low dose suppression by "natural" drugs (herbs) specific for a disease/diseased organ.

Hunner's ulcer (glomerulations): A painful, slow-to-heal ucer of the urinary bladder.

Hydrodistention: Stretching of the bladder by filling it with water.

Hydroxyzine: Typically an anti-anxiety or antihistamine medication, but also used by some physicians to treat Interstitial Cystitis.

Hysterectomy: Surgical removal of the uterus through the abdominal wall or vagina.

IC (Interstitial Cystitis): Inflammation and irritation of the bladder of unknown cause. Common symptoms include frequent and/or painful urination.

Immunoglobulin E (IgE): An immunoglobulin that attaches to mast cells in the respiratory and intestinal tracts and plays a major role in allergic reactions.

Implanted peripheral nerve stimulator: A surgically implanted electrode used to modulate bladder activity ("bladder pacemaker").

Incontinence: The inability to retain urine, semen or feces because of loss of sphincter control or cerebral or spinal lesions.

Inflammation: Localized heat, redness, swelling, and pain resulting from injury or illness.

Inguinal: Relates to the groin, which is the lower abdomen and inner thigh area of the body.

Inguinal hernia: Bulging of the intestines through the abdominal wall into the groin region.

Inhalant: A medication or compound suitable for inhaling (drawing in by breath).

Injection: The forcing of a fluid into a vessel, tissue, or cavity intramuscularly or under the skin.

INR: International Normalized Ratio

Interstitial Cystitis (IC): Inflammation and irritation of the bladder of unknown cause. Common symptoms include frequent and/or painful urination.

Intravesical: Situated or occurring within the bladder.

Irritable Bowel Syndrome (IBS): The bowel is overactive or excitable with symptoms of abdominal discomfort, cramping, and increased bowel activity.

IUD: Intrauterine device used for birth control purposes.

IV: Intravenous (within or into a vein).

Kidneys: A pair of organs in the back of the abdominal cavity. Their function is to maintain proper water balance, control acid-base concentrations and eliminate certain wastes as urine.

Kidney stones: Stones made in the kidney. The stone normally begins as a tiny speck of solid material deposited in the middle of the kidney. Over time, more material clings to the speck, until a stone develops.

Laparoscopy: Examination of the abdominal area with a small camera which is passed through a tube inserted into a small cut in the abdominal wall.

L-arginine: The natural form of arginine, a non-essential amino acid.

Leukocyte: A white blood cell or corpuscle.

LFTs: Liver Function Tests

Likert scale: Ordinal scale with discrete categories.

Liver: The largest organ in the body. The liver secretes bile is the site of a great many metabolic functions.

Lumbosacral/vertebral disc disease: Disease of disks found in the spinal column of the lower back. Symptoms include back pain and problems with bowel and bladder function.

Lupus: A connective tissue disease characterized by inflammation. It can affect different parts of the body, especially skin, joints, blood, and kidneys.

Lyme disease: A disease carried by certain kinds of ticks. It starts with fever, fatigue, headache, and stiff neck, and may include nervous system and heart problems. Arthritis may occur several weeks to months later.

Malignant: Growing worse; resisting treatment, said of cancerous growths.

Mast cell metabolites: Substances made in mast cell.

Mast cells: A large tissue cell resembling basophil that does not circulate in the blood.

Menopause: The complete ending of the menstrual cycle, including both ovulation and menstrual periods. This can occur naturally or as a result of a complete hysterectomy (including removal of the ovaries).

Menstrual: Relating to the periodic flow of blood (period) from the uterus in females.

Menstrual cycle: The periodic series of changes occurring in the uterus and related organs associated with a woman's period as well as the time between periods.

Menstrual period: The periodic flow of blood from the uterus.

mg: Milligram

Migraine headache: A type of headache which usually involves severe pain, nausea, and is sometimes proceeded by an "aura" or signal that the pain is about to begin.

Mind/Body techniques: Self-visualization, self-hypnosis, deep breathing, yoga, music used as treatment.

Miscarriage: The spontaneous ending of a pregnancy at any time before the fetus could have survived after birth.

ml: Milliliter

Mucosa: A mucous membrane or moist tissue layer that lines the hollow organs and cavities of the body.

Narcotics: Drugs that dull the senses, induce sleep, and become addictive with prolonged use.

Nasal: Pertaining to the nose. Uttered through the nose.

Neurectomy: Surgery to interrupt nerves by severing or removing the nerve.

Neurogenic: Originating from nervous tissue.

Neurologic disease: Disease involving the nervous system.

Neurostimulation: An electrical device used to stimulate nerves.

Nitrite: A salt of nitrous acid. Nitrites dilate blood vessels, reduce blood pressure, depress motor centers of the spinal cord, and act as antispasmodics.

Nocturia: Excessive urination during the night.

Norplant: A method of birth control that consists of a fan-like arrangement of 6 matchstick-shaped capsules implanted beneath the skin of the woman's arm, just above the elbow.

NSAID (nonsteroidal anti-inflammatory drug): A drug that has analgesic, anti-inflammatory and antipyretic (anti-fever) action. Drugs of this type have been used extensively in treating arthritis and general inflammation.

Open prostatectomy: Excision of part or all of the prostate gland through an abdominal incision.

Oral: Concerning the mouth.

Oral medications: Medications taken by mouth; swallowed.

Orgasm: A state of physical and emotional excitement that occurs at the climax of sexual intercourse.

Ovaries: Female reproductive glands that produce eggs for fertilization.

Pap smear: a medical test that involves examination of a sample taken from a woman's cervix to detect early stages of cervical cancer.

Patch: Treatment that is applied on the epidermis and passes through.

Pathogenesis: The origin and development of a disease.

Pathology: The study of the nature and cause of disease, which involves changes in structure and function.

Pathophysiology: The study of how normal physiological processes are altered by disease.

Pelvic floor therapies: Biofeedback, electrical stimulation, physical therapy, pelvic floor muscle rehabilitation (Kegel exercises).

Pelvic Inflammatory Disease (PID): Infection of the uterus, fallopian tubes, and adjacent pelvic structures that is not associated with surgery or pregnancy.

Pelvic radiation therapy: Use of x-rays to treat cancer in the pelvis.

Pelvis: The bony structure formed by the innominate bones, the sacrum, the coccyx, and the ligaments uniting them. The structure serves as a support for the vertebral column and for articulation with the lower limbs.

Perineal: Concerning, or situated on the perineum.

Perineum: The area between the vulva (vaginal opening and surrounding areas) and the rectal opening in the female and between the scrotum and rectal opening in the male.

Peripheral electrical stimulation: Transvaginal/transanal probe, transcutaneous patch delivers electrical stimulation to cause inhibition of an overactive bladder and strengthen pelvic floor muscle.

Permeability: The quality of being capable of allowing the passage of fluids or substances in solution.

pH: Hydrogen ion concentration

Physiology: The science of the functions of the living organism and its components and of the chemical and physical processes involved.

PID (Pelvic Inflammatory Disease): Infection of the uterus, fallopian tubes, and adjacent pelvic structures that is not associated with surgery or pregnancy.

Placebo: An inactive substance.

Platelet: A round or oval disk, found in the blood of vertebrates. Platelets play an important role in the blood coagulation, hemostasis, and blood thrombus formation.

Positive culture: A diagnostic test that shows growth (therefore presence) of a suspected organism.

Positive urine culture: A diagnostic test that shows growth of bacteria in the urine.

Prolapse: A "falling" or dropping down of an organ or internal part, such as the uterus or rectum.

Prostate: A male gland that surrounds the urethra just below the bladder.

Prostate surgery: Surgery of the male gland that surrounds the urethra, just below the bladder.

Prostatitis: Inflammation of the prostate.

Psychotherapy: A method of treating disease, especially nervous disorders, by mental rather than physical means.

PTT: Partial Thromboplastin Time

QID: 4 times a day

Randomized: In research, a method used to assign subjects to experimental groups. Before this step every attempt is made to ensure that the subjects are as nearly equivalent as possible.

Rectal: Pertaining to the rectum.

Rectocele: A bulge which occurs when the rectum protrudes or "falls" into the vagina.

Rectum: The lower part of the large intestine.

Regional anesthesia: Anesthesia that is nerve or field blocking, causing insensiblity over a particular area.

Remission: A long period of time in which symptoms of a disease lessen or disappear.

Residual urine volume: The amount of urine left in the bladder after urination.

Rheumatoid arthritis (RA): A type of arthritis in which the patient's immune system attacks his/her own joints.

SC: Subcutaneously (beneath the skin).

Scleraderma: A chronic manifestation of progressive systemic sclerosis in which the skin is taut, firm, and edematous, limiting movement.

Secretagogue: That which stimulates secreting organs.

Sedative: An agent that exerts a soothing or tranquilizing effect. Sedatives may be general, local, nervous, or vascular.

Serious Adverse Event (SAE): 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 (6).

Serum: The clear fluid that separates from blood when it clots.

Sexually transmitted disease: A disease acquired as a result of sexual intercourse with an infected individual.

Sinusitis: Inflammation of the sinuses surrounding the nose.

Sjogren's Syndrome: A syndrome that includes dry mouth, dry eyes, purple spots on the face and enlargement of the salivary (spit) gland.

Steriods: A type of hormone naturally made by the body which can also be manufactured and given as pills or shots. Anabolic steroids are the ones used by athletes to increase muscle size and strength. Anti-inflammatory steroids, such as cortisol, are used to decrease inflammation in several types of diseases.

Sublingual: Beneath or concerning the area beneath the tongue.

Submucosal: Layer of the areolar connective tissue under a mucous membrane.

Symptomatic Urethral Diverticulum: Symptoms include pain; dyspareunia; recurrent urinary tract infection; dysuria, or post void dribbling.

Synthetic: Artificially prepared.

Tagamet (cimetidine): A histamine H_2 receptor antagonist. It inhibits gastric secretions and is indicated for treatment of gastric and duodenal ulcers.

Thrombus: A blood clot that obstructs a blood vessel or a cavity of the heart.

Topical: Pertaining to a definite surface area; local.

TID: Three times a day

Tissue: A group or collection of similar cells and their intercellular substance that act together in the performance of a particular function. The primary tissues are epithelial, connective, skeletal, muscular, glandular, and nervous.

Transdermal: Treatment that is applied on the epidermis and passes through.

Transvaginal surgery: Surgery through the vagina or across its wall.

Tubal ligation: A procedure which makes a woman sterile (unable to become pregnant) by tying off or cutting the tubes from the ovaries to the uterus.

Tuberculous cystitis: Inflammatory condition of the bladder caused by tuberculosis.

TUIBN: Transurethral Incision of Bladder Neck

TUIP: Transurethral Incision of the Prostate

TUMT: Transurethral Microwave Therapy

TUNA: Transurethral Needle Ablation

TURP: Transurethral Resection of the Prostate

Ultrasound: The use of intermittent high-frequency sound waves to take pictures of the body's inner organs by recording their echoes.

Ureter: A tube that carries urine from the kidneys to the bladder.

Ureteral calculus: An abnormal concretion, commonly called a stone, located within the ureter.

Urethra: The tube that carries urine from the bladder to the outside of the body.

Urethra dilated or dilation: Stretching the urethra by passing a tube through it.

Urethral calculi, active: Painful episode of calculi (stones) lodged in the urethra that may have no other urinary symptoms. Treatment depends on the size, shape and position of the stone.

Urethral catheterization: Passing a catheter (or tube) through the urethra and into the bladder for withdrawal or urine or placement of medication into the bladder.

Urethral dilation: Expansion of the urethra.

Urethral diverticulum: Small sacs or pouches caused by the protrusion of the inner lining of the urethra.

Urinalysis: A battery of test of urine including measurements of physical characteristic, microscopic examination and chemical testing.

Urinary incontinence surgery: One of several types of surgical procedures to treat incontinence.

Urinary Stones: Concretion formed in urinary passages.

Urinary tract infection (UTI): Infection of the kidneys, bladder, or prostate gland.

Urinate: To pass urine from the bladder; void; pass water.

Urination: The act of voiding urine.

Urine Culture: Single drop of fresh urine is spread thinly on a nutrient gel and incubated. Any bacteria present will multiply and be analyzed.

Urodynamic evaluation (CMG): The study of bladder pressures during filling and urination, and of the force of the urinary stream.

Urologist: A doctor who specializes in urinary-tract disorders.

Uropathogen: A microorganism capable of causing disease of the urinary tract.

Urothelium: Epithelial (cellular, avascular) layer of the urinary tract.

Uterus: A female organ for carrying and nourishing a baby from conception to birth; womb.

Vagina: The passageway between the uterine cervix and the outside opening.

Vaginal delivery: Birth of a baby through the vagina.

Vaginal infection: An infection of the vagina.

Vaginitis: On-going inflammatory condition caused by fungus or bacteria associated with itching and vaginal discharge.

Void: To evacuate the bladder.

Voiding Diary: Record of urinary frequency and amount over a 24 hour period.

Vulvodynia: A nonspecific syndrome that has no known cause. It is characterized by pain, esp. during sexual intercourse; itching and discomfort.

Acronyms/Abbreviations

AE = Adverse Event
AESAE = Adverse Event/ Serious Adverse Evenet Form
APTT: Activated Partial Thromboplastin Time
BCG = Bacillus Calmette-Guerin
BPH = Benign Prostatic Hypertrophy
BSYM1 = Baseline Symptoms 1 Form
BSYM2 = Baseline Symptoms 2 Form
CARDS = Symptom Ranking Cards
cc = Cubic Centimeters
Co-PI = Co-Principal Investigator
CFR = Code of Federal Regulations
CFS = Chronic Fatigue Syndrome
CRF = Case Report Form
CRSCK = Crosscheck Form
CTMC = Connective Tissue Mast Cell
DCC = Data Coordinating Center
DEF = Deferral Criteria Form
DEMO = Demographics Form
DIARYREC = Medication Diary Record Form
DMS = Data Management System
DPCS = Data Processing Cover Sheet
ELIG = Eligibility Confirmation and Randomization Form
EXAM = Physical Exam Form
EXCL = Exclusion Criteria Form
FDA = Food and Drug Administration
FUSYM = Follow-up Symptoms Form
GAGs = Glycosaminoglycans
GCP = Good Clinical Practice
IBS = Irritable Bowel Syndrome
IC = Interstitial Cystitis
ICCTG = Interstitial Cystitis Clinical Trials Group
ICDB = Interstitial Cystitis Data Base
IgE = Immunoglobulin E
IM = Intramuscular
INCL = Inclusion Criteria Form
INR: International Normalized Ratio
IRB = Institutional Review Board
IU = International Unit
IV = Intravenous
LAB = Lab Results Form
LFT = Liver Function Test
MED = Medical History Form
MEDTRAC = Study Medication Tracking Log
mg: Milligram
ml: Milliliter
MOP = Manual of Procedures

MOS = MOS Sexual Functioning Scale
NIDDK = National Institute of Diabetes, Digestive and Kidney Diseases
NIH = National Institute of Health
NSAID = Nonsteroidal Anti-Inflammatory Drug)
PCHK = Phone Contact Checklist
PDF = Portable Data Files
PDR = Physician's Desk Reference
pH = Hydrogen ion concentration
PHONE = Telephone Contact Form
PI = Principal Investigator
PID = Pelvic Inflammatory Disease
PP&AS = Publications, Presentations and Ancillary Studies
PTCLOSE = Patient Close-out Form
PTCONT = Patient Contact Information
PTDIARY = Patient Daily Medication Diary
PTLOG = Patient Log
PTT = Partial Thromboplastin Time
QID = 4 times a day
RA = Rheumatoid Arthritis
RCT = Randomized Clinical Trial
RC = Research Coordinator
REF = Patient Refusal Log
RUNIN = Run-in Dosage Record Form
RUNINMED = Run-in Medication Dispensing Log
SAE = Serious Adverse Event
SC = Subcutaneously
SCHK = Screening Contact Checklist
SF-36 = Health Status Questionnaire
STCLOSE = Study Close-out Form
STOP = Clinical Center Stop Point Form
STVISIT = Standard Visit Inventory Form
SYMPROB = Interstitial Cystitis Symptom Index and Problem Index
TID = Three times a day
TRANS = Patient Transfer Form
TUIBN: Transurethral Incision of Bladder Neck
TUIP: Transurethral Incision of the Prostate
TUMT: Transurethral Microwave Therapy
TUNA: Transurethral Needle Ablation
TURP: Transurethral Resection of the Prostate
ULOG = Urine Sample Tracking Log
UNIVWIS = University of Wisconsin Symptom Survey
UNMASK = Unmasking Record Form
URINE = Urine Screening Form
UTI = Urinary Tract Infection
UTRAC = Urine Sample Tracking Form
VCHK = Clinic Visit Contact Checklist (VCHK)
VOID = Voiding Diary
VTSCH = Visit Schedule

Appendix A

Appendix B

Appendix C

Appendix D