

# **Interstitial Cystitis Clinical Trials Group (ICCTG)**

**Protocol #2: A Randomized, Multicenter Clinical Trial to Evaluate the Efficacy of Intravesical Bacillus Calmette Guerin (BCG), for the Treatment of Interstitial Cystitis (IC)**

## **MANUAL OF PROCEDURES (MOP)**

**Interstitial Cystitis Clinical Trials Group (ICCTG)  
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## Manual of Procedures

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## **INTRODUCTION**

Interstitial cystitis (IC) describes a typically painful, debilitating and chronic syndrome of the urinary bladder. The presentation of symptoms can be quite variable among patients, leading several authors to posit that IC is a multifactorial syndrome with several proposed etiologies, some of which may be interrelated.<sup>1</sup> The major etiologic theories include: 1) increased bladder epithelial permeability, 2) activation of bladder mast cells, 3) allergic or autoimmune processes, 4) toxic substance(s) in the urine, 5) occult infection, 6) neuropathic changes, and 7) neurogenic inflammation.<sup>2</sup>

Since the etiology of IC remains unclear, directing treatments towards the specific cause(s) of the symptoms is problematic. Various IC treatments are used. Some are directed specifically to one of the proposed etiologies, whereas others are purely empirical. At this time, there is very little knowledge to help clinicians choose which treatments may be most beneficial for specific patients.<sup>3</sup>

In most cases of IC, treatment choices are made by trying the safest and least invasive options first, and then progressing to other treatments (which have more potential morbidity) if the initial treatments do not relieve symptoms effectively.<sup>4</sup> Combining treatments is often needed to improve functional outcome.<sup>5</sup> In theory, combined treatments that address different proposed pathophysiologies (e.g., hydroxyzine and pentosan polysulfate) would be especially beneficial. ICCTG RCT #1, which is currently in progress, is the only clinical trial formally addressing this issue.

Having failed conservative therapy, patients with refractory interstitial cystitis choose to undergo various intravesical treatments to obtain symptom relief. Many of these treatments, however, have failed to demonstrate sustained benefit.<sup>3</sup>

Intravesical Bacillus Calmette-Guerin (BCG) is a novel therapy for the treatment of IC. Although this therapy has been used for years in the treatment of bladder cancer, its exact mechanism of action is unknown.<sup>6</sup> Preliminary studies evaluating its effect in the treatment of IC have shown promising results. Confirmation of these results requires further clinical trial investigation.<sup>6,7</sup>

# **1 Study Design, Objectives, & Endpoints**

## **1.1 Study Design & Objectives**

This ICCTG randomized clinical trial (RCT #2) will utilize a two-arm design to evaluate the efficacy of intravesical BCG in patients with interstitial cystitis, as compared to an intravesical placebo.

The primary objectives of this trial are:

1. To compare treatment with six instillations of BCG to sham treatment with six instillations of saline for effects on symptoms and overall well being in patients with interstitial cystitis (IC).
2. To evaluate changes in urinary markers over time and correlate these changes with changes in symptoms over the same period.
3. To evaluate measures of symptoms and quality of life, including the O’Leary-Sant and Wisconsin symptom indices, and validate their use as endpoints in clinical trials.
4. To obtain additional information on re-induction of intravesical BCG.
5. To obtain information on long-term response of those patients determined to be responders at the completion of Phase 1 of treatment

## **1.2 Study Time Line & Endpoints**

All participants who meet eligibility criteria at baseline screening (a two-to-four week period), will be stabilized on their current IC medications prior to randomization to one of the two treatment arms. Immediately after randomization, there will be a two-week window in which the first instillation must occur. The instillation regimen will require that the interval between treatments be a minimum of six days and a maximum of three weeks. No more than three weeks may lapse between instillations. Each participant is expected to receive total of six instillations (BCG or saline). Instillations will be scheduled according to the participant’s tolerability. The six instillations can be given weekly within six consecutive clinic visits, but all instillations, even if fewer than six, must be administered within a ten-week visit schedule.

For the six months following the intravesical instillations, each participant will continue to be monitored for safety, use of concomitant medications (especially narcotics and medications for IC), quality of life, IC symptoms, and urinary biomarkers.

The primary endpoint will be evaluated at the participant’s Visit 15/Week 34 following randomization in the post-treatment follow-up phase. Participants will be identified as responders and non-responders at week 34 based on their response to the global assessment question and their use of medications for IC symptoms.

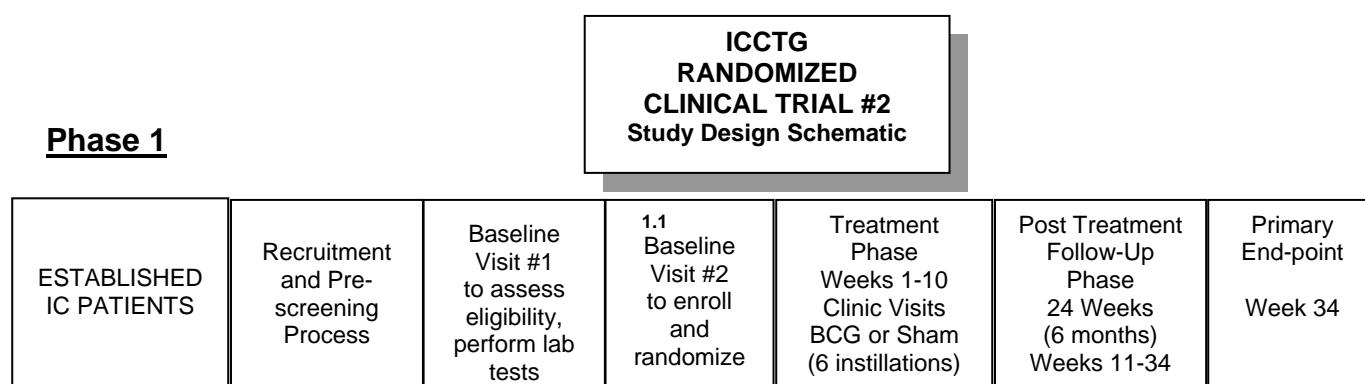
The study consists of two phases as outlined below. Phase I, consisting of initial treatment and follow-up for primary and secondary endpoints, represents the primary phase of the study.

Phase 2 -Non-Responders will be primarily descriptive, and will provide additional information related to open-label BCG treatment for all “non-responders” in Phase I who choose to undergo a

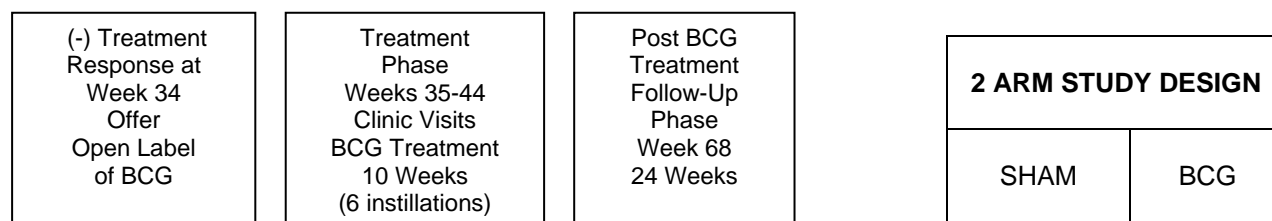


second course of treatment. Phase 2R-Responders will also be primarily descriptive. This phase will provide information on the long-term response of those patients determined to be “responders” at the completion of Phase 1 of treatment. Any participant who **withdraws** from the study **prior to** Visit15/Week 34 (primary endpoint), **will not** be eligible to receive open-label BCG (Phase 2) or be followed as a responder (Phase 2R).

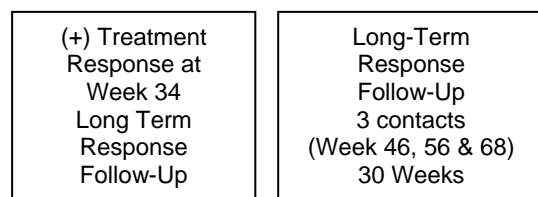
**Figure 1**



**Phase 2 – Non-Responders – Open Label BCG Treatment**



**Phase 2R – Responders – Long-Term Response**



**1.3 General Protocol Policy**

**1.3.1 *Changing the Protocol***

The objectives of the ICCTG RCT #2 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.

### **1.3.2 *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 others. 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 minor impact on the current course of the ICCTG RCT #2 can be properly handled with a letter to each member of the Steering Committee. Proposed changes with greater impact on the course of the ICCTG RCT #2 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 Participant Enrollment**

### **2.1 Participant Population & Recruitment**

#### **2.1.1 *Participant Population***

The study population will be drawn from patients with a confirmed diagnosis of IC, sometime in the past with the results from a cystoscopy/hydrodistention. Any IC participant presenting with symptoms of urinary frequency in conjunction with urinary pain/discomfort persisting for at least 24 weeks will be considered a candidate for enrollment into the study. Participants must satisfy the eligibility criteria in order to be entered into this study.

#### **2.1.2 *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. Each Clinical Center is responsible for accruing as many participants as possible. Because the best methods to achieve recruitment goals depend largely on the organizational structures of the individual clinics, each Clinical Center is also responsible for determining how to best recruit participants from its local population. Some recruitment methods are described below:

- Participants who have participated in, and successfully completed, ICCTG RCT #1 can be candidates for ICCTG RCT #2, upon meeting the screening criteria.
- Potential participants can and will be identified by considering the current participant population in the PI's own clinical (Urology) practice.

- Clinical Centers can recruit potential participants through self-referral, referrals from the medical practices of other urologists, and colleagues of the PI in the surrounding medical community.
- The Interstitial Cystitis Association (ICA) will announce the study on its web site, which will refer interested participants and clinicians to the geographically appropriate investigator.
- A National Institutes of Health (NIH) Sponsored Research Press Release will be arranged prior to the start of ICCTG RCT #2.
- When the study has been officially introduced to the media and the public, ICCTG RCT #2 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.

## 2.2 Pre-Screening

- Each Clinical Center will develop a pre-screening eligibility checklist based on the patient population seen in the urology practice, or the medical community from where patients will likely be referred to the study.
- Every potential study participant will be pre-screened, either over the phone or in person, in order to confirm that (s)he meets the minimal necessary criteria to be eligible to participate in this study.
- If prescreening via 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, requirements for participation--such as intravesical treatment, restricted and excluded medications, Participant's Daily Medication Diary, Void Diary--and the length of time the participant may 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 in order to reduce the number of potential participants scheduled for Visit 1. **The RC should NOT give the potential participant information about study-specific inclusion criteria (such as the grade or severity of symptoms, or the length of time the symptoms must have been present).**
- If pre-screening determines the potential participant is eligible and willing, the RC should schedule a time to review and complete the informed consent and to schedule (Baseline) Visit 1.
- The potential participant should receive a copy of the informed consent either in person, by mail or by fax.

- The RC should allow the potential participant time to consider the study obligations and discuss the study with family members before signing the consent form.
- The informed consent form must be signed in the presence of the PI or the RC **prior to Visit 1** procedures.
- The RC will instruct the potential participant to bring all his/her medications (prescription and over-the-counter) to Visit 1 in order to review concomitant medications and medication diaries with the participant.

## 2.3 Informed Consent

Each clinical center is responsible for ensuring that informed consent is obtained from each participant according to the guidelines of its local Institutional Review Board (IRB), and State Department of Health requirements. The informed consent form must be obtained (signed and dated by the participant) **prior** to initiation of any study related activity. Specifically, the following must be accomplished during the informed consent process:

- The participant must be informed that participation in the study is **voluntary** and that refusal to participate will involve no penalty or loss of benefits.
- The participant must be informed that the study involves **research**.
- The participant must be informed of any **alternative procedures**.
- The participant must be informed of any reasonable foreseeable **risks**.
- The participant must be informed of any **benefits** from the research.
- An outline of safeguards to protect participant **confidentiality** must be included, as well as an indication of which parties are allowed to review the record and of the participant's right to withdraw without penalty. This should be balanced with a discussion of the effect withdrawals have on the study, and the responsibility a participant has, within limits, to continue in the study if (s)he decides to enroll.
- The participant must be informed of his/her right to have **questions answered** at any time and **who to contact** for answers, or in the event of research-related injury.
- The participant must be informed that (s)he will be notified of any safety-related **changes** in the protocol that might affect his/her willingness to continue in the study.
- Participants consented and entered into the trial prior to Protocol Amendment #2 for Phase 2R must be re-consented at primary endpoint, if they are determined to be "responders"
- The participant must be informed as to whether or not any **compensation** will be offered for participation in the study, and whether any medical treatments are available.

<p><b>An informed consent must be obtained from the participant before any study procedures are performed or any medications are altered.</b></p>
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### **2.3.1 Administration of Informed Consent**

The participant is screened to confirm his/her eligibility by reviewing the inclusion, exclusion and deferral criteria.

Once deemed eligible, the RC will provide the potential participant with a copy of the Informed Consent Form and ask him/her to read a few sentences aloud to ascertain whether the potential participant needs assistance with the written material. If the participant or their legal representative cannot read the written material, then an impartial witness should be present for the entire consent process. After the participant has had a chance to ask questions and has signed the consent form, the witness would then sign and date the consent, to affirm the process. (See Protocol Appendix A *Consent Form*). **NOTE:** For non-English speaking participants, the individual clinical center must provide a professionally translated, IRB approved version of the consent form and all supporting materials. In addition, a clinical research staff member who is fluent in the participant's native language or a professional interpreter will be utilized to explain the study and answer the participant's questions.

The consent form should be reviewed in a comfortable setting where the participant is able to make a free choice without pressure. Ample time should be given to allow the participant to thoroughly read and process the information.

If the participant wishes to take the Informed Consent Form home before reaching a decision, then (s)he may do so. At the subsequent visit, the RC should answer any questions raised by the participant.

The participant should be made aware of his/her responsibilities through the Screening phase and the Treatment/Follow-up phase. The importance of continued follow-up is stressed. This is balanced with a discussion of the effect of participant withdrawal on the study.

The Informed Consent Form **must** be **personally** signed and dated by the participant or his/her legal representative, and the authorized person obtaining consent. It is recommended that the Principal Investigator (PI) also sign the consent form. A participant should not be asked to sign the consent statement if (s)he has any doubts about enrolling or if the clinic staff believes (s)he does not understand what his/her participation would involve. Under *no* circumstance is any study information to be collected or study procedures performed for the specific purpose of ICCTG RCT#2 **before** the participant has signed the informed consent form.

The RC will maintain the **original** consent document in the participant's confidential file with other confidential documentation, and provide a copy of the signed and dated informed consent(s) to the participant. A second copy of all informed consent(s) should be made as a back-up and stored together in the study-confidential file. In addition, a signed/dated progress note should be made in each participant's file that the informed consent process took place prior to any study procedures.

This same consent process as outlined above, will be followed for those patients who as a result of Protocol Amendment #2, required re-consenting to in order to participate in Phase 2R.

To ensure confidentiality, the RC will not send copies of the consent form(s) to the DCC or keep any copies of the Informed Consent Form with the case report forms (CRFs).

## **2.4 Confidentiality**

### General Information

Extensive efforts will be made to ensure and maintain participant confidentiality, except as required by the regulations. All identifying information **must** be maintained in a secure area at all times and **must never** appear on CRFs. Consent forms and source documentation **must** be maintained in a separate folder from the CRFs. If source documentation has to be made available for data audits, **copies** of the source documents should be forwarded to the DCC with only Participant ID number visible and personal information obscured.

The DCC staff has access to the *Participant ID* number for data management purposes. All communication between the DCC staff and the clinical center staff regarding participant data occurs via the *Participant ID* number only.

All CRFs and source documents sent to the DCC **must** have all participant identifiers, other than the *Participant ID* number, obscured. However, please never obscure information on the original/source documents.

The staff at the DCC **will not** have access to any participant locator or identifying information available to the clinical center.

### **2.4.1 Participant ID Number (PTLOG)**

A Participant Log (**PTLOG**) has been developed for each clinical center. It includes columns for the unique Participant ID numbers for ICCTG RCT #2, participants' names, initials, randomization (drug packet) numbers and other relevant information. After the participant has signed the informed consent document, the participant is logged in the PTLOG and assigned a Participant ID number. Each participant should be assigned the next available Participant ID number.

All communication with the DCC regarding individual participants must be through the Participant ID number. Once a Participant ID number has been assigned, it should never, for any reason, be reassigned. Participant Log 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 5-digit Participant ID number is composed of two identifiers:

- The first 2 digits indicate the clinical center numbers.
- The last 3 digits indicate the sequential ordering of participants.

Each Clinical Center will have a discrete range of ID numbers corresponding to the Clinical Center numbers listed below. For example Participant ID # 01012 describes Clinical Center #01, University of Pennsylvania and Participant ID number #012.

The Clinical Center numbers are as follows:

- 01 = University of Pennsylvania
- 02 = New England Medical Center
- 03 = University of Rochester
- 04 = University of Maryland
- 05 = University of Oklahoma
- 06 = William Beaumont Hospital
- 07 = Henry Ford Hospital
- 08 = Queens Hospital, Ontario, Canada
- 09 = Stanford University Medical Center
- 10= Santa Clara Medical Center (Satellite of Stanford University Medical Center)

**Table XX.X: Participant ID Log:**

<b>Participant ID #</b>	<b>Name (First, Middle Last)</b>	<b>Medical Record Number</b>	<b>Date Informed Consent Signed</b>	<b>Randomized to RCT #2? (Yes/No)</b>
0 1 0 0 1	John J. Doe	A1234567890	0 6 / 1 8 / 2 0 0 1	No
0 1 0 0 2	Pat X. Reed	C2345678901	0 6 / 2 0 / 2 0 0 1	Yes
0 1 0 0 3	Linda S. White	E3456789012	0 6 / 2 2 / 2 0 0 1	No

## **2.5 Screening/Baseline Phase**

- Screening consists of, at a minimum, two screening/baseline visits: Visit 1 and Visit 2.
- If at any time during the screening process the patient is found to be ineligible, they must be informed of this fact as soon as possible.
- If the participant seems eligible at Visit 1, Visit 2 must be 7 – 28 days from Visit 1.
- During the screening period, the RC will work with the participant to determine a “stabilized” dose of any IC medications which the participant is currently taking on a variable or PRN Schedule. The participant will be informed that they may take less than this dose, but should try not to take more, and will be permitted to use breakthrough medications for symptom flares.
- Participants must meet eligibility criteria before undergoing procedures for randomization into the study. Eligibility must be confirmed within 24 hours of randomization, and therefore the ELIG CRF must be filled out based on the information collected or confirmed at Visit 2.

- Symptom scores are measured at Visits 1 **and** 2. Both sets of scores are used to determine eligibility.
- **If a potential participant is not randomized within four weeks (28 days) after Visit 1, the participant must be re-screened with the informed consent reviewed again and Visit 1 procedures and data collection repeated.**
- The re-screened participant maintains the **same** assigned Participant ID (**PT ID**) number, and should not be assigned a new number. The participant will be re-entered into the Participant ID Log with the appropriate new information pertaining to date of informed consent and whether or not the participant was successfully randomized.
- Participants who initially are deferred from entry in the study based on deferral criteria may be reconsidered for inclusion at a later date, **if the condition(s) resolves** according to the specified time frame. A participant previously **excluded** based on the exclusion criteria **cannot** be re-screened.

## **2.5.1 Study Eligibility Criteria**

### **2.5.1.1 Inclusion Criteria**

A participant must meet all of the following criteria to be eligible to participate in ICCTG RCT #2:

1. Participant must be at least 18 years of age.
2. Participant must sign and date the informed consent.
3. Participant must have received a minimum of 12 weeks of treatment with some standard form of therapy or combination of therapies for IC. The treatment must have occurred after diagnosis of IC and administered in response to the participant's IC symptoms. Potential previous therapies include, but are not limited to: tricyclic antidepressants, hydroxyzine, other antihistamines, DMSO, pentosan polysulfate, heparin, NSAIDS, and anticholinergics.
4. Participant (male or female) must agree to use a medically approved method of birth control.
5. Participant must report a urinary frequency of at least 11 times per 24-hour day, on average over the previous four weeks. This frequency criterion must be met at each of the two baseline-screening visits as reported by the participant.
6. Participant must report a pain/discomfort score of 4 or greater on a 0 - 9 Likert scale. This pain/discomfort criterion must be met at **each** of the two baseline-screening visits.
7. These reported urinary symptoms of frequency and pain/discomfort must have been present for at least the previous 24 weeks prior to the first baseline screening visit.



8. Participants must report in the baseline voiding diary at least one voided volume greater than or equal to 75cc in a 24 hour period.

### **2.5.1.2 Exclusion Criteria**

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

1. Active tuberculosis that requires ongoing therapy.
2. Immuno-compromised patients and/or known positive HIV test results.
3. Known allergy to or intolerance of BCG, or any of its components as reported by the participant or derived from their medical records.
4. Previous treatment with intravesical BCG.
5. Unable to void spontaneously.
6. Any imminent change in residence, that could compromise compliance.
7. Unlikely to be compliant due to unmanaged medical or psychological problem including dementia, aphasia or other deficits of cognition or speech/language function that will interfere with her/his ability to complete study.
8. Substance abuse or dependency problem within the past two years for which the participant received no treatment.
9. Severe, debilitating, concurrent medical conditions including severe coronary artery disease, azotemia, moderate to severe hepatic insufficiency, systemic cancer requiring treatment, or similar severe conditions.
10. Previous treatment with Cytosan<sup>®</sup>/cyclophosphamide.
11. A history of pelvic radiation treatment, bladder calculus, tuberculous cystitis, neurologic disease affecting bladder function, bladder cancer or cancer in situ, or urethral cancer. Any other neoplastic process currently requiring systemic, non-prophylactic treatment.
12. Previous augmentation cystoplasty, cystectomy or cystolysis, neurectomy (i.e. hypogastric nerve plexus ablation) or implanted peripheral nerve stimulator, which has affected bladder function.
13. Currently has an active urethral calculus, ureteral calculus, urethral diverticulum.
14. A current history of vesicoureteral reflux.

### **Exclusion criteria for men only**

1. Having a residual urine volume >150 cc by ultrasound or catheter (determined at Visit 1).
2. Currently being treated for chronic bacterial prostatitis as documented by a positive urine culture.
3. History of prostate cancer.

### **Exclusion criteria for women only**

1. Currently pregnant or breastfeeding.

### **2.5.1.3 Deferral Criteria**

There are several physical conditions for which a participant will be deferred from entry into the study. The following list identifies the conditions for deferral and the criteria that a participant must meet in order to be evaluated further for entry into the study:

1. If a participant has initiated any new medications for IC during the past four weeks, (s)he will be deferred until (s)he has been on the same dose for at least four4 weeks.
2. Within six weeks prior to study enrollment, if a participant has undergone bladder instrumentation such as urethral dilation, urodynamics, bladder cystoscopy or bladder biopsy under general or regional anesthesia, (s)he will be deferred until at least six weeks from the date of the procedure.
3. If a participant has undergone hydrodistention within six weeks prior to study enrollment, (s)he will be deferred until at least 12 weeks from the date of the procedure.
4. If a participant has had a positive urine culture (>100,000 col. ct) during the past six weeks, (s)he will be deferred until the participant has been without the condition for at least six weeks.
5. Participating in another intervention study or received an investigational drug or device within four weeks prior to screening.
6. If a participant has active genital herpes **or** has had active genital herpes during the past 12 weeks, (s)he will be deferred until the participant has been without the condition for at least 12 weeks.
7. If a participant has had any intravesical treatment (i.e. DMSO, Heparin, cystostat) other than BCG within 12 weeks prior to study enrollment, (s)he will be deferred until at least 12 weeks after the last treatment received.

8. Participants treated with botulinum toxin injections for voiding dysfunction within 24 weeks prior to baseline will be deferred until 24 weeks after last treatment received.
9. History of incontinence surgery or any other bladder or urethral surgery within the past 24 weeks, which could interfere with bladder function.
10. Participants must have been off treatment with pentosan polysulfate (Elmiron®) for a minimum of four weeks prior to randomization.

**Deferral criteria for women only:**

1. If a participant has active vaginitis, she will be deferred until she is free of the condition.
2. If a participant has had any form of transvaginal surgery, hysterectomy, prolapse surgery, vaginal delivery or C-section, she will be deferred until at least 24 weeks from the date of the procedure.
3. Participants must have completed breastfeeding for 24 weeks prior to study enrollment.

**Deferral criteria for men only:**

1. Having had a TURP, TUIP, TUIBN, TUMT, TUNA, balloon dilation of the prostate, open prostatectomy or any other prostate treatment such as cryotherapy or thermal therapy, participant will be deferred until or at least 24 weeks from the date of the procedure.

If the participant is deferred at either Visit 1 or Visit 2, (s)he must begin the screening process again, beginning at Visit 1. This includes all CRFs and procedures normally scheduled at Visit 1. 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 been resolved.

Before scheduling Visit 1, the RC should contact the participant by telephone close to the ending date of the deferral period to:

- Review the study with the participant,
- Determine whether the condition is absent or has subsided, and
- Ascertain if the participant is still interested in beginning the screening process again.

**2.5.2 (Baseline) Visit 1**

Informed consent is obtained from the participant before any study procedures or any medications are altered. Visit 1 is estimated to take two hours, not including the time for the

informed consent process. The following CRFs and events will be completed with the potential participant at this visit:

#### **2.5.2.1 Participant Contact Information (PTCONT)**

- The participant-completed PTCONT form will collect pertinent participant information, e.g. full name, address, telephone number and alternative contact information.
- The PTCONT form will be kept in a locked filing cabinet, separate from the participant's study binder.
- It will **not** be forwarded to the DCC.
- It contains confidential data and will **not** be entered and verified in the DMS.

#### **2.5.2.2 Eligibility Confirmation (ELIG)**

- Potential participant **must** satisfy all inclusion, exclusion and deferral criteria on ELIG, and as described in the protocol.
- Eligibility must be met by all participants within 24 hours of randomization. **The ELIG CRF is not completed at Visit 1**, but a photocopy of the CRF may be used if desired as a screening tool. The RC may also review the CRF verbally with the participant, although they are not to mark it at this visit. **The ELIG CRF is to be officially completed at Visit 2 and entered into the data management system (DMS) prior to randomization.**
- If the participant fails to meet any of the inclusion, exclusion, or deferral criteria, the visit should be terminated immediately.
- If the participant is deferred, the RC will complete the pertinent information on the ELIG CRF in the space provided and on the attached Comments Sheet, and maintain the CRF in participant's study binder.
- The RC will record the longest possible date of deferral until the participant is eligible for re-screening.
- After the deferral time has elapsed, and if the participant is still interested in participating, a new informed consent will be signed and the participant will be re-screened to meet the eligibility criteria.
- If there are no deferral issues, the RC will continue with the screening process.
- Eligibility will be verified with the participant's medical records at the clinical center or with the medical records from another treatment facility.

### **2.5.2.3 Baseline Symptom 1 (BSYM1)**

- The participant-completed BSYM1 form will determine the severity and duration of the participants IC symptoms for inclusion in the study.
- Participants not meeting the qualifying scores will be excluded from the study.
- BSYM1 will be entered and verified in the DMS **after** Visit 1, but prior to Visit 2, for eligible participants.

### **2.5.2.4 Clinical Laboratory Tests (LAB)**

- A CBC will be ordered with electronic differential including WBC, RBC, Platelets, Hematocrit, Hemoglobin, Granulocytes, Total Lymphocytes, Monocytes.
- A Serum Pregnancy Test will be ordered on all women of child-bearing potential.
- Blood samples will be sent to the clinical center's designated laboratory for analysis.
- The results of the blood tests and the serum pregnancy test will be recorded on the LAB form.
- Laboratory results must be within normal limits at Visit 1, in order for the participant to be eligible for the study. The Principal Investigator will determine if the results are "Normal" or "Abnormal" for participation in the trial. Participants with abnormal laboratory results should be informed of deferral or exclusion from the study.
- LAB will be entered and verified in the DMS after Visit 1, but prior to Visit 2, for eligible participants.

### **2.5.2.5 Urine Screening (URINE)**

- Dipstick analysis will be performed on urine samples.
- A urine sample will also be sent to the appropriate laboratory for urine culture.
- Results will be recorded on URINE.
- A residual urine volume on male participants will be measured by ultrasound or catheter, by the PI or his/her designee and recorded on URINE.
- URINE will be entered and verified in the DMS after Visit 1, but prior to Visit 2, for eligible participants.

### **2.5.2.6 Medical History (MED)**

- The RC-administered MED form will collect basic information about past medical conditions.

- Responses on MED will be verified with participant's medical records at the Clinical Center or another treatment facility.
- MED will entered and verified in the DMS **after** randomization, at Visit 2.

#### **2.5.2.7 Demographics (DEMO)**

- The participant will complete the DEMO CRF at Visit 1.
- DEMO will be entered and verified in the DMS, **after** randomization, at Visit 2.

#### **2.5.2.8 Participant Med. Diary (PTDIARY)/Concomitant Med (CMED)**

- As instructed at initial contact, the participant will bring all prescribed and/or over-the-counter medications (s)he is currently taking to the clinical center at Visit 1.
- The RC will review all of the medications with the participant to determine his/her use of concomitant medications. This will also help determine the participant's use of exclusionary or restricted medications. The participant will be instructed in stopping or limiting the use of these medications.
- The start dates of all concomitant medications will be noted.
- A master list of concomitant medications will be developed on CMED, and updated at various visits as identified in the Visit Schedule (**VSTSCHI and VSTSCHII**), during the course of the study.
- The RC will provide a copy of the master list to the participant.
- Eligible participants will receive a sufficient number of diaries, to be completed between Visits 1 and 2.
- The participant should be instructed in completing PTDIARY, using the photocopied master list as a reference, and returning the completed diaries at Visit 2.
- Participants will be stabilized and requested to maintain the same dose of IC medications throughout the duration of Phase I (Baseline to Week 34).
- **When possible, record medications in milligrams (mgs).**
- CMED will **not** be entered in the DMS at Visit 1; PTDIARY is an administrative CRF.

#### **Voiding Diary (VOID):**

- A one-day voiding diary (VOID) will be given to participant at Visit 1, to be returned at Visit 2.

- The RC will explain the diary and review the instructions for recording voids.
- The RC will give the participant a standard urine measuring-cup to record the amount voided.
- VOID information will be entered and verified in the DMS after the randomization at Visit 2.
- The RC will check the date of onset of a female participant's menstrual cycle and order a serum pregnancy test (see **Clinical Laboratory Results** above).

**Note:**

- If blood and urine specimens cannot be obtained at Visit 1, the participant can return to the clinical center at a later date, as long as the time constraints defined previously have been met.
- If a residual urine volume (males only) cannot be determined at Visit 1, another visit may be scheduled **prior** to Visit 2.
- If it is determined that the participant is not eligible based on the information obtained from the laboratory results or procedures, the screening process should be discontinued.

### **2.5.3 Ending Visit 1 with the Participant**

- If any conditions have been identified which make the participant ineligible, the RC will terminate the visit.
- If a participant is deemed eligible for the study, the RC will remind the participant that (s)he must **not** begin any new treatments or medications (including herbs) for his/her IC between Visit 1 and Visit 2.
- In addition, participants must be stabilized on the dose of their current IC medications prior to randomization (Visit 2). The RC and the participant should work together to determine a dose for each medication the participant is currently taking on a variable or PRN dosing schedule. The chosen “stable” dose should be a dose at which the participant feels comfortable maintaining for the 34-week duration of the study. The participant should be informed that they will be allowed to take less than this dose at any time, but should try not to take more. They should also be informed that during the study, they will be allowed to take “breakthrough” medications (as determined by the Principal Investigator) for increases in IC symptoms and will be informed as to what “breakthrough” medications will be available to them.
- **Participants must NOT be told that the definition of response for the primary endpoint of the study will be partially determined by their use of IC medications in the last month of follow-up, nor that their medication use may determine their**

**opportunity to receive open-label BCG.** The RC should simply stress that in order to determine the effectiveness of the study treatment, the participant needs to stay at or below the baseline or stabilized dose of their medication. If the participant is already on a non-varying dose of a medication, that will be their stabilized dose for purposes of the study. **The selection of a stabilized dose will be required for all prescribed medications that the participant is taking for the treatment of IC.** This includes narcotic analgesics. Non-prescribed IC treatments that the participant is taking will not be required to follow this rule. Medications for conditions other than IC will also be exempted.

- The RC will schedule Visit 2 according to the parameters described in the previous sections.

#### **2.5.4 Screening Failures Determined Between (Baseline) Visits 1 & 2**

There are certain eligibility requirements, determined between Visit 1 and Visit 2, which can make the potential participant ineligible for ICCTG RCT #2. These include:

- Significant or abnormal clinical laboratory results.
- Positive urine culture. This will defer a participant until a negative urine culture has been recorded within the time parameters described previously.
- Positive Serum Pregnancy test.
- New IC treatments started between Visits 1 and 2.

#### **2.5.5 (Baseline) Visit 2**

Visit 2 must occur **no less than 1 week (7 days)** and **no more than four weeks (28 days)** after Visit 1. It is estimated to take 1.5 – 2 hours. The participant must **not** have initiated any new treatments or medications for his/her IC between Visit 1 and Visit 2. During this visit, the participant will also have an opportunity to ask questions and express concerns related to the study. At Visit 2, the potential participant will return to the clinic for the following CRFs and events:

##### **2.5.5.1 Clinical Laboratory Results (LAB)**

- Laboratory results will be reviewed with the participant.
- If results from the CBC or differential are outside the Clinical Center's normal reference ranges, the PI will determine whether the abnormality presents a medical risk to the participant.
- If a clinically significant abnormality is noted, the PI will determine whether the participant must undergo further evaluation prior to enrollment into the study.



#### **2.5.5.2 Urine Screening (URINE)**

- Dipstick and culture results will be reviewed with the participant.
- If results are outside the Clinical Center's normal reference ranges, the PI will determine whether the abnormality presents a medical risk to the participant.
- If a clinically significant abnormality is noted, the PI will determine whether the participant must undergo further evaluation prior to enrollment into the study.

#### **2.5.5.3 Participant's Daily Med. Diary (PTDIARY)/Concomitant Med. (CMED)**

- The RC will review the PTDIARY with the participant at Visit 2, before randomization, to ensure that the participant understands how to complete it.
- Use of exclusionary medication(s) between Visit 1 and 2 will make the participant ineligible.
- If participant is unsure, exclusionary and restricted medications should be reviewed again.
- If necessary, the RC should update the original master list of medications and give an updated copy to the participant.
- Eligible participants should receive sufficient PTDIARYs to cover the time period between Visit 2 and 3.
- CMED should be entered and verified in the DMS after randomization.

#### **2.5.5.4 Voiding Diary (VOID)**

- The RC will collect and review VOID, completed by the participant between Visits 1 and 2, while the participant is still in the clinic. The RC will note any errors and then will **again** review the instructions for completing VOID with the participant.
- The RC will check the date of onset of a female participant's last menstrual cycle to determine if a pregnancy test is indicated.
- The participant **must** have recorded at least one void greater than or equal to 75 cc.
- If the participant is ineligible, the visit should be stopped immediately.
- VOID is entered and verified in the DMS after the randomization.

#### **2.5.5.5 Baseline Symptoms 2 (BSYM2)**

- The participant-completed BSYM2 form will confirm the severity and duration of the participant's IC symptoms for inclusion in the study.

- BSYM2 data will be entered and verified in the DMS prior to randomization for eligible participants.

#### **2.5.5.6 Eligibility Confirmation (ELIG)**

- **Eligibility is officially determined at Visit 2. The RC must review the entire ELIG CRF with the participant at this visit,** and complete the CRF for entry into the DMS.
- Current birth control methods will **again** be assessed with participant.
- If there are any changes between Visits 1 and 2, the participant will be deferred until (s)he becomes eligible for recruitment.
- If there are no deferral issues, the RC will continue with the remaining Visit 2 procedure(s).
- If the participant fails any inclusion, exclusion, or deferral criteria, the visit will be terminated.
- ELIG will be entered and verified in the DMS for eligible participants, at Visit 2.

#### **Note:**

- If a participant is deferred, RC will complete the pertinent information on ELIG and the attached Comments Sheet (COMM) and maintain the CRF in the participant's study binder.
- The RC will record the longest possible date of deferral until the participant will be eligible for re-screening.
- If the participant is still interested in participating after the deferral time has elapsed, a **new** informed consent will be signed and the participant will be **re-screened**.

#### **2.5.5.7 Physical Exam (EXAM)**

- The physical exam will be performed by the PI or his/her designee (as identified on the FDA Form 1572) and recorded on the EXAM CRF.
- A pelvic examination will be performed on female participants.
- A digital rectal exam will be performed **only** on male participants.
- If the participant is unable to undergo a physical exam, another visit can be scheduled prior to Visit 2.

- EXAM data is entered and verified in the DMS, after the randomization.

### **2.5.5.8 Symptom Questionnaires**

When the RC is confident that the participant is eligible to participate in ICCTG RCT #2, (s)he should provide a quiet location for the participant to complete the following symptom questionnaires:

**IC Symptom & Problem Index (SYM)**

**Health Status Questionnaire (SF-36)**

**MOS Sexual Functioning Scale (MOS)**

**University of Wisconsin Symptom Survey (WIS)**

- The RC should review the participant-completed symptom questionnaires for completeness and legibility, prior to the participant's departure from the clinic.
- Symptom questionnaires are entered and verified in the DMS after the randomization.

### **2.5.6 Ending Visit 2 with the Participant**

A sufficient number of PTDIARYs will be given to the participant at the end of Visit 2, to be completed between Visit 2 and Visit 3. A photocopy of the updated master list of concomitant medications will be provided to the participant, for reference, when completing the next set of diaries. The participant will be instructed to return the PTDIARYs to the RC at Visit 3. The participant will be given written instructions in preparation for the treatment at Visit 3 (See **Treatment** Procedures). A tentative schedule for treatment visits will be given to the participant. The participant will be informed that this schedule will be subject to change, depending on the outcome of each instillation.

The administrative and data CRFs that are completed to process the visit will be organized in the study binder. If the participant is eligible, the RC will proceed to computer randomization. If the participant is ineligible, the data entered and verified at Visit 1 will be deleted from the clinical center application and the participant will be informed of his/her ineligibility.

### **2.5.7 Scheduling Treatment Visits 1 to 6/Visits 3 to 8**

The participant will be scheduled for Visit 3, the first *study treatment* visit. Visit 3 should be scheduled **as soon as possible** after Visit 2, but **no more than** two weeks after Visit 2. Subsequent treatment visits should be scheduled once a week thereafter, for a total of six weeks, preferably on the same day, but at least six days apart. A maximum window of 3 weeks between treatments is allowed for scheduling problems or irritative side effects that the participant may experience, but every effort should be made to adhere to the six week treatment schedule. All treatments will be concluded at the end of 10 weeks from randomization, regardless of how many instillations the participant has received.

## 2.6 Randomization Procedure

### 2.6.1 *Computer Randomization*

The inclusion and exclusion criteria will be reviewed and checked against the symptom questionnaires, medication use, voiding diary and lab results at the screening visits. The average baseline symptoms scores and the average voids per day over Visits 1 and 2 will be calculated. If the participant is eligible for the study, the RC will perform computer randomization. Since the participant does not start treatment at Visit 2, eligibility data collected at Visit 2 can be entered and verified after Visit 2 has ended, but **within 24 hours** of Visit 2 completion. **The DMS is designed to prevent randomization, if more than 24 hours have elapsed.**

The process that leads up to computer randomization into the Data Management System (DMS) includes:

- Entry and Verification of CRFs from Visit 1, prior to Visit 2:
  - BSYM1
  - URINE
  - LAB
- After Visit 2 has ended, entry and verification of CRFs from Visit 2, prior to randomization:
  - BSYM2
  - ELIG
- After Visit 2 has ended, single entry randomization:
  - RAND
- All other data collected at Visits 1 and 2 must be entered and verified **after** computer randomization.

The DMS is designed to prevent ineligible participants from being randomized. If the eligibility data for a participant proves a participant is **ineligible**, the DMS will **not** allow data entry. If the data entered are 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 used for intravesical treatments (BCG or Placebo) for the participant. ***Once the five-digit randomization number is obtained, the RC will notify the clinical center pharmacist of the randomization number.***

Once randomization is completed, a computer-generated schedule for monthly follow-up visits from Week 14 (Visit 10) to Week 34 (Visit 15) can be viewed. If the participant completes treatment in six consecutive visits, four weeks prior to Visit 10, an optional follow-up visit can be scheduled (Visit 9) during this time period.

If the computer system is non-functional at the time of a participant's randomization, a manual backup system has been established.

The University of Pennsylvania's Investigational Drug Service (IDS) and the Clinical Center Pharmacist will know the treatment received by the participant, for unmasking purposes.

### **2.6.2 Back-up Randomization**

In the event of a computer failure at the clinical center and/or the Data Coordinating Center (DCC) during randomization, the RC will call the DCC randomization pager number **[(215) 374-9931]**, which will be available from 0900 to 2000 EST, Monday through Friday. Since there is a “grace period” of 24 hours after Visit 2, it is estimated that the need for manual randomization will be **very limited**.

A member of the Clinical Data Management team will return the phone call and ask the RC for the following information:

- BSYM2
- ELIG
- RAND
- Randomization (drug packet) number of the most recently randomized participant (the last randomization number assigned). [If the RC is unsure, (s)he can consult Penn Investigational Drug Service for this information.]
- Confirmation of Visit 1 data entry and verification.
- Faxed copies of BSYM2, ELIG and RAND for manual audit at the DCC. (A manual audit will check data on the faxed CRF against data provided during the phone call).

When the DCC representative confirms the participant's eligibility, (s)he will:

- Assign the next randomization number.
- At the earliest possible time, enter and verify the CRF data into the database.
- Confirm the randomization number generated electronically with the manually assigned number.
- Notify the RC when the data management system is operational again.

## **2.7 Participant Follow-up Visit Schedule**

Once randomization is completed, the DMS will generate a monthly participant follow-up visit schedule. Monthly follow-up visits from Week 14 (Visit 10) to Week 34 (Visit 15) can be viewed.

## **2.8 Treatments 1 to 6/Visits 3 to 8**

Treatment 1, referred to as Visit 3, **must** begin within **two** weeks of Visit 2, from the date of randomization. All attempts should be made to ensure compliance with the visit schedule for treatment. In the treatment phase of the study, BCG or placebo solution will be instilled into the bladder (see **Treatment Procedures**).

The instillation treatment procedure will be repeated once each treatment, for a total of six treatments within a 10 week period of time from the date of randomization. The interval between instillations will be a **minimum of 6 days and a maximum of three weeks. No more than 3 weeks may lapse between treatments.** Therefore, treatment schedules must take into consideration the following:

- Treatment visits will be scheduled according to participant's tolerability.
- Some participants may not receive all six-study treatments.
- All intravesical treatments must be administered within a 10-week visit schedule.
- The treatment regimen will require the interval between treatments to be a minimum of 6 days and a maximum of 3 weeks.

Information obtained during the instillations, as well as information obtained at post-treatment follow-up phone calls, will be recorded. Participants will be instructed to report any adverse reactions to the RC or the PI without delay. Participants will be monitored for use of restricted and exclusionary medications.

The menstrual cycle and birth control methods of female participants will also be monitored. Participants should avoid sexual intercourse during the 48 hours following each treatment instillation. Although sexual transmission of BCG has not been reported, it is required that a condom be used for intercourse during this period.

### **2.8.1 *Treatment 1/Visit 3 (Specific)***

CRFs completed at this visit:

- Adverse Events and Serious Adverse Events (AE)
- Clinical Laboratory Results (LAB)
- Instillation/Dosing information (DOSE)
- Participant Medication Diaries (PTDIARY)
- Concomitant Medications (CMED)
- Telephone Contact During Treatment Phase (PHNTP)
- Symptom Assessment Guidelines (SAG)
- Urine Sample Tracking for Biomarkers (UTRAC)

Prior to the start of the first treatment, the RC or the PI will:

- Confirm that no new IC treatments were initiated.
- Review and record on the adverse events (AE) form any clinical problems or events since the last study contact.
- Collect PTDIARYs from the participant.
- Update CMED, if there are any changes in medication use.
- Give an updated copy of the CMED form to the participant.
- Order a serum pregnancy test based on the last menstrual period for females, if needed.
- Confirm the use of medically approved contraception.
- Review with the participant the written Pre-Treatment Instructions given to them at the end of Visit 2. (See Treatment Procedures).

When it has been determined that treatment may proceed:

- The participant's temperature will be obtained and recorded on DOSE (CRF) *prior to* the instillation.
- The pharmacy will be notified to prepare and deliver the treatment solution.
- The participant will be "prepared" for the treatment procedure. A urine specimen will be collected and checked for nitrites and, if necessary, microscopic bacteria.
- A urine specimen will be collected for biomarkers via catheterization. (Catheterized urine specimens will ONLY be obtained prior to Treatment 1 [Visit 3] and prior to treatment 4 [Visit 6]).
- The time that the treatment solution was prepared at the pharmacy will be checked on the label.
- A determination will be made that the treatment solution was prepared **no more than two hours ago**. (If the treatment solution was prepared more than two hours ago, it will be returned to the Pharmacy and a freshly prepared treatment solution obtained.)
- The preparation time will be noted on DOSE.
- The instillation of the treatment solution will be performed as described in the Protocol for Administration of BCG – Appendix C and **Treatment Procedures**.
- Any unused treatment solution will be measured and recorded on DOSE.

- Post-Instillation observation of the participant will be performed as described in the Protocol for the Administration of BCG - Appendix C and **Treatment Procedures**.

Prior to dismissal the RC will:

- Review the written post-treatment discharge instructions with the participant as described in the Protocol Appendix F and **Treatment Procedures**.
- Provide written 24-hour Clinical Center contact information in the event of problems.
- Instruct the participant to take an oral temperature at bedtime on the night of treatment and again at bedtime on the following night.
- Instruct the participant regarding the two follow-up telephone calls as described in the protocol and the visit schedule.
- Tentatively schedule the next treatment visit.
- Review with the participant the written instructions regarding preparations for the next study visit as described in the Protocol Appendix F.
- Give the participant sufficient number of PTDIARYs to be completed between Visits 3 and 4.
- If needed, give the participant a copy of the updated master list of concomitant medications for reference.
- Remind the participant not to begin any new treatments for his/her IC.

### **2.8.2 Treatment Follow-up Phone Calls**

On Day 1 and Day 2 after each treatment, a Registered Nurse or Physician will contact the participant by telephone to:

- Ask the participant about any side effects or adverse experiences and record them on the AE form.
- Ask the participant if any medications were stopped or started and remind the participant to record them on the PTDIARY.
- Ask the participant's bedtime temperature reading from the previous evening, and record the results on the Telephone Contact During Treatment "PHNTP" CRF.
- If a participant cannot be reached, the RC should leave a message for the participant to call the RC or the PI.

The CRFs completed at this visit, including PHNTP, will be entered and verified in the DMS. This must be accomplished prior to the next scheduled visit.



### **2.8.3 Treatments 2 to 6/Visits 4 to 8 (General)**

The conduct and procedures for Treatments 2 to 6, referred to as Visits 4 to 8, are the same as Treatment 1/Visit 3, [see previous section – **Treatment 1/Visit 3**, and Visit Schedule (VSTSCHI) for details] with the exception of the urine specimen for the biomarkers study. A urine specimen will not be collected for the biomarkers study at Treatments 2, 3, 5, and 6 (Visits 4, 5, 7 and 8). Pre-treatment catheterized urine specimens for the biomarkers study are **only** collected at Treatment 1/Visit 3 and Treatment 4/Visit 6. The participant will be instructed to collect an additional urine specimen for the biomarkers study **six hours after the 4<sup>th</sup> treatment**, as described in the Protocol Appendix F and **Treatment Procedures** Section 6. Each treatment visit is followed by two days of telephone follow-up by a registered nurse or physician. In addition, the participant is given a VOID form to complete and return at the Post-Treatment Clinic visit at week 18/ Visit 11. The voiding log (VOID) is to be completed during one 24-hour period in the week prior to Visit 11.

### **2.8.4 Treatment 6/Visit 8 (Specific)**

CRFs completed at this visit:

**Note:** The following CRFs are completed prior to the participant receiving treatment.

- Adverse Events and Serious Adverse Events (AE)
- Clinical Laboratory Results (LAB)
- Follow-up Symptoms (FUSYM)
- IC Symptom & Problem Index (SYM)
- Health Status Questionnaire (SF-36)
- MOS Sexual Functioning Scale (MOS)
- University of Wisconsin Symptom Survey (WIS)

The following CRFs are completed after treatment.

- Instillation/Dosing information (DOSE)
- Concomitant Medications (CMED)
- Participant Medication Diaries (PTDIARY) - to be returned at Visit 11/Week 18
- Voiding Diary (VOID) – to be completed within one week of Visit 11/Week 18
- Telephone Contact During Treatment Phase (PHNTP)
- Symptom Assessment Guidelines (SAG)
- Treatment Stop Point (TSTOP)

### **2.8.5 End of Treatment/Visit 8**

The registered nurse or physician will proceed with instillation of the treatment solution as described in Protocol –Appendix C and **Treatment Procedures** Section 6. Post-treatment telephone calls will be made by the registered nurse or physician on Day 1 and Day 2 after treatment to assess adverse experiences and use of concomitant medications.

If the participant completes all six instillations **prior** to the end of the 10-week treatment window, an optional clinic or phone visit can be scheduled at the discretion of the PI and the RC. Assessments completed at this visit are the same as a post-treatment follow-up phone visits.

CRFs completed at this visit, including treatment follow-up data, will be entered and verified in the DMS. This will be accomplished prior to the next scheduled visit.

See **Participant Withdrawal and Withdrawal Consent/Premature Termination from the Study or Open-Label Trial (Section 2.11.3)**, if the participant terminates prematurely from follow-up in the study.

**NOTE:** If the participant decides to discontinue treatment before receiving 6 instillations or 10 weeks of treatment, the Treatment Stop (TSTOP) CRF should be completed. Withdrawal from treatment (especially by participant choice) does not necessarily require withdrawal from the study, unless participant withdrawal from the study is directed by the study site investigator. If possible, the participant should be encouraged to remain in the study and complete the post-treatment follow-up visits until Visit 15.

## **2.9 Post Treatment Follow-up (Optional Visit 9)/Visits 10 through 15 (Gen.)**

Post-treatment follow-up Phone Visits 10, 12 and 14 will be scheduled at weeks 14, 22, and 30. Treatment follow-up Clinic Visits 11, 13 and 15 will be scheduled at weeks 18, 26, and 34. All attempts should be made to ensure compliance with all scheduled follow-up visits. However, a **two-week visit window (plus/minus one week)** will be allowed in the post treatment follow-up period.

### ***2.9.1 Post-Treatment Weeks 14, 22, 30/Phone Visits 10, 12 and 14***

CRFs completed at this visit:

- Adverse Events and Serious Adverse Events (AE)
- Clinical Laboratory Results (LAB)
- Standard Visit Inventory (STVST)

The investigator or study coordinator will interview the participant to determine:

- Adverse experiences
- Concomitant medication use (recorded on PTDIARY)
- Possible pregnancy
- Other laboratory tests, if necessary

Participants will be reminded to complete within one week of the next clinic visit and bring with them to that visit:

- Voiding Diary (VOID)

Data collected during phone visits will be entered and verified in the DMS. If a laboratory test is needed, a visit to the laboratory or clinic will be scheduled to collect the required specimens.

The participant will complete PTDIARIES between Clinic Visits 8 and 11 and between Phone Visits 14 and Clinic Visit 15. PTDIARIES will **NOT** be maintained between Clinic Visit 11 and Phone Visit 14.

### **2.9.2 Post Treatment Weeks 18, & 26/Clinic Visits 11 & 13**

CRFs completed at this visit:

- Adverse Events and Serious Adverse Events (AE)
- Clinical Laboratory Results (LAB)
- Participant Medication Diaries (PTDIARY) – **only at Visit 11**
- Concomitant Medications (CMED) – **only at Visit 11**
- Voiding Diary (VOID)
- Follow-up Symptoms (FUSYM)
- Standard Visit Inventory (STVST)
- IC Symptom & Problem Index (SYM)
- Health Status Questionnaire (SF-36)
- MOS Sexual Functioning Scale (MOS)
- University of Wisconsin Symptom Survey (WIS)

The RC will:

- Assess any adverse experiences, since the last contact.
- Assess birth control methods.
- Assess female participants of childbearing potential for possible pregnancy.
- Collect and review PTDIARYs and update CMED as needed, giving the participant an updated copy.
- Collect and review VOID and give the participant a urine measuring-cup and a copy of VOID to return at the next clinic visit. Instruct the participant to complete the diary in **one** 24-hour period within one week of the next clinic visit.
- Have the participant complete the symptom questionnaires.
- Enter and verify data in the DMS.

### **2.9.3 Clinic Visit Response Assessment - Week 34 Final Post-Treatment Follow-up/Visit 15**

CRFs completed at this visit:

- Adverse Events and Serious Adverse Events (AE)
- Clinical Laboratory Results (LAB)
- Urine Screening (URINE)
- Participant Medication Diaries (PTDIARY) – **only if participant continues into Phase II**
- Concomitant Medications (CMED)
- Voiding Diary (VOID) – **give only if participant continues into Phase IIR**
- Physical Exam (EXAM) – **no pelvic exam**
- Follow-up Symptoms (FUSYM)
- Standard Visit Inventory (STVST)
- IC Symptom & Problem Index (SYM)
- Health Status Questionnaire (SF-36)
- MOS Sexual Functioning Scale (MOS)
- University of Wisconsin Symptom Survey (WIS)
- Urine Sample Tracking (UTRAC)
- Urine Log (ULOG)
- Endpoint Worksheet (ENDPT)
- Study Stop Point (SSTOPI)
- Participant Close-out (PTCL)
- Study Close-out (STCL) – **if participant ends study**

The participant will undergo the following repeat procedures:

- Physical examination
- Urinalysis
- Urine culture
- Urine specimen for biomarkers study
- CBC with electronic differential
- Serum  $\beta$ -HCG (women of child-bearing potential only)
- Assessment of current birth control methods
- Review of all participant information and laboratory reports by the Principal Investigator and the Research Coordinator within one week of the final post-treatment visit to determine the participant's response to the study treatment.

## **2.10 Response Determination & Reinstillation of BCG – Treatment Phase II**

### **2.10.1 Non-responders:**

Participants determined to be non-responders at Visit 15/Week 34 will be offered a 6-treatment course of open-label BCG instillation (Treatment Phase II). NOTE: Any participant who discontinues treatment prematurely or withdraws from the study prior to Visit 15/Week 34 will not be eligible for open-label BCG.

**Non-responders** are those who:

- Report a score of 1 to 5 on Question #6 on Follow-up Symptoms (FUSYM)

**or**

- Report an increased use of IC medications during weeks 31 to 34 as compared to baseline screening (compare CMEDs at Visits 2 and 15)

**or**

- Report initiation of new IC medications during weeks 31 to 34 (compare CMEDs at Visits 2 and 15)

**or**

- Report new or increased use of narcotic medications from weeks 31 to 34 (See CMED at Visit 15), or request narcotics at any time during weeks 31 to 34.

An example of the CRF Endpoint Worksheet (ENDPT) is provided in Appendix D of MOP to assist the RC and PI in evaluating the participant's primary endpoint response. This worksheet can be used to compare medication usage at baseline with medication usage in the last 4 weeks of follow-up (Weeks 31 to 34).

The study treatment visit schedule as maintained in Phase I will be continued throughout Phase II [Refer to Visit Schedule II (VSTSCHII) and **Treatment Procedures**, Section 6]. All post-treatment follow-up visits in Phase II, except for the final visit, will be **phone visits**. Participants may be seen in the clinic at the discretion of the PI and the RC. The final visit of Phase II will be a clinic visit.

### **2.10.2 Responders:**

Responders are those who fulfill both of the following two criteria:

1. Report a score of 6 or 7 on Question #6 on Follow-up Symptoms (FUSYM)
- and**
2. Report no increase in pre-study IC medications, and no initiation of new IC medications, and no new or increased use of narcotic medications during the final 4 weeks of the follow-up phase – between Visits 14 and 15/Weeks 31 to 34.

Those participants determined to be responders at Week 34/Visit 15 (See Section 4.4.1 of the protocol), will not be permitted to receive open-label BCG instillation therapies on protocol after completing Phase I of this study.

Participants determined to be responders will be offered Phase IIR of the study. If participants agree, Phase IIR will involve 3 telephone contacts (or clinic visits, if preferred). The Visit Schedule (VSTSCHIIR) lists the CRFs to be completed at each of the 3 visits for responders - Week 46/Visit 22, Week 56/Visit 25 and Week 68/Visit 28.

Participants will primarily be contacted by phone. For telephone visits, participants will receive CRFs to be completed by mail, with a self-addressed stamped envelope for mailing the completed CRFs back to the RCs. Participants should be instructed to mail the completed CRFs prior to the visit call made by the RCs, to review discrepancies at the telephone visit.

If a clinic visit is scheduled based on the participant's preference, participants will complete the CRFs listed for the visit at home, prior to the clinic visit.

## **2.11 End of Study**

At the end of Phase I, the Phase I Study Stop form (SSTOPI) and Participant Close-out form (PTCL) should be filled out. If the Participant is not continuing to Phase II, the RC and PI should also complete the Study Close-out (STCL) form. If the participant is a non-responder and chooses to continue on to Phase II, then the SSTOPII and STCL forms should be filled out at the end of Phase II.

### **2.11.1 Visit Windows & Missed Study Visits**

The visit windows for the treatment and post-treatment follow-up contacts have been described in the previous sections of this manual. Days refer to calendar days, not business days. A participant must come to the clinic to make up a missed visit. This visit must be scheduled at the earliest available time, preferably within the window. It is also desirable to schedule initial visits early in the visit window in the event they are missed due to unforeseen circumstances. Visits should **not** be split up to perform some procedures on a different day, unless there is no other way to complete the visit. If the participant is not interested in continuing participation, or is lost to follow-up, the RC should contact the participant and close him/her out of the study (see **Participant Withdrawal and Withdrawal of Consent/Premature Termination from the Study or Open-label Trial** in Section 2.11.3).

### **2.11.2 Additional Visits**

Additional visits may be required for the participant's normal medical care. Except for recording Serious Adverse Events, data CRFs are not completed for additional visits.

### **2.11.3 Participant Withdrawal & Withdrawal of Consent/Premature Termination from the Study or Open-label Trial**

There are several reasons a participant can withdraw prematurely from the study. They may be:

- Use of unacceptable concomitant medications.
- A positive pregnancy test.
- A clinically significant, abnormal laboratory results.
- Adverse events or serious adverse events.
- A request to transfer to another Clinical Center **during** the treatment phase.
- Dissatisfaction with treatment.
- Loss of interest in the study.
- Lost to follow-up

If a participant indicates that (s)he no longer wants to participate in the study, 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 via 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 can continue to receive my regular care and treatment at this clinic.

The following CRFs need to be completed at the time of withdrawal:

- **All** visit and end of study CRFs
- TSTOP and SSTOP1/SSTOP2 (depending on the study phase)
- PTCL
- STCL

### **2.11.4 Participant Transfer**

It is possible for an ICCTG study participant to transfer to another ICCTG-participating Clinical Center 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 Clinical Center in which (s)he was enrolled.

Participants **cannot** transfer during the screening **or** treatment phase to another Clinical Center. If a participant indicates his/her desire to transfer to another ICCTG Clinical Center after the treatment phase is completed, the following will occur.

The RC at the Originating Center will:

- Contact the RC at the Receiving Center to inform of the transfer.
- Schedule the first clinic visit at the Receiving Center.
- Complete Participant Transfer (TRANS) as described in the following chapter.

- Send copies of the participant's study folders, medical records and TRANS to the Receiving Center.
- Provide the participant with contact information for the Receiving Center.

The RC at the Receiving Center will:

- Complete the remainder of TRANS.
- Complete PTCONT.
- Have the participant sign the Clinical Center-specific Informed Consent.
- Provide the RC and PI contact information, in case of an emergency.

In case of a temporary transfer where the participant needs to be seen at a participating Clinical Center on a temporary basis, the Originating Center RC will contact the Receiving Center RC and share relevant information (e.g. visit number, medical issues, etc.) with the RC. (S)he will also notify the DCC so that arrangements can be made to enter and verify the data collected for the visit. The DCC will review the procedures with both RCs to facilitate a smooth transition.

### **3 Participant Safety**

#### **3.1 Risks & Benefits**

##### **3.1.1 *Risks***

- Before giving consent to participate in this study, the Principal Investigator must inform the participant of all potential risks related to participation in this study. Specifically, risks related to receiving intravesical BCG, as outlined in the Informed Consent (See Protocol *Appendix A*) and outlined in the BCG Package Insert (Protocol *Appendix B.*); risks related to venipuncture; and risks related to catheter insertion (See Protocol *Appendix A*).
- After each intravesical treatment, the Research Coordinator will review with the participant the post-treatment discharge instructions that outline specific safety precautions. The research coordinator and participant will both sign the instruction form. A copy of the instructions will be given to the participant, and the original copy kept in the participant's source documents.

##### **3.1.2 *Benefits***

**There may be no direct benefit to the participant by participating in this study. Some of the following advantages may be stressed:**

- Participation can help investigators gain further knowledge about the use of BCG in the treatment of IC.
- Participants will maintain direct contact with Clinical Centers and Research Coordinators.



## 3.2 **Adverse Event**

**Study participants must be evaluated at each clinic visit and telephone contact for Adverse Events.** Please refer to the two main Adverse Event categories below (AE's & SAEs). For each AE, the site should determine the appropriate category and then follow the corresponding instructions for recording and reporting the event.

### 3.2.1 **Definition of an Adverse Event [AE]**

An **Adverse Event (AE)** is any untoward (unwanted) medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product which *does not necessarily have to have a causal relationship with the study treatment*. An adverse event can therefore be **ANY unfavorable and unintended** sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can include any clinically significant worsening of a pre-existing condition or an overdose (a dose higher than that prescribed by the healthcare provider).

### 3.2.2 **Recording & Reporting Adverse Events (AE's)**

All adverse events will be reported to the on site Investigator and recorded on the Adverse Event/Serious Adverse Event [AE] form. Investigators are responsible for explaining each AE and assessing its relationship, if any, to the study medication. The site will ALSO notify their IRB, according to routine event reporting requirements.

### 3.2.3 **Definition of a Serious Adverse Event (SAE)**

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at **ANY** dose:

- **Results in death;**
- Is **life-threatening** (e.g., the patient is in immediate risk of death from the event);
- Requires **inpatient hospitalization or prolongation of existing hospitalization,**
- Results in persistent or **significant disability/incapacity** (e.g., the event is a substantial disruption of a person's ability to conduct normal life functions) or
- Is a **congenital anomaly/birth defect.**

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.

**Note:** Keep in mind that the SAE definition focuses on the “outcome” of the event, and the SAE may involve only one, or possibly more, of the above criteria. To ensure that no confusion or misunderstanding occurs in understanding of the difference between the terms serious and severe, which are not synonymous, the following note of clarification is provided:

The term “severe” is often used to describe the intensity or severity of a specific event (as mild, moderate, or severe myocardial infarction). The event itself, however, may be of relatively minor medical significance, such as severe headache. This is **not** the same as “serious,” which is based on patient/event **outcome or action** criteria, usually associated with events that pose a threat to a patient’s life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

### **3.2.4 Recording & Reporting Serious Adverse Events (SAEs)**

The RC is responsible for immediately notifying the on-site Investigator of any Serious Adverse Event. The Clinical Site is then responsible for reporting SAEs to the DCC within 24 hours of first knowledge of the event via telephone, followed by a facsimile, which includes both the corresponding Adverse Event/Serious Adverse Events [AE] form and the **MedWatch 3500** form. In addition, the clinical site must promptly report all SAEs to their **IRB via written/dated notification** in accordance to their specific IRB reporting requirements. **Copies of all such correspondence must be maintained in the site’s main study binder.** All SAEs must be followed with appropriate medical management until resolved.

Within one working day of first knowledge, the DCC Project Manager, or their designee, will notify NIH/NIDDK and the External Advisory Board of all SAEs. The University of Pennsylvania IRB will also be notified. In addition, NIH/NIDDK will appropriately notify the Licensed Product Holder and the FDA.

***Note: Deaths occurring within thirty days of study medication cessation must be reported as above.***

### **3.2.5 IND Safety Reports (21CFR 312.32)**

The Sponsor, (NIH/NIDDK) or their designee, shall notify the FDA and all participating investigators in a written IND safety report of any AE **associated with the use of the drug** that **is both serious and unexpected**, (e.g., not consistent with the current Investigator Brochure and/or product labeling, as outlined in *Appendix H of Protocol*).

The Sponsor shall also notify FDA by telephone or by facsimile transmission of *unexpected fatal or life-threatening* event *associated with the use of the drug* as soon as possible but in no event later than 7 calendar days after the sponsor’s initial receipt of the information, and notify investigators as soon as possible, but no later than 15 calendar days from initial discovery.

The DCC will disseminate these IND safety reports to the investigational sites and the Sponsor will notify the licensed product holder.

**Site Requirements:** Upon receipt of an IND SAFETY REPORT, each Investigational site is responsible to copy the IND report and immediately submit the copy to their IRB, maintaining the original and dated documentation of IRB submission (via cover letter) within the ICCTG Study Binder.

### 3.2.6 Procedure for Reporting Adverse Events

The following outlines the sequence to be followed in the reporting of adverse events:

#### Procedure for Reporting Adverse Events

Study participants must be evaluated at each clinic visit and telephone contact for Adverse Events

Please refer to the two main Adverse Event categories below:

Serious Adverse Event Reporting and Routine Adverse Event Reporting

For each Adverse Event, the clinical site should determine the appropriate category and then follow the corresponding outline of reporting of the event.

The Clinical Investigator asks: “Is the event serious?”

- *death*
- *life-threatening*
- *results in or prolongs hospitalization*
- *results in persistent or significant disability or incapacity*
- *congenital anomaly/birth defect*

#### YES

##### Serious Adverse Event Reporting

Clinical site:

- determines relationship to study drug
- notifies DCC within 24 hrs of knowledge of event by phone & faxes required documentation to DCC
- notifies site IRB according to reporting requirements

Data Coordinating Center:

- notifies NIH/NIDDK and EAC within 24hrs of knowledge of event
- prepares IND safety report
- distributes safety report to all clinical sites as soon as possible but no later than 15 days from initial discovery

NIH/NIDDK

- Notifies FDA
- Notifies Licensed Product Holder

#### NO

##### Routine Adverse Event Reporting

Clinical site:

- report to site investigator
- record on case report form
- notifies site IRB according to reporting requirements

Data Coordinating Center:

- prepares cumulative reports
- distributes @ quarterly Steering Committee
- distributes quarterly to NIH/NIDDK, EAC
- prepares annual IND report

NIH/NIDDK

- Submits annual IND report to FDA

### **3.3    Unmasking**

The University of Pennsylvania Investigational Drug Service (PENN IDS) will ship the unblended study drug supply to each clinical site pharmacist. Separately, PENN IDS will ship to the clinical site research coordinator, blinded envelopes containing the treatment to which each participant is randomized. The blinded envelopes will be contained within a plastic case secured with a coded seal and are to be kept in a lock secured area, accessible only by the Principle Investigator or Research Coordinator.

It is anticipated that unmasking will be a very rare occurrence and will only happen under the most critical of situations. The unmasking process should be initiated very carefully and only in situations that are serious or life-threatening to the participant only. Each participant should have the pager number of the RC at the onset of the trial, should such an emergency occur. In the event of such an occurrence:

- The RC will immediately contact the Principal Investigator (PI).
- The PI or PI designee will decide whether or not to unmask the drug.
- If it is determined that the treatment should be unmasked, (s)he will instruct the RC to break the seal for the participant's secured envelope and notify the PI of the treatment assignment.
- Only in a most extreme event will the clinical site pharmacist be contacted to reveal the treatment assignment (i.e., severe weather conditions prevent the RC or PI from traveling to the clinical site to retrieve the envelope).
- The RC will contact the DCC by phone within one working day of the unmasking with an explanation of the need for unmasking. This will be followed by a fax to the DCC of the explanation in writing and the unmasking case report form (UNMASK), both signed by the PI.

#### **Storage of Unmasking Envelopes**

Envelopes must be kept in a locked area (i.e. drawer or cabinet) at the clinical site. Only the PI and the RC are to have the key to access the drawer.

#### **Return of Unmasking Envelopes**

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

## 4 Data & Administrative Case Report Forms

### 4.1 Personnel ID Numbers

Each Clinical Center staff member involved in data collection or review for ICCTG RCT #2, will be identified by the last 4 digits of their Social Security Number (SSN). This information will be forwarded to the DCC prior to the start of the study and updated as personnel changes occur at the Clinical Center.

### 4.2 Acquisition of Case Report Forms from the DCC

The Case Report Forms (CRFs) are provided to the clinical centers in electronic format on the web server as PDF (portable document format) files. Each clinical center is responsible for printing all data and administrative CRFs. CRFs necessary for each visit are grouped together, to streamline the printing process. Data CRFs and Administrative CRFs are available individually too. CRFs that may need additional pages for multiple records are also provided on the web server.

### 4.3 General Instructions for the Completion of Data Case Report Forms

Two types of CRFs are used for this study:

- **Data CRFs** - containing participant data, are entered in the database.
- **Administrative CRFs** - primarily used for study organization, are not entered in the database.

The RC should check the CRFs in a packet against the Visit Schedule (VSTSCHI, VSTSCHII, or VSTSCHIIR) to confirm that all CRFs are available before a clinic or a telephone visit with the participant. Missing CRFs in a visit packet will be printed from the web server prior to the visit. As amendments occur, clinical centers will be notified and current versions will be made available within the application files on the web server.

#### **General instructions:**

- All CRFs should be completed in **black** ink. Pencil, blue ink or red ink are **not** to be used.
- No responses should be left blank.
- **UNK** should be filled in any space left unanswered.
- If the participant is unsure of a response, (s)he should use his/her "**best estimate**" rather than leave the question unanswered.

- It is important that the RC completes the header information ***before*** administering the CRFs to insure easy identification in case of separated pages, or multiple participant visits in a day.
- Participant ID number will be determined on the Participant Log (PTLOG) during screening.
- The RC is responsible for reviewing all the completed CRFs.
- All personal identifiers should be obscured or “blacked out” from copies of lab or procedure reports and other source documentation and the study identifying information (Participant ID and Participant Initials) should be recorded, prior to forwarding copies to the DCC. **All originals should retain personal identifying information.**

#### **4.3.1 Case Report Forms Completion**

Directly under the CRF heading are instructions for the Research coordinator to determine whether the CRF is completed by the PI, RC, participant, or a combination of these. This information also includes when (visit number) the CRFs are administered. Detailed instructions for each CRF are described later in this chapter.

##### **Participant Completed CRFs:**

- “Participant completed” CRFs are self-reports, to be completed by the participant.
- The RC should be readily available to answer any questions that the participant may have.
- The RC may interview participants who require assistance in completing the CRFs.
- Since the participant may find some of the information on the CRFs to be sensitive, whenever possible, the participant should be encouraged to complete the CRFs alone.
- Before the participant leaves the clinic, the RC should review the CRFs for completeness.
- Once the RC reviews the CRFs, the RC should complete the RC ID number in the header.

##### **Principal Investigator or Research Coordinator Completed CRFs:**

- Research Coordinator completed CRFs, should be completed by the RC.
- Principal Investigator completed CRFs should be completed by the PI or the PI’s designee (as identified on FDA Form 1572).

- These CRFs are **not** completed by the participant, but are administered to the participant by the PI or the RC by interviewing the participant and asking specific questions on the CRFs.
- The PI or the RC is responsible for getting an appropriate response from the participant if the participant's response is unclear, incomplete, or irrelevant.
- The PI or 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 response, without leading the participant or influencing the content of the response (creating bias in his/her response).
- 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 the importance of the question.
- All CRFs to be completed by the RC or the PI should be completed during the visit, unless awaiting a lab report.
- The RC should review the CRFs for completeness and legibility before the participant leaves, in case additional information or clarification is needed.
- The RC should review all **PI completed** CRFs for completeness and legibility, and enter the RC ID number in the header. **The PI or PI designee should initial the CRF, for documentation.**

#### **4.3.2 Review of Completed Case Report Forms**

- The RC should review all CRFs for legibility, accuracy, and completeness ***before*** they are entered into the database.
- If the RC identifies an error while reviewing the CRFs, the error should be corrected on the completed CRF 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.

#### **4.3.3 CRFs for ICCTG RCT #2:**

<b>CRF Name</b>	<b>CRF Code</b>	<b>Type of CRFs</b>
Adverse Events and Serious Adverse Events	AE	Data CRF
Baseline Symptom 1	BSYM1	Data CRF
Baseline Symptom 2	BSYM2	Data CRF
Clinical Laboratory Results	LAB	Data CRF
Concomitant Medications	CMED	Data CRF
Demographics	DEMO	Data CRF
Eligibility Confirmation	ELIG	Data CRF
Follow-up Symptoms	FUSYM	Data CRF
Health Status Questionnaire	SF36	Data CRF
IC Symptom and Problem Index	SYM	Data CRF
Instillation/Dosing Information	DOSE	Data CRF
Medical History	MED	Data CRF
MOS Sexual Functioning Scale	MOS	Data CRF
Participant Close-out	PTCL	Data CRF
Physical Exam	EXAM	Data CRF
Randomization	RAND	Data CRF
Standard Visit Inventory	STVST	Data CRF
Study Close-out	STCL	Data CRF
Study Stop Point	SSTOPI or SSTOPII	Data CRF



<b>CRF Name</b>	<b>CRF Code</b>	<b>Type of CRFs</b>
Telephone Contact During Treatment Phase	PHNTP	Data CRF
Treatment Stop Point	TSTOP	Data CRF
University of Wisconsin Symptom Survey	WIS	Data CRF
Unmasking Record	UNMASK	Data CRF
Urine Screening	URINE	Data CRF
Voiding Diary	VOID	Data CRF
Comments Sheet	COMM	Administrative CRF
End-Point Worksheet	ENDPT	Administrative CRF
Participant Contact Information	PTCONT	Administrative CRF
Participant Daily Medication Diary	PTDIARY	Administrative CRF
Participant Log	PTLOG	Administrative CRF
Participant Transfer	TRANS	Administrative CRF
Participant Collected Urine Sample Tracking for University of Iowa	PUTRAC	Administrative CRF
Symptoms Assessment Guidelines	SAG	Administrative CRF
Urine Sample Tracking Log	ULOG	Administrative CRF
Urine Sample Tracking	UTRAC	Administrative CRF

## 4.4 Directions for Completing Data CRFs

This section provides specific instructions on how to complete each data CRF. **The CRFs are addressed in alphabetical order by CRF title.** If, after consulting this section, you are still unsure of how to complete them, please contact the ICCTG Data Manager(s) at the DCC.

### **Header Information:**

**Participant ID:** This is determined by the RC and logged in the PTLOG at each clinical center. It is a five-digit number that is unique to the clinical center and the participant. Once assigned, a participant's ID is not deleted or transferred to another study participant.

**Participant Initials:** The first letter from each of the first, middle and last name of the participant are noted in the space provided for the initials. An X is used when the participant does not have a middle name.

**Clinical Center:** As described in the previous chapter, a 2-digit number identifies each clinical center. The numbers range from 01 – 10.

**Visit Number:** Contact Weeks have been identified in the protocol when specific events happen during the course of the study, the open-label BCG trial, or Phase IIR. These contact weeks have been translated into Visit Numbers. See Visit Schedules I, II, and IIR (VSTSCHI, VSTSCHII, and VSTSCHIIR) to facilitate data management and analyses at the Data Coordinating Center.

**CRF Date:** This is the date of the clinic or phone visit. If AEs are recorded between two visits, the CRF date should be the date of the **next scheduled** visit and **not** the date of call.

**RC ID:** RC ID is the last 4 digits of the Research Coordinator's social security number.

### **4.4.1 Adverse Event / Serious Adverse Event (AE)**

**Purpose:** To collect information on any Adverse Event(s) (**AE**) or Serious Adverse Event(s) (**SAE**) that the participant experiences during the course of the study.

**NOTE:** Any AE/SAE reported by a randomized participant, even if no study drug has been administered, **MUST** be recorded, whether or not the participant thinks it is significant.

**Who:** RC and PI completed. The PI determines whether study-related and grades the severity of the event (toxicity) using the National Cancer Institute's (NCI) Common Toxicity Criteria (CTC), Version 2.0 (see Appendix E - **Common Toxicity Criteria (CTC)**).

**When:** The RC completes the CRF each time the participant experiences an AE/SAE during treatment and follow-up phases, either reported at a Phone Contact or a Clinic Visit, or if the participant contacts the study personnel to report an AE/SAE, between Phone Contacts or Clinic Visits. A new CRF is used at each contact/visit. Multiple AE/SAEs can be documented on the same CRF during a single Phone Contact or a Clinic Visit.

This CRF is completed, starting from Visit Numbers 3 through 15 during Phase I, and if the participant qualifies, Visit Numbers 16 through 28 during Phase II. If the participant chooses to continue through Phase IIR, this CRF records SAEs only for Visits 22, 25, and 28.

### **General Directions:**

Refer to Section 4.3, in addition to the directions below.

The following items are listed in the same order in which they appear on the CRF. When completing the CRF, please refer to the coding key on page 2.

**Visit Number:** The Visit Number in the header will be the current visit number, if the AE/SAE is being reported during a scheduled visit. If a participant contacts the RC between scheduled visits, the *next* visit number is entered (i.e., if the CRF is completed between Visit #03 and Visit #04, the Visit Number would be 04).

**CRF Date:** CRF Date on the first page of the AE will be entered in the database as date of the visit even if these AE's may have been recorded between visits. Contacts made with the participant may be recorded on the Comments Sheet (COMM), identifying the AE #s and the date of contact when the participant reported the AE(s).

**Question #1:** Any AE's/SAEs reported by the participant between visits are recorded for the current visit and this question is checked as "Yes" and AEs with the grade, frequency, etc. are recorded in the log. If the participant does not have any AEs to report, this question is checked as "No."

**Adverse Event Number (AE#):** This is a 3-digit sequential number starting with '001', '002', '003', etc. This number repeats during the study **only** if the event being recorded is a continuation or a closure of an event previously recorded, with the same grade, duration and frequency, as when originally recorded. Each newly reported event is recorded with the next, new, sequential number.

**Event Code:** Event Code number is a 6-digit number identified by referring to the coded list of Common Toxicity Criteria (CTC) developed by the National Cancer Institute.

**Date of Onset:** Record the date of onset of the symptoms that the participant experienced, even if the date lasted one day or less. If the event is continued from a previous visit and considered a follow-up AE, mark (X) in the box, leaving the date of onset field blank.

**Grade:** The **PI** will grade the AE/SAE, 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 event and using the code provided in the coding key on page 2.

**Duration:** Using the code provided in the coding key, record whether the event lasted for minutes, hours, days, or unknown.

**Frequency:** Using the code provided in the coding key on page 2, record the frequency of the episodes.

**Relationship to Study Drug:** The **PI** will determine, whether the AE/SAE was related to the study medication, using the coding key provided on page 2.

**Action taken Regarding Study Drug:** The **PI** will determine whether an interruption or discontinuation of the study drug is necessary. The coding key is provided on page 2 of the CRF.

**Treatment for Event:** The **RC** will code whether the participant received any form of *treatment from a physician* for the event. Only physician prescribed/recommended treatment is recorded.

**Outcome:** Record the outcome using the codes provided in the “Outcome” column on page 2, based on the details of the AE/SAE. Codes with an asterisk to the left of the number are coded as SAEs. Please follow the instructions in Section 4.4.1.3 –Serious Adverse Events Documentation Procedures.

**Date of Resolution:** Record the date of resolution of the symptoms that the participant experienced, even if the date lasted one day or less. If the event is unresolved at the end of the clinic or phone visit, mark (X) in the box, leaving the date of resolution field blank.

**Was the Event Serious:** This will be determined by the **PI**. *Outcome* coded 3 through 7 is considered **serious**. All AEs and SAEs require a **PI signature and date**.

**Specify Event (CTC criteria):** This information is linked to the *Event Code*. Record the *Event Name*, as specified in the CTC criteria for the event code number being used.

**Description of Event/Comment:** Describe the AE/SAE based on the information provided by the participant. Anything transcribed directly from the participant should be set apart by quotation marks. Treatments, if prescribed by the physician, should also be described in this space. Attempts should be made by the **RC** to include all pertinent information, for monitoring and reporting purposes at the DCC.

**PI ID:** Should be the *last 4 digits* of the social security number of the clinical center Principal Investigator.

All AEs and SAEs are signed and dated by the **PI**. When recording a new AE/SAE, complete the entire AE record in the table. *If the AE/SAE is not yet resolved, follow-up should continue until the event is resolved. Because of this, the RC should review all previously reported AE/SAEs at every visit.*

Additional AE pages, without Question #1, have been provided if multiple pages are needed to record multiple AEs for a visit.

#### **4.4.1.1 Continuing Adverse Events**

All continuing AEs should be recorded at *each visit* until they are resolved.

When reporting an ongoing recorded event, use the same 3-digit AE# as when the event was first recorded, as well as the same Event Code, Grade, Duration and Frequency. Mark (X) in Date of Onset field and Date of Resolution field. The outcome should be coded as 2 – Ongoing. The description should indicate this is an ongoing report of a previously recorded AE/SAE, along with any other information the RC believes is critical.

When resolving a previously recorded event, use the same 3-digit AE# as was used when the event was first recorded, as well as the same Event Code, Grade, Duration and Frequency. Mark (X) in Date of Onset field. The outcome should be coded as 1 – Resolved, and the date of resolution recorded. The description should indicate that this is a resolution of a previously recorded AE/SAE, along with any other information the RC believes is critical/pertinent.

If a previously recorded event still exists, but has changed in grade/duration/frequency, the event should be treated as a new event, and the original event should be “closed out” as resolved.

#### **4.4.1.2 Serious Adverse Events Notification Procedure**

**\*Please also refer to MOP Sections 3.2.4, 3.2.5, and 3.2.6 for Serious Adverse Event Reporting**

For each Serious Adverse Event (SAE), the RC will notify the clinical center PI, who will assess and confirm the seriousness of the adverse event (CTC toxicity grades 3, 4, or 5 and Outcomes category of 3 through 7).

The clinical center PI will notify his/her local IRB, according to established procedures, as well as the DCC at the University of Pennsylvania within twenty-four (24) hours of the first report of the event.

The telephone and fax numbers for the DCC contacts are listed in the ICCTG RCT #2 study directory.

In addition to completing/faxing the completed CRF (AE) to the DCC, the RC will also complete and fax a **MedWatch** 3500 Form

#### **4.4.1.3 Serious Adverse Events Documentation Procedures**

This procedure generally applies to an SAE that is reported by the participant after the event has been resolved or is reported and resolved prior to the visit.

Each Serious Adverse Event will be documented on the AE CRF by the RC using a minimum of two lines that will have the same Adverse Event Number. The purpose of the first line is to document the Event at the point in time when the Event is regarded as “Serious”, and the outcome documents a coding of 3 or more. The purpose of the second line is to document the Serious Adverse Event at point in time when it is considered “Resolved”.

On the first line documenting the SAE, the RC will enter the “Date of Onset” for the SAE and the corresponding data for “Grade”, “Duration”, “Frequency”, “Relationship to Study Drug”, “Action taken”, “Treatment”, “Outcome”, and “Was the Event Serious?” as it was for that “Date of Onset”. The “Date of Resolution” will not be filled in on this line. Instead the check box will be marked to indicate it as continuing.

On the second, or final, line documenting the SAE, the RC will use the same AE number that was used on the first line for that SAE. For the “Date of Onset” field, the check box will be marked to indicate the SAE as continuing. The data for “Grade”, “Duration”, “Frequency”, “Relationship to Study Drug”, “Action taken”, “Treatment”, and “Outcome” will then be entered as it was at the time the Event was considered “Resolved”. At this point “Outcome” will be entered as a “1”, the “Date of Resolution” for the SAE will be recorded, and a “0” will be entered for “Was the Event Serious”.

#### **4.4.2 Baseline Symptoms 1 (BSYM1)**

**Purpose:** To collect information on the participant's assessment of his/her general urinary discomfort and/or pain, urgency, frequency, and sexual pain. This CRF is used with Eligibility Confirmation (ELIG) and Randomization (RAND) to determine if a participant is eligible to enter the study.

**Who:** Participant completed.

**When:** This CRF is completed at Visit 1 only.

#### **General Directions:**

Self-explanatory.

**Question 1:** To qualify for the study, the participant should score 4 or more on the scale.

**Question 3:** To qualify for the study, the participant should urinate 11 times or more in a 24-hour period, checking box 3 or 4.

**Question 4:** To qualify for the study, the participant should have the symptoms for 24 weeks or more, checking box 2 or 3.

The RC should review the participant’s responses for completion and legibility.

#### **4.4.3 Baseline Symptoms 2 (BSYM2)**

**Purpose:** To collect information on the participant's assessment of his/her general urinary discomfort and/or pain, urgency, frequency, and sexual pain. This CRF is used with Eligibility Confirmation (ELIG) and Randomization (RAND) to determine if a participant is eligible to enter the study.

**Who:** Participant completed.

**When:** This CRF is completed at Visit 2 only.

##### **General Directions:**

Self-explanatory.

**Question 1:** To qualify for the study, the participant should score 4 or more on the scale.

**Question 3:** To qualify for the study, the participant should urinate 11 times or more in a 24-hour period, checking box 3 or 4.

The RC should review the participant's responses for completion and legibility.

#### **4.4.4 Clinical Laboratory Results (LAB)**

**Purpose:** To record the results of study-specific laboratory tests.

**Who:** RC and PI completed.

**When:** This CRF is completed prior to Baseline/Screening Visit 2, end of study Visit 15 and **when clinically indicated**, during Phase I. It is **also** completed at the end of the open-label BCG trial /Visit 28 and when clinically indicated for participants who qualify for Phase II.

##### **General Directions:**

The PI will review the laboratory results to determine the eligibility of the participant for the study, if the results are outside of the normal ranges of the institution.

At Baseline/Screening Visit 1 and end of study Visit 15, urine culture results are recorded on the Urine Screening CRF (URINE). Urine culture results for all other visits are recorded on the LAB CRF.

While the other test results are quantitative, serum pregnancy test result and urine culture result (recorded at Visits other than baseline or end of treatment) is reported as negative or positive. ***A positive serum pregnancy result will lead to the participant's termination from the study.***

LAB is completed when the results of the blood tests are available. The CRF Date listed in the header is the date that the CRF 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 ordered/performed. The **PI** should determine whether the results are clinically significant. For all follow-up visits, significant results are recorded as AEs/SAEs and reported on AE CRF. Write “-I” if LLN and ULN are not applicable to a sample. Documentation for the waiver should be forwarded to the DCC **prior** to the start of the study.

Multiple laboratory tests can be ordered between visits and their results recorded on this CRF with the Visit Number as the next visit that the participant is scheduled for and the CRF Date as the date of the next scheduled visit. For example, if the CRF is completed between Visits 10 and 11, the Visit Number is 11 with the CRF completion date for Visit 11. The Comment Sheet (COMM) can record pertinent data, e.g. date of completion between visits, etc. Date of Specimen should record the actual date when the tests were ordered.

Additional LAB pages, without Question #1, have been provided if multiple pages are needed to record multiple laboratory results for a visit, but only **one** specimen date will be recorded **per page**.

Source documentation for LABs will be maintained in the study binder. All personal identification information should be obscured or “blacked out” and Participant ID Number, Participant Initials and Visit Number should be recorded to identify the source documentation on **copies** sent to the DCC. The originals should **retain** personal identification information. LAB CRF has to be signed and dated by the PI.

**PI ID:** Should be the **last 4 digits** of the social security number of the clinical center Principal Investigator.

#### **4.4.5 Concomitant Medications (CMED)**

**Purpose:** To collect information from the Participant's Daily Medication Diary (PTDIARY) to record all medications/supplements/vitamins currently taken by the participant, while in the study or the open-label BCG trial.  
To monitor the use of exclusionary, restricted, IC and breakthrough medications.  
To monitor the response rate, as outcome to the study drug.

**Who:** RC Completed.

**When:** This CRF is completed at Visits 2 through 8, Visits 11 and 15 during Phase I. If the participant qualifies for the open-label BCG trial, the CRF is also completed at Visits 16 through 21 and Visit 28 during Phase II. If the participant chooses to continue through Phase IIR, this CRF is also completed at Visit 28.

#### **General Directions:**

Medications refer to prescription or non-prescription drugs, over-the-counter drugs, vitamins, nutritional supplements or herbal remedies. RCs should document name, dose and frequency of use for each medication.



The information for this CRF is obtained from the Participant Daily Medication Diaries (PTDIARYs) to track any medications taken during the study. Starting at Visit 2 and continuing until Visit 11 and again from Visit 14 to Visit 15, ***any new medications started, any dose changes on previously recorded medications, or any recorded medications stopped***, should be transcribed from the PTDIARYs onto this CRF. PTDIARYs will not be maintained between Visits 11 and 14.

***BCG instillations will not be recorded on CMED.***

“**Critical**” medications are those medications that the participant is **prescribed** for his/her IC symptoms and that are essential to the endpoint analysis to determine a participant’s responder or non-responder status. These include Tricyclic Antidepressants, Sedating Antihistamines (H1 Blocker), Anticonvulsants, Alpha2-Adrenergic Agonist Agents, Intravesical therapies (e.g. DMSO, Clorpactin, Heparin) and Narcotic Analgesics.

“**Non-critical**” medications are those medications that the participant may use prescribed or over-the-counter for conditions other than IC or as dietary supplements. The use of these medications would not be essential to the end-point analysis to determine a participant’s responder or non-responder status.

The master list of participant’s medications, developed by the RC and given to the participant for reference at baseline, includes ALL medications taken by the study participant on a daily and/or PRN/as-needed basis. Based on this master list, the participant is instructed to record changes (skipped or reduced doses, start and stop dates for new or reported medications) to the master list at each visit where reporting on concomitant medications (CMEDs) is required. The RC decides whether the master list needs to be updated at each visit.

***\*\*Please Note the distinction in the following\*\*:***

Medications taken on a **PRN/as-needed** basis, and **NOT** critical to the trial are recorded as “**PRN**” in the Total Daily Dose column of the CMED CRF and changes are recorded only when a listed medication is stopped or a new PRN medication is started.

Medications “**critical**” to the trial that are taken on a **PRN/as-needed** basis, (exclusionary, restricted, or primary endpoint-related medications) **are recorded with a Total Daily Dose** which is specific in the amount (e.g. **in mgs, and not tablets**) frequency, route, start and stop dates on the CMED CRF.

***During Phase I,***

- All over-the-counter and prescription medications at Visits 2, 3, 4, 5, 6, 7, 8, 11, and 15 are recorded on CMED.
- At Clinic Visit 11 (Week 18), the participant is instructed that s/he will have a 3-month period (from Week 19-30) during which s/he **does not** complete PTDIARYs.

- At Phone Visit 12 (Week 22) and Clinic Visit 13 (Week 26) and Phone Visit 14 (Week 30), the participant is asked about adverse experiences and medication use in general, to ensure participant safety and protocol compliance.
- At Clinic Visit 13 (Week 26), the participant is given a four-week supply of PTDIARYs with instructions ***not*** to record medication information until a call from the Research Coordinator at Phone Visit 14 (Week 30).
- Starting with end of Visit 14 (Week 31), the participant will again record all medications taken on a daily basis, till the end of Phase I Clinic Visit 15 (Week 34).
- The RC will collect PTDIARYs from the participant at Clinic Visit 15 (Week 34).

**Note:** At the discretion of the RC and/or the PI, some participants may continue to maintain PTDIARYs during the 3-month break period (Week 19-30), if the interruption may prove disruptive to the participant in the data collection process for CMEDs.

Medications that were recorded at earlier scheduled visits without stop dates are recorded again during the last four weeks, without a start date but with the box checked indicating that the medications are continued from previous visit. New medications, or changed doses on previously recorded medications, are recorded with a start date.

***During Phase II:*** PTDIARYs and a self-addressed stamped envelope will be given to the participant at Visit 21 (Treatment 6), to be mailed back to the Clinical Center at Phone Visit 24 (Week 52) of the Phase II open-label BCG trial. The participant will be reminded about this at Phone Visit 22 (Optional Visit).

***During Phase IIR:*** At visit 25 the participant will be reminded that from week 65 (4 weeks prior to Visit 28) to week 68 (visit 28) it will be necessary to complete PTDIARYs. Before week 65, PTDIARYs and a self-addressed, stamped envelope will be either given or mailed to the participant.

Additional PTDIARYs are mailed to the participant prior to Phone Visit 27 (Week 64). The participant is instructed to complete PTDIARYs between Phone Visit 27 (Week 64) and Clinic Visit 28 (Week 68), to be returned at Clinic Visit 28.

**Question #1:** This is reported as 0 (No), if the participant does not report use of any new medications or report stopping a previously recorded medication. If a change is reported at the visit, this question is answered as 1 (Yes) and the number of records to be reported is completed.

**Line #:** This is a 3-digit sequential number which begins with “001,” “002,” “003,” etc. This sequential number repeats during the study only if the medication recorded at a visit is a follow-up record to a previously recorded medication.

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

**Drug Name:** This is the generic name for the medication/treatment, generated from the *Medication Reference* tool.

**Total Daily Dose (TDD):** This information is obtained from PTDIARYs completed by the participant. The RC must multiply the *Strength of the dose* (the individual dose amount) by the *Total Number of Doses per 24 Hours*. When recording combination drugs, e.g. Tylenol 3, the TDD column should record TDD for the “critical” component of the medication – Codeine.

Medications taken on a **PRN/as-needed** basis, and **NOT** critical to the trial are recorded as “**PRN**” in the Total Daily Dose column of the CMED CRF and changes are recorded only when a listed medication is stopped or a new PRN medication is started.

Medications “**critical**” to the trial that are taken on a **PRN** basis, (exclusionary, restricted, or primary endpoint-related medications) are recorded with a Total Daily Dose which is specific in the amount (**e.g. recorded in mgs and not tablets**), frequency, route, start and stop dates on the CMED CRF.

**Unit:** Select the *most specific* response possible, based on the information in the PTDIARYs.

**Route:** Select the *most specific* response possible, based on the information in the PTDIARYs.

**Start Date:** It is the date when the participant starts a new medication or changes the 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. If a medication is recorded at a previous visit and the TDD, Unit and Route remain unchanged, start date is not recorded again and the box is checked instead.

**Stop Date:** It is the date the participant stops taking the medication, if applicable. If a medication is recorded at a previous visit and the TDD, Unit and Route remain unchanged, start date is not recorded again and the box is checked instead.

**Was this an exclusionary or restricted medication?:** Answer “yes” or “no” based on the Exclusionary and Restricted Medications List. (See *MOP Appendix A*)

**Was this medication taken by the participant for his/her IC?:** This is transcribed directly from the PTDIARYs and based on the IC medications listed in the protocol and in *MOP Appendix C*.

**Was this medication taken by the participant for pain?:** This is transcribed directly from the PTDIARY and based on the therapeutic categories of “*breakthrough*” medications listed in the protocol – Section 4.3.1 and *MOP Appendix B*.

Additional CMED pages, without Question #1, have been provided if multiple pages are needed to record multiple concomitant medications for a visit.

If a drug code for a concomitant medication that the participant has recorded is unavailable in the Medication Reference Tool on the web application, the RC should call the Clinical Data Manager at the DCC. If the Clinical Data Manager is unable to locate the information for the

RC, the medication and other relevant data will be recorded on a log maintained at the DCC and the Clinical Data Manager will develop a code and enter the data in CMED at the DCC.

#### **4.4.6 Demographics (DEMO)**

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

**Who:** Participant completed.

**When:** This CRF is completed at Screening/Baseline Visit 1 only.

##### **General Directions:**

Self-explanatory.

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

**Question #11:** For participants who answer "No" for question #10, record "Not applicable."

The RC should review the participant's responses for completion and legibility.

#### **4.4.7 Eligibility Confirmation (ELIG)**

**Purpose:** To determine and ensure the participant's eligibility for entry into the study.

**Who:** RC completed and PI reviewed.

**When:** This CRF is completed at Screening/Baseline Visit 1 **and** 2, prior to randomization.

##### **General Directions:**

This CRF contains inclusion, exclusion and deferral criteria as described in the protocol. It is used as a verbal screening tool at Visit 1, and completed at Visit 2. If the participant meets all the inclusion, exclusion and deferral criteria, then the data are entered and verified in the Data Management System (DMS) to randomize the participant. ELIG, for a deferred participant, is maintained in the study folder till the participant's condition is resolved, or deferral time has elapsed and the participant is re-screened. A **new** ELIG is completed at re-screening.

The RC will need the following CRFs as reference to answer inclusion, exclusion and deferral questions on ELIG:

- Baseline Symptoms 1 (**BSYM1**)
- Baseline Symptoms 2 (**BSYM2**)
- Clinical Laboratory Results (**LAB**)
- Urine Screening (**URINE**)
- Voiding Diary (**VOID**)

**Inclusion Criteria:** Questions 4 to 10

A participant can be male or female.

Questions 5 to 10 must be coded as “Yes/1.”

**Exclusion Criteria:** Questions #11 to #31.

**Note:** Questions **16, 17 and 18** have been shaded on the CRF, indicating that the criteria are not relevant to the screening process. Data entry screen has also been disabled for these questions.

Question 46 has been added to the ELIG form to record current history of vesicoureteral reflux. A “Yes/1” response will disqualify a participant from the study.

Questions 11 to 31 must be coded as “No/0” or “N/A / 99” for gender-specific questions.

**Deferral Criteria:** Questions 32 to 45.

Questions 32 to 45 must be coded as “No/0” or “N/A / 99” for gender-specific questions.

Dates are provided for administrative purpose only and **not** entered in the database.

Comments/notes are recorded in the space provided on the last 2 pages.

PI will sign and date the CRF at the conclusion of the assessment for eligibility.

#### **4.4.8 Follow-up Symptoms (FUSYM)**

**Purpose:** To collect information on the participant's assessment of his/her general urinary discomfort and/or pain, urgency, frequency, and sexual pain and the participant's assessment of his/her IC symptoms (global assessment, *primary endpoint* information) at the end of treatment and through the follow-up phase.

**Who:** Participant completed.

**When:** This CRF is completed at Clinic Visits 8, 11, 13 and 15, during Phase I and if the participant qualifies, at Clinic Visit 28 of the open-label BCG trial during Phase II. If the participant chooses to continue through Phase IIR, this CRF is also completed at Visits 22, 25, and 28.

#### **General Directions:**

**Question # 4a:** This question needs a response *only* if the if the participant checks a “No” response in question # 4.

**Question #5:** A participant will respond "not applicable" if (s)he is not sexually active and checks a “No” in questions # 4.

**Question #6:** All effort should be made to get the participant to respond to this *primary endpoint question*. At visit 15, a response of 1 to 5 (with other qualifying criteria described in the protocol and the MOP) will partially determine the participant's eligibility for the open-label BCG trial, qualifying him/her as a non-responder. The participant must **NOT** be told that their eligibility for open-label BCG depends partly on this question.

Participant's response to this question at Visit 15 (Week 34) is very critical to the determination of the participant's eligibility to participate in Phase II open-label BCG trial.

The RC should review the participant's responses for completion and legibility.

#### **4.4.9 Health Status Questionnaire (SF-36)**

**Purpose:** To collect information on 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 CRF is completed at Visits 8, 11, 13 and 15, during Phase I and if the participant qualifies for the open label BCG trial, at Visit 28 during Phase II.

#### **General Directions:**

Self-explanatory.

The RC should review the participant's responses for completion and legibility.

#### **4.4.10 IC Symptom & Problem Index (SYM)**

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

**Who:** Participant completed.

**When:** This CRF is completed at Visits 8, 11, 13 and 15, during Phase I and at Visit 28 of the open label BCG trial, during Phase II. If the participant chooses to continue through Phase IIR, this CRF is also completed at Visits 22, 25, and 28.

#### **General Directions:**

Self-explanatory.

The RC should check the participant's arithmetic for Symptom Index Total Score and Problem Index Total Score.

The RC should review the participant's responses for completion and legibility.

#### **4.4.11 Instillation/Dosing Information (DOSE)**

**Purpose:** To collect dosing, instillation and safety information during the treatment phase.

**Who:** RC completed.

**When:** This CRF is completed at Visits 3 through 8, during Phase I and at Visit 16 through 21 of the open label BCG trial, during Phase II.

**General Directions:**

**Question #1:** Refers to medically approved birth control methods other than abstinence.

**Question #2:** N/A / 99 is checked for males or post-menopausal women.

**Question #3:** This is gender-specific question and N/A / 99 is checked for females.

**Question #4:** A Yes/1 or No/0 should be checked at Visits 3 and 6 and N/A / 99 checked at all other treatment visits.

**Question #s 5 and 5a:**

If the urine is nitrite positive, a microscopic analysis should be done.

If microscopic analysis is positive, a urine culture is ordered and recorded on the LAB CRF.

If the urine culture is positive, an adverse event is recorded on the AE CRF and the instillation/treatment is scheduled after the urine nitrite is negative.

If the urine culture is positive and treatment is stopped or rescheduled, questions 6 through 16 are not answered. If the treatment for the current visit is rescheduled for another time, a new DOSE will be completed, entered and verified. DOSE completed at the initial visit will then be considered an administrative CRF and will not be entered and verified. If the treatment is skipped completely for the current visit, only data available for questions 1 through 5 will be entered.

A solution *must* be instilled within 2 hours of preparation or returned to the institution's Pharmacy for a replacement solution.

**Question #s 6 – 16:** These are completed only if the participant receives treatment during the visit.

**4.4.12 Medical History (MED)**

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

**Who:** RC completed.

**When:** Screening/Baseline Visit 1.

**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 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 CRF is completed at Visits 8, 11, 13 and 15, during Phase I of the study and at Visit 28 of the open label BCG trial, during Phase II.

#### **General Directions:**

Self-explanatory.

Not Applicable is checked for gender-specific questions and if the participant is not sexually active.

The RC should review the participant's responses for completion and legibility.

#### **4.4.14 Participant Close-out (PTCL)**

**Purpose:** To query the participant and the RC about the study medication.

**Who:** Participant and RC completed. Participant completes questions 1, 2 and 3. RC answers question 4.

**When:** This CRF is completed at Visit 15 or premature termination from the study during Phase I **only**.

#### **General Directions:**

PTCL *must* be completed for every randomized participant when (s)he stops participating in the study in Phase I. If the participant is unavailable to complete the questionnaire, the RC should complete question # 4.

If this CRF is completed between scheduled visits, the RC will record the next Visit Number and the current date in the header.



**Question #s 1, 2 and 3:** The participant completes these questions.

**Question #4:** The RC completes this question.

This is a “single” “close-out” CRF in the database and can be entered and verified, as needed.

#### **4.4.15 Physical Exam (EXAM)**

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

**Who:** PI completed or his/her approved designee. The RC must review this CRF prior to data entry.

**When:** This CRF is completed at Screening/Baseline Visit 2 and end of study/Visit 15 during Phase I. It is also completed at the end of the open-label BCG trial/Visit 28.

Pelvic Exam is not required or recorded at Visits 15 and 28.

#### **General Directions:**

**Question #1:** The RC will record the ID number of any PI, co-investigator or sub-investigator at their clinical center performing the physical exam, who is *also listed on the FDA form 1572*.

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

#### **4.4.16 Randomization (RAND)**

**Purpose:** To electronically (on the web application) or manually (with DCC’s assistance) randomize an eligible participant into the study.

**Who:** RC and PI completed.

**When:** This CRF is completed at the end of Visit 2, after the participant is evaluated for eligibility into the study.

#### **General Directions:**

Comments/notes can be made on the attached Comments Sheet.

**Question #1:** Participant must meet *all* eligibility criteria at Visits 1 *and* 2.

**Question #2:** The RC will record the ID number of the clinical center Principal Investigator.

**Question # 3:** The 5-digit number generated by the application or assigned by the DCC must be recorded. This number should correspond to the number on the study solution at treatment visits.

The clinical center PI must review, sign and date the completed CRF.

#### **4.4.17 Standard Visit Inventory (STVST)**

**Purpose:** To collect information on safety assessment in the post-treatment follow-up phase.

**Who:** RC completed.

**When:** This CRF is completed at Visits 9 through 15 during Phase I, and for qualified participants, Visits 22 through 28 of the open-label BCG trial during Phase II.

#### **General Directions:**

Self-explanatory.

**Question #1:** Refers to medically approved birth control methods other than abstinence.

**Question #2:** Check N/A /99 for males or post-menopausal women.

**Question #3:** At Visit 15 only in Phase I and Visit 28 only in Phase II. N/A should be checked for all other Visits.

#### **4.4.18 Study Close-out (STCL)**

**Purpose:** This CRF 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 CRF is completed at Visit 15 for the participant who completes Phase I of the study, *or* at Visit 28 for the participant who qualifies for Phase II of the open-label BCG trial, *or* when the participant withdraws prematurely from either Phase I or Phase II of the study. If the participant chooses to continue through Phase IIR, this CRF is also completed at Visit 28.

#### **General Directions:**

STCL *must* be completed for every randomized participant when (s)he stops participating in the study which includes an point of Phase I, any point of Phase II Non-Responder Open-label BCG, or any point of Phase IIR Responder Long Term.

If this CRF is completed between scheduled visits, the RC will record the next Visit Number and the current date in the header.

**Question #1:** Comments are optional and *are not* entered in the database.

This is a “single” “close-out” CRF in the database and can be entered and verified, as needed. This CRF must *not* be entered in the database until all other participant data (single and packet CRFs) have been entered and verified.

#### **4.4.19 Study Stop Point (SSTOPI & SSTOP II) – Phases I, II, and IIR**

**Purpose:** To record the date and the primary reason for a participant's termination from the follow-up phase of the study or the open-label BCG trial.

**Who:** RC completed.

**When:** SSTOPI is completed at Visit 15 for the participant who completes Phase I of the study, or when the participant withdraws prematurely from the post-treatment follow-up phase of the study.

SSTOPII is completed at Visit 28 or at premature termination from the post-treatment follow-up phase of the open-label BCG trial. If the participant chooses to continue through Phase IIR, this CRF is also completed at Visit 28

#### **General Directions:**

**SSTOPI** must be completed for every randomized participant who stops participation in post-treatment follow-up during Phase I of the study. Questions 1 and 2 are coded with an appropriate response, based on the participant's status in the study at the time of completion/withdrawal.

**SSTOPII** must be completed when participation ends at Visit 28 or at premature withdrawal during Phase II. One appropriate reason must be recorded for premature termination.

If these 2 CRFs are completed between scheduled visits, the RC will record the next Visit Number and the CRF completion date in the upper right hand corner.

If the participant discontinues because of unacceptable concomitant medications, the RC will verify that this medication is properly recorded on the PTDIARY and hence recorded on CMED.

If the participant discontinues because of a positive pregnancy test, the RC will indicate the date of the test, attach a copy of the test results to the participant's study chart and record the result on LAB.

If the participant discontinues because of out-of-range 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. The RC will also complete LAB.

If the participant discontinues 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 AE.

If the participant transfers to another randomization site, the RC will complete TRANS.

**SSTOPI** and **SSTOPII** are “single” “close-out” CRFs in the database and can be entered and verified, as needed.

**SSTOPI and SSTOPII Question #1:** If the checked response is “No,” questions 1a and 1b *must* be completed. Only one most applicable and appropriate reason must be checked.

**SSTOPI Question #1a and 1b:** If question #1 is checked as “Yes,” questions 1a and 1b are skipped and response to question # 2 is checked.

**SSTOPII Question #1a and 1b:** If question #1 is checked as “Yes,” questions 1a and 1 b are skipped.

**SSTOPIIR Question #1a and 1b:** If question #1 is checked as “Yes,” questions 1a and 1 b are skipped.

**SSTOPI Question #2:** A response must be checked for this question. If the participant terminates prematurely, check “N/A.” If the participant qualifies for the open-label trial, check “Yes.”

#### **4.4.20 Telephone Contact During Treatment Phase (PHNTP)**

**Purpose:** To record post-instillation temperature, assess for adverse experiences and use of concomitant medications.

**Who:** RC completed.

**When:** This CRF is completed on Day 1 and 2 after Visits 3 through 8 during Phase I of the study and Day 1 and 2 after Visits 16 through 21 of the open-label BCG trial during Phase II.

If necessary, an additional call can be made to the participant and noted on the CRF.

#### **General Directions:**

**Question 1 (Day 1 and 2) or # 2 (Additional Day):** If the participant is unavailable when the RC calls, questions 2 through 5 (or 6 for addition contact) will *not* be answered.

**Question 3a (Day 1 and 2) or # 4a (Additional Day):** The participant should record his/her temperature at bedtime on the night of treatment and again the following night after treatment, and report it to the RC during the call.

**Question #4 (Day 1 and 2) or # 5 (Additional Day):** The RC will grade the BCG-specific symptoms/events on the Symptoms Assessment Guidelines and record the information on AE.

**Question # 5 (Day 1 and 2) or # 6 (Additional Day):** The participant will be reminded to record use of concomitant medications on PTDIARY and the RC will note use on the master copy of the CMED.

#### **4.4.21 Treatment Stop Point (TSTOP)**

**Purpose:** To record whether a participant successfully completed 6 instillations or 10 weeks of study treatment. To record the date and the primary reason for a participant's withdrawal from the treatment in either the randomized phase of the study or the open-label BCG phase of the study.

**Who:** RC completed.

**When:** This CRF is completed at the final treatment visit (or at premature withdrawal from treatment) for each phase of the study. If the participant completed all six instillations in Phase I, then the CRF would be completed at Visit 8. If the participant completed all six instillations in Phase II, then the CRF would be completed at Visit 21.

#### **General Directions:**

TSTOP must be completed for every randomized participant who stops participation in the treatment phase during Phase I and Phase II of the study. Question 1 is coded with an appropriate response, based on the participant's status in the study at the time of treatment completion or withdrawal.

If the CRF is completed between scheduled visits, the RC will record the next Visit Number and the CRF completion date in the upper right hand corner.

If the participant discontinues because of unacceptable concomitant medications, the RC will verify that this medication is properly recorded on the PTDIARY and hence recorded on CMED.

If the participant discontinues because of a positive pregnancy test, the RC will indicate the date of the test, attach a copy of the test results to the participant's study chart and record the result on LAB.

If the participant discontinues because of out-of-range 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. The RC will also complete LAB.

If the participant discontinues 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 AE.

**TSTOP** is a “single” “close-out” CRF in the database, and can be entered and verified as needed.

**Question #1:** If the checked response is “No”, questions 1a *must* be completed. Only one applicable and appropriate reason must be checked.

**Question #1a:** If question #1 is checked as “Yes,” questions 1a is skipped.

This is a “single” “close-out” CRF in the database, and can be entered and verified, as needed.

#### **4.4.22 University of Wisconsin Symptom Survey (WIS)**

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

**Who:** Participant completed.

**When:** This CRF is completed at Visits 8, 11, 13 and 15, during Phase I of the study and at Visit 28 of the open label BCG trial, during Phase II. . If the participant chooses to continue through Phase IIR, this CRF is also completed at Visits 22, 25, and 28.

#### **General Directions:**

The participant completes this scale within the context of reporting the symptoms (e.g. "how much did you experience the following symptoms *today*").

The RC should review the participant’s responses for completion and legibility.

#### **4.4.23 Unmasking (UNMASK)**

**Purpose:** To document the unmasking of treatment assignment because of unforeseen circumstances. The unmasking envelope will contain an adhesive backed label that identifies which treatment arm the participant is assigned to. This label is to be placed on the unmasking (UNMASK) CRF.

**Who:** RC completed, in collaboration with the PI.

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

#### **General Directions:**

UNMASK envelope is contained within a tamper-evident container at the Clinical Center. These envelopes are kept in a secured location while the participant is in the study. If it becomes necessary to unmask the study medication, this CRF, along with a report explaining, in detail the need for unmasking, should be faxed to the DCC within 3 days of verbal reporting to the DCC of the unmasking. The PI signature and date must appear on this CRF before it is faxed to the DCC.

This is a “single” CRF in the database and can be entered and verified, as needed.

Also see Section 3.3 *Unmasking*.

#### **4.4.24 Urine Screening (URINE)**

**Purpose:** To record the results of *pre-randomization* urine dipstick and culture (all participants) and the residual urine volume (males only) and end-of-study urine results.

**Who:** RC completed.

**When:** This CRF is completed at Visit 1 (*prior* to Visit 2) and end of study/Visit 15 during Phase I of the study and at Visit 28 of the open-label BCG trial during Phase II.

#### **General Directions:**

This CRF is completed when the pre-randomization urine dipstick, culture results (all participants) and the residual urine volume results (males only) are available.

Source documentation for URINE should be kept in the participant's study binder. All personal identification information is maintained on the originals, but should be obscured or "blacked out" and Participant ID number and Visit Number should identify the source documentation, when copies are sent to the DCC.

**Question #2:** If the results are abnormal, the RC will indicate which of the specific tests listed are normal and which are abnormal. *Abnormalities in the dipstick may require further microscopic analysis of urine.*

**Question #3:** If the urine colony culture result is greater than  $10^5$  of uropathogens, the potential participant must be deferred.

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

Residual volume is *not* measured at Visit 15.

#### **4.4.25 Voiding Diary (VOID)**

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

**Who:** Participant completed.

**When:** This CRF is completed for Visits 2, 11, 13 and 15 during Phase I of the study and for Visit 28 during Phase II. . If the participant chooses to continue through Phase IIR, this CRF is also completed at Visits 22, 25, and 28.

## General Directions:

The Voiding Diary is completed during a 24-hour period during the week prior to the next clinic visit. The participant will bring the diary with him/her to the clinic. The RC will provide several photocopies of the second page of VOID and a measuring container in which the participant will measure the void. The RC will complete the header information (Participant ID, Participant Initials, and the Visit Number). The rest of the header information will be completed when the participant returns the voiding diary. When reviewing the CRF after completion, the RC should pay special attention to the following:

- If the CRF indicates that a woman of childbearing potential has skipped one full menstrual cycle (**30 days** or more), a serum pregnancy test **must** be ordered. If the test is positive, the participant **must be withdrawn** from treatment.

## During Phase I:

- At Visit 1, the participant receives a copy of the voiding diary that is completed and returned at Visit 2.
- At Visit 8, the participant receives a copy of the voiding diary that is completed and returned at Visit 11.
- At Visit 11, the participant receives a copy of the voiding diary that is completed and returned at Visit 13.
- At Visit 13, the participant receives a copy of the voiding diary that is completed and returned at Visit 15.

## During Phase II:

At Visit 21, the participant receives a copy of the voiding diary that is completed and returned at Visit 28.

## During Phase IIR:

At visit 15, the participant receives copies of the voiding diaries that are completed before visits 22, 25, and 28. The diaries are returned either at clinic visits (if the participant agrees to them), or they are mailed to the clinic by the participant.

## 4.5 Directions for Completing Administrative Case Report Forms

Administrative CRFs are **not** optional and must be included in the participant's study folder as a reminder to be completed at every visit. Administrative CRFs are sent with the data packets requested by the DCC.



#### 4.5.1 Comments Sheet (COMM)

**Purpose:** This CRF records any relevant information for a visit or a CRF. It can be attached to the CRF or used to record “Progress Notes” for a visit.

**Who:** RC (or PI) completed.

**When:** This CRF is completed on an as needed basis.

#### General Directions:

Self-explanatory.

#### 4.5.2 Endpoint Worksheet:

**Purpose:** To record endpoint information to determine a participant’s responder or non-responder status.  
(An example of the CRF Endpoint Worksheet (ENDPT) is provided in Appendix D of the MOP to assist the RC and PI in evaluating the participant’s primary endpoint response.)

**Who:** RC completed.

**When:** This administrative CRF **MUST** be completed at the end of Visit 15 (week 34) to determine participant status for continuing into the open-label BCG trial.

#### General Directions:

In order to utilize Visit 15/Week 34 visit time with the participant efficiently, columns 2A, 2B and 2E should be completed **prior** to the participant’s scheduled visit at the clinic. Additional CMED data that may need to be added, based on the participant’s PTDIARY information, can be added at the time of the visit.

The RC needs to refer to 3 data CRFs to determine participant status – FUSYM (Follow-up Symptoms) at Visit 15, STVST (Standard Visit Inventory) at Visit 15 and CMEDs (Concomitant Medications) data from Visits 2, 3, 4, 5, 6, 7, 8, 11 and 15.

**Non-responders** are those who:

- Report a score of 1 to 5 on Question #6 on Follow-up Symptoms (FUSYM)
- or**
- Report an increased use of IC medications during weeks 31 to 34 as compared to baseline screening (compare CMEDs at Visits 2 and 15)

or

- Report initiation of new IC medications during weeks 31 to 34 (compare CMEDs at Visits 2 and 15)

or

- Report new or increased use of narcotic medications from weeks 31 to 34 (See CMED at Visit 15), or request narcotics at any time during weeks 31 to 34.

**Responders** are those who fulfill **both** of the following **two** criteria:

- ❖ Report a score of 6 or 7 on Question #6 on Follow-up Symptoms (FUSYM)

and

- ❖ Report no increase in pre-study IC medications, and no initiation of new IC medications, and no new or increased use of narcotic medications during the final 4 weeks of the follow-up phase – between Visits 14 and 15/Weeks 31 to 34.

- A (Global Assessment Response – **GAR**) of **1 to 5** on Question 1 on this CRF at Visit 15 (Week 34), indicates that the participant does not feel that there is significant clinical improvement of his/her IC symptoms. This makes the participant **fail one of the two criteria needed** to be a study Responder. Thus, Question #2, which helps determine increased use or initiation of new IC medications between Visits 14 and 15 (Weeks 31 and 34) does not get completed. The RC then skips to Question #3, and checks the “Non-responder” status.
- A (Global Assessment Response – **GAR**) of 6 or 7 on Question 1 on this CRF at Visit 15 (Week 34), indicates an improvement of his/her IC symptoms and the participant is considered a **responder for 1 of 2 criteria needed to determine endpoint status.**

The table provided in Question #2 to determine prescribed IC medication status between Visits 14 and 15 (Weeks 31 to 34), is then completed. All prescribed IC medications coded as “1” in column **2F** determines the participant a **Responder**. Medications coded as “2” in column **2F** makes the participant a **Non-Responder**.

**Prescribed IC Medications** recorded at Visit 2 and new prescribed IC medications started after Visit 2 are noted in 2A. New or increased doses of “critical” IC medications requested by the participant between Visits 14 and 15, whether prescribed or denied, are also recorded for endpoint determination. IC medications started after Visit 2 but discontinued prior to Visit 14, are not recorded in 2A.

Combination drugs (e.g. Tylenol w/Codeine) are noted with the total Daily Dose for the component that is critical to determine the endpoint.

Total Daily Dose is recorded in mgs in columns 2C and 2E.

- Question #3 makes the **final determination** of the participant's endpoint status where the appropriate box of the participant's status is checked, based on the outcome of the worksheet data from Question #s 1 and 2.

The Endpoint Worksheet **MUST** be signed and dated by the Clinical Center PI.

- A responder is not offered the option of continuing into Phase II open-label BCG trial.

A non-responder can be offered the open-label trial if the LAB results, EXAM, etc., from Visit 15 appear to be non-significant and all other eligibility criteria are met.

#### **4.5.3 Participant Contact (PTCONT)**

**Purpose:** To collect participant's contact information, and is strictly confidential. This CRF should *never* be forwarded to the DCC.

**Who:** Participant completed at screening and RC updated at subsequent visits, if needed.

**When:** This CRF should be completed at Visit 1, immediately following the completion of the informed consent document. It is updated at subsequent visits if necessary.

#### **General Directions:**

If a participant's contact information changes during the course of the study, a new CRF should be completed and filed with previously completed CRFs.

#### **4.5.4 Participant's Daily Medication Diary (PTDIARY)**

**Purpose:** To record medications (both prescription and over-the-counter) that the participant takes on a daily basis.

**Who:** Participant-completed at home.

**When:** Every evening while on study, beginning with the day following Visit 1.

#### **General Directions:**

The RC provides the participant with *one* booklet for *each* week of the study. The RC completes the front page of the booklets, indicating weeks and dates.

The participant will bring **completed** diaries to each visit. It is important that the RC review and correct, with the participant, any ambiguous entries while the participant is still in the clinic, since **CMED** is completed from this diary.

Instructions and a list of restricted and excluded medications (**Appendix A**) are provided to the participant.

**Note:**

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

Referring to the photocopy of his/her medications, the participant is instructed to record new medications, changes in medications, and medications (s)he has stopped each day.

If the participant has stopped taking a medication in between visits, (s)he should record the stop date in the margin (i.e. Ortho-Cyclen – last day).

The master list of participant’s medications, developed by the RC and given to the participant for reference at baseline, includes ALL medications taken by the study participant on a daily and/or PRN basis. Based on this master list, the participant is instructed to record changes (skipped or reduced doses, start and stop dates for new or reported medications) on the PTDIARY. The RC may update the master list at each visit, if needed, based on the changes recorded on PTDIARY and CMED.

- at Clinic Visit 11 (Week 18), the participant is instructed that s/he will have a 3-month period (from Week 19-30) during which s/he **does not** complete PTDIARYs.
- at Clinic Visit 13 (Week 26), the participant is given a four-week supply of PTDIARYs with instructions **not** to record medication information until a call from the Research Coordinator at Phone Visit 14 (Week 30). Starting with end of Visit 14 (Week 31), the participant will record again all medications taken on a daily basis, till end of Phase I Clinic Visit 15 (Week 34).
- The RC will collect PTDIARYs from the participant at Clinic Visit 15 (Week 34).

**Note:** At the discretion of the RC and/or the PI, some participants may continue to maintain PTDIARYs during the 3-month break period (Week 19-30), if the interruption may prove disruptive to data collection for CMEDs.

**During Phase II:** PTDIARYs and a self-addressed stamped envelop will be given to the participant at Visit 21 (Treatment 6), to be mailed back to the Clinical Center at Phone Visit 24 (Week 52) of the Phase II open-label BCG trial. The participant will be reminded about this at Phone Visit 22 (Optional Visit).

**During Phase IIR:** At visit 25 the participant will be reminded that from week 65 (4 week prior to Visit 28) to week 68 (visit 28) it will be necessary to complete PTDIARYs.

Before week 65, PTDIARYs and a self-addressed, stamped envelope will be either given or mailed to the participant.

Additional PTDIARYs are mailed to the participant prior to Phone Visit 27 (Week 64). The participant is instructed to complete PTDIARYs between Phone Visit 27 (Week 64) and Clinic Visit 28 (Week 68), to be returned at Clinic Visit 28.

#### **4.5.5 Participant Log (PTLOG)**

**Purpose:** To record *all* participants who have signed the informed consent document whether or not they are 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 Participant ID number (PT ID).

#### **General Directions:**

This is a site-specific CRF.

#### **4.5.6 Participant Refusal Log (REF)**

**Purpose:** To record the reason why 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 REF should be sent to DCC on a regular basis (once a month).

#### **4.5.7 Participant Transfer (TRANS)**

**Purpose:** To notify the DCC and the Receiving Center when a participant transfers from one Clinical Center to another during the post treatment follow-up phase.

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

**When:** When a participant transfers to another Clinical Center.

### **General Directions:**

The Originating Center completes page 1 of this CRF and includes a copy of TRANS with the participant's study binder, which gets mailed to the Receiving Center. *A copy also should be mailed to the DCC.*

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

A participant *cannot* be transferred to another Clinical Center during the treatment phase of the study or the open-label BCG trial.

Also see section 2.11.4 – *Participant Transfer*.

### **4.5.8 Participant Collected Urine Sample Tracking for University of Iowa (PUTRAC)**

**Purpose:** To log information about the processing and shipment of the participant-collected urine sample to University of Iowa.

**Who:** RC completed.

**When:** Urine is collected at Visit 6 (Sample 2) *6 to 8 hours after* the fourth treatment. The CRF is completed at Visit 7 in Phase I of the study only.

### **General Directions:**

It is important to note if the participant has agreed to participate in the Biomarker Study, in Question #1. The RC notes the date and time the urine sample was collected by the participant, the date the sample was received by the RC at the Clinical Center, and the date and time the sample was processed at the Clinical Center in Question #s 2 through 6. When the sample is shipped to University of Iowa, the shipping date should be noted on the CRF. Checkboxes have been provided if fewer than expected numbers of specimens are collected at the visit. This information helps the DCC track urine specimens available at University of Iowa laboratory.

The RC signs and dates the CRF when the sample is processed and frozen. The RC initials and dates next to Question #7, when the sample is shipped.

The RCs will fax copies of the completed CRFs to the DCC when the urine specimen is shipped to the University of Iowa.

### **4.5.9 Symptoms Assessment Guidelines (SAG)**

**Purpose:** To use as a guide for assessing (by phone) symptoms that the participant may develop in the 48-hour period after receiving intravesical treatment.

**Who:** RC completed.

**When:** Day 1 and Day 2 (possibly Day 3) after the participant receives treatment for Visits 3 through 8 during Phase I of the study or Visits 16 to 21 during Phase II of the open-label BCG trial.

**General Directions:** It is recommended that the RC refer to this form as a guide to use when conducting a telephone assessment of the participant's physical response to treatment.

#### **4.5.10 Urine Sample Tracking (UTRAC)**

**Purpose:** To log information about processing and shipment of the urine sample to each of the four-biomarker/banking laboratories.

**Who:** RC completed.

**When:** Urine is collected at Visits 3, 6 and 15.

#### **General Directions:**

Question #1 refers to the participant's consent to participate in the Biomarker Study. Question #s 2 and 3 record the date and time of urine collection. Once the urine is processed at the clinical center, the processed specimen will be frozen at various temperatures (see **Laboratory Specimen Processing Procedures**) for different banking repositories and date and time of storage is noted on Questions 4 and 5 on the CRF. Question # 6 has checkboxes to record reasons the four laboratories do not receive the expected numbers of specimens from the Clinical Centers. **Space is provided to record** comments if there is a problem with the specimen(s). The comments section is also to be used to record each specimen as either "Voided" or "Catheterized". The RC signs and dates the CRF when the specimen is frozen.

As outlined in the laboratory procedures, the date of shipment to the banking laboratories is also noted in the space provided, with the RC's initials and date when the CRF is completed.

The RCs will fax copies of the completed CRFs to the DCC when the specimens are shipped to the various laboratories.

#### **4.5.11 Urine Sample Tracking Log (ULOG)**

**Purpose:** To log information about each participant's urine sample shipped, in order and by date, to the biomarker/banking laboratories.

**Who:** RC completed.

**When:** When the frozen urine is batched and shipped.

#### **General Directions:**

This revised CRF provides a tracking system for specimens shipped from the Clinical Centers and the specimens received at the laboratories.

RCs will include a copy this CRF in the container when shipping specimens. The laboratory receiving the shipment is identified in the header. The initials of the sender, receiver, date of shipment and receiving date are also recorded. Participant information, and number of specimens are noted by the RCs.

The left half of the CRF will be completed by the RCs, accounting for the specimens shipped. The right half (shaded part) of the CRF notes the total number of usable specimens available to the laboratories from the CCs and will be completed by the laboratory personnel. Damaged or unusable specimens, if any, received at the laboratories, are accounted for on this administrative CRF.

ULOG will be faxed to the DCC by the laboratories upon receiving the specimens.

#### **4.6 Data Entry & Verification in the Database**

- The RC should review the data prior to entry and verification in the database.
- Only designated data entry personnel should enter and verify data.
- Data can be entered and verified by the same person.
- Participants who meet (Baseline) Visits 1 and 2 screening criteria are registered into the database.
- Registered participants who fail the eligibility criteria at Baseline Visit 2 are deleted from the database.
- Only screened and eligible participants are randomized into the study.
- Participants once randomized cannot be deleted from the database.
- The CRFs for a particular Visit (packet entry) will appear in sequential order to be entered (refer to Data Entry List). Single CRFs (PTCL, STCL, TSTOP, SSTOPI/SSTOPII and UNMASK) are entered in a separate entry process.
- All visit packets and single CRFs for randomized participants should be entered in the database ***and*** verified.
- ***CRFs for a visit should not be entered or verified in the database until all CRFs in that packet are completed.***
- The “Missing CRF” button is clicked for CRFs not completed at a visit. The “Missing Visit” button is clicked for a missed visit.
- At verification, a data 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.

- Specific instructions for updating the database are found in Section 8.

#### **4.7 Manual Audits**

Each Clinical Center is responsible for submission to the DCC, *copies* of all CRFs and related source documentation on the first *two (2)* recruited participants for each available visit. These CRFs will be logged into the Data Management System (DMS) to track audit status. They will be audited against the data entered and verified in the DMS and also manually checked for completeness and accuracy in coding by checking against source documentation. Discrepancies will be brought to the attention of the respective Research Coordinators in the form of queries and responses will be expected as described in the chapter on Queries. CRF' and supporting data *may* be mailed to the DCC prior to entry and verification.

#### **4.8 Submission of Case Report Forms to the DCC**

The DCC may request additional copies of any CRF or visit packets for any study participants at any time during the course of the study. Copies of CRFs could be requested for several reasons, including data auditing and CRF completion review. If a request is made, the Clinical Center is responsible for making photocopies of all requested CRFs. The original CRFs should remain in the participant's study binder and the *photocopies* sent to the DCC. All personal identifiers should be removed from the copies sent to the DCC. All multi-page CRFs should be stapled and the visit packet should be paper-clipped. It is preferred that copies should be sent to the DCC via overnight mail. To ensure data quality, it is very important that response to requests be made as soon as possible.

All CRFs and correspondence to the DCC regarding CRFs should be addressed to:

(Data Manager Name)  
ICCTG Clinical Data Manager  
University of Pennsylvania  
Clinical Research Computing Unit  
Suite 560,  
3535 Market Street  
Philadelphia, PA 19104 – 3309

## 5 Queries

Queries will be sent to the Research Coordinators in response to errors logged by the Data Management System (DMS) when it views the verified data in the application against a set of rules, written to validate the data. A query can also be generated by a manual review of the verified data against an expected set of data standards, by the Data Management staff at the DCC.

### 5.1 Types of queries generated by the database

There are several types of queries sent to the Clinical Centers that are generated by the DMS.

#### 5.1.1 *Missing Fields*

Collected data will be reviewed for completeness at the Clinical Centers *prior to* entry and verification. A data field on a CRF that is left blank in the application will be logged as an error by the DMS and will be queried; e.g., if a medical history question was left blank, the RC can inform the DCC of the missing field soon after the data is entered and verified (*in the same format as the query sent by the DCC*) or a query will be sent by the DCC requesting the information.

If a query is sent to the Clinical Center, the RC will attempt to find the correct response or provide an explanation. If the data are available, the CRF will be faxed with the response. An explanation is acceptable when a response is left blank for a reason. For example, halfway through the participant's follow-up, the PI may request CBC but not differential. Therefore, when completing the LAB CRF, the data fields for Granulocytes, Total Lymphocytes and Monocytes will be left blank. When this is queried, the acceptable response to the query would be that these "tests were not ordered".

#### 5.1.2 *Skip Patterns*

Skip patterns account for fields that should or should not be answered, depending on the response to the first question in the series. For example, the "significance" question on LAB should only be answered at follow-up visits. If significance is coded at screening, it will be queried because the field should be left blank, since participant *should* meet the laboratory criteria. Conversely, if the coding is missing at follow-up, it will also be queried, because it should *not* be left blank.

If a skip pattern query is sent to the RC, and a change is warranted, the CRF with the correction should accompany the faxed response to the DCC.

#### 5.1.3 *Range Checks*

Many fields have a specific range of expected responses, which is designed to include approximately 95% of the population. For example, a participant's height has both a low range and a high range, and anything outside of those ranges *may* generate a query. The range check query is sent to confirm the value entered because it is higher/lower than the expected range.

The RC should confirm data in question in his/her response to the DCC. A copy of the CRF is not needed with the response. If a correction to the entered data is necessary, a copy of the CRF should be faxed with the response.

#### **5.1.4 Logic Checks**

These checks review the data to ensure the data is logical, e.g., men should respond “NA” to female-oriented questions, and women should respond “NA” to male oriented questions. A CRF should accompany a faxed response to the query when entered data needs to be corrected.

### **5.2 Types of queries generated by manual monitoring**

#### **5.2.1 Monitoring Checks**

These checks monitor the data for completeness and accuracy. Data Management staff at the DCC will manually view the data and queries will be sent for data that looks incomplete or appears to conflict with the design of the study. The Research Coordinators will manage these queries in a similar manner as outlined above for the database-generated queries. If changes are necessary, a faxed response with the corrected CRF will be expected. An explanation, without data change, can be sent by e-mail. Types of monitoring queries include:

- **Safety issues** – AE’s, SAEs, CMED and LAB coding issues.
- **Study Procedures** – Participant Termination Status, Data Entry and Verification Status.

#### **5.2.2 Manual Audits**

Manual audits will be performed by the DCC on all CRFs at available visits, on the first 2 recruited participants in the study at each Clinical Center. The CRFs will be audited for accuracy in entry and verification as well as CRF completion and accuracy in coding, by reviewing source documentation. Any discrepancies noted during audits will be forwarded to the Clinical Center RC’s in the form of queries. Corrections will be faxed to the DCC with the original query and an explanation will be acceptable if sent by e-mail.

### **5.3 Managing Queries**

#### **5.3.1 Receiving Queries from CDM**

Queries will be sent via email, and will contain the following information:

- Participant ID
- Participant Initials
- CC ID
- Contact Week
- Form Name
- Form Date
- RC ID

- Date Queried
- Description of the Problem
- The subject line of each query identifying an electronically generated query (Query – Participant #/CW/CRF name) or a monitoring query (Monitoring Query – Participant #/CW/CRF name).
- The subject line indicating the query as a second or third attempt at seeking response from the Clinical Center (Second Query – Participant #/CW/CRF name).

### 5.3.2 Making Corrections Based on Queries

- All queries e-mailed by DCC will be printed by the RC's. At Clinical Centers with more than one RC, the lead RC will inform the DCC at the start of the study how they would like to receive the queries – if one RC at the Clinical Center receives all queries or the RC ID on the CRF determines who receives the queries.
- The RC's will be responsible for identifying the correction to be made or providing an explanation. DCC Data Management staff will be available to assist the RC's in resolution of the queries, if needed.
- If a query results in a correction, the correction must be included on the query and documented on the original CRF (initialed and dated).
- If it is determined that a correction is not needed, an explanation (e.g. test not done, participant's height is correct), should be thoroughly documented on the query.
- All queries should be initialed and dated and then filed with the participant's study binder.
- Any questions regarding the queries should be directed to the individual at the DCC that originated the query.

### 5.3.3 Query Response to the DCC

- Queries can be returned to the DCC via email **or** fax. A copy of the response e-mailed or faxed to the DCC, is retained in the participant's study binder.
- Explanations that do **not** require changes to the database can be e-mailed to the DCC.
- The response to the query is addressed to the individual at the DCC who originated the query.
- **Original text must be “quoted”** if responding to the query by email.
- ***Include the corrected CRF with the original query, when changes are necessary to the entered data.***
- ***A copy of the corrected CRF without the original query will not be accepted as a response at the DCC.***
- A dedicated fax line [(215) 573-4790] is available at the DCC to accept query responses and data sent from the Clinical Centers.
- Responses to safety-related queries are expected at the DCC in 3 working days. Responses to all other queries are expected at the DCC in 5 working days.

### **5.3.4 Managing Responses to Queries**

<b>Type of Query</b>	<b>Data Change Necessary</b>	<b>No Data Change/Explanation</b>
Missing Fields	Response by fax; include CRF	Response by e-mail; CRF not necessary
Skip Patterns	Response by fax; include CRF	N/A
Range Checks	Response by fax; include CRF	Response by e-mail; CRF not necessary
Logic Checks	Response by fax; include CRF	Response by e-mail; CRF not necessary
Monitoring Checks	Response by fax; include CRF	Response by e-mail; CRF not necessary
Manual Audits	Response by fax; include CRF	Response by e-mail; CRF not necessary

## **6 Treatment Procedures**

### **6.1 Patient Pre-Treatment & Post -Treatment Instructions**

The research coordinator will review pre-treatment and post-treatment instructions with the patient before each treatment. Clinical center phone or beeper contact numbers will be provided to the patient at each instruction session.

#### **Pre-Treatment Instructions**

1. Do not drink anything for **four** hours prior to treatment.
2. Bring something to occupy yourself such as books, tapes, etc. Some people like to bring their own special pillow for comfort.
3. You may bring another person along to keep you company after your treatment.
4. At each visit you will be asked if you have changed any of your medications, or had any illness or side effects since your last treatment. Please have this information with you.
5. Please bring the “Post-Treatment Discharge Instructions” you received at your prior treatment visit with you to your next treatment visit.
6. If you have any questions or concerns, please feel free to contact us at \_\_\_\_\_.

#### **Post-Treatment (discharge) Instructions**

The research coordinator and the patient will sign and date the post-treatment (discharge) instructions. The patient is given a copy of the instructions, and the original is kept with the patient’s records and is considered a source document.

1. Resume normal activity according to how you are feeling.
2. During the six hours after treatment, pour 1 cup of bleach (such as Clorox®) into the toilet each time you urinate and let the mixture stand in the toilet 15-20 minutes before flushing. You must sit down while urinating to avoid splashing.
3. Wash your hands and genital area thoroughly after you urinate.
4. Drink plenty of fluids.
5. Take and record your temperature (by mouth) once at bedtime on the night of your treatment and again the following night. Record your temperature on page two of these instructions.
6. You will be called by phone on each of the two days after your treatment. You will be asked to report your temperature and answer questions about your health.

7. Contact your study doctor (phone number) **immediately** if you experience a high fever (101.3°F) or flu-like symptoms that lasts longer than 2 days, or if you feel generally unwell after 2 days.
8. Go to the nearest hospital emergency room if you experience:
  - Severe skin rash
  - High amounts of blood in your urine
  - Severe pain when passing urine
  - Contractions of your bladder muscle
  - If you cannot pass urine
  - For male patients: If your testicles become painful and swollen
9. Please bring this paper with you if you should need to visit a hospital near your home that is different from the study doctor's clinic.

**Patient Instructions: Day ONE Following Treatment Visit**

The time the study coordinator will call for my temperature reading, any new medication I am taking or have stopped taking, and any changes in my health:

DATE: \_\_\_\_\_

TIME: \_\_\_\_\_

Temperature as indicated on the oral thermometer: \_\_\_\_\_

DATE: \_\_\_\_\_

TIME: \_\_\_\_\_

**Patient Instructions: Day TWO Following Treatment Visit:**

The time the study coordinator will call for my temperature reading, any new medication I am taking or have stopped taking, and any changes in my health:

DATE: \_\_\_\_\_

TIME: \_\_\_\_\_

Temperature as indicated on the oral thermometer: \_\_\_\_\_

DATE: \_\_\_\_\_

TIME: \_\_\_\_\_

PLEASE REMEMBER TO BRING THE DISCHARGE INSTRUCTION SHEETS TO YOUR NEXT SCHEDULED VISIT.

### **6.1.1 Patient Instructions for Urine Collection After the 4<sup>th</sup> Treatment Visit**

The following instructions will be reviewed with the patient after the 4<sup>th</sup> treatment is completed.

#### **Patient Instructions Urine Collection Six Hours After 4<sup>th</sup> Treatment**

You will be given the following material for collecting this urine sample:

- A small cup in which to collect the specimen
- A small specimen tube which contains a stabilizing agent (preservative)
- A packaged antiseptic wipe
- A plastic disposable eyedropper for transferring a sample of urine into the specimen tube
- A plastic zip-lock bag to contain the urine sample with a paper towel inside.

This urine sample is to be collected approximately 6 to 8 hours **AFTER** you receive your 4<sup>th</sup> BCG treatment.

Cleanse your genital area with the antiseptic wipe (female patients wipe the labial area, male patients wipe the head of the penis).

Void into the small cup. Once you void at least 30 cc of urine, use the plastic eyedropper to remove about 12 cc of urine from the small cup. Add the 12 cc of urine to the urine specimen tube that contains the stabilizing agent.

Next, place the cap on the urine specimen tube securely and invert gently several times.

The remainder of the urine can be discarded in the toilet.

Put the urine specimen into the zip-lock bag, and store it at refrigerator temperature either in the Styrofoam box provided or in a cooler. A cold pack or ice must be kept in the container with the specimen at all times.

It is important that you bring the specimen back to your study site as soon as possible (within two weeks). **Do not freeze** this urine specimen.



## **6.2 Intravesical Administration of Study Agent**

*Bladder catheterization of patient and intravesical administration of Study Agent may ONLY be performed by a Registered Nurse or Physician, competent in the intravesical instillation of BCG.*

### **I. Pre-Instillation**

#### **A. Initial Visit for First Instillation:**

1. Upon presentation to office, the pharmacy is contacted to reconstitute and prepare solution.
2. Position patient in lithotomy and prepare skin and genitalia in a standard manner with antiseptic solution.
3. Prepare for catheterization (lubrication, etc.).
4. Perform urethral catheterization.
5. Dipstick urine for nitrites.
6. If nitrites are absent, proceed with instillation.  
(GO TO NEXT SECTION: **Instillation of Solution**).
7. If nitrites are present on dipstick analysis, perform microscopic examination of urine. If microscopic examination reveals bacteria, consider empiric antibiotic therapy for bacterial UTI. Perform urine culture and postpone instillation pending results of urine culture. In 24-48 hours, the urine culture results will be available. If the urine culture is negative, proceed with instillation. If the urine culture is positive, complete antibiotic therapy and proceed with instillation after UTI is appropriately treated.

#### **B. Subsequent Visits for Repeat Instillations:**

1. Query patient regarding adverse effects including gross hematuria, etc.
2. Record patient temperature.
3. In the absence of adverse effects, proceed as per section I.A.1.
4. If adverse effects from prior therapy are ongoing, obtain voided urine specimen, assess adverse effects and manage adverse effects appropriately as per protocol and, when appropriate, at the discretion of the Principal Investigator at the site.

### **II. Instillation of Solution**

1. The solution is reconstituted and prepared in the pharmacy, placed in a standard blinded syringe, bagged appropriately and maintained at room temperature.
2. Upon transport to the clinic, the syringe is removed from pharmacy bag.
3. The syringe is attached to the previously placed indwelling urethral catheter.
4. The solution is instilled slowly over 1-2 minutes. The time of day that the instillation is performed is recorded.
5. If the syringe is completely (successfully) emptied into the bladder, the syringe, catheter and catheterization kit with gloves and other materials are removed together as one unit.

If the syringe cannot be completely emptied into the bladder (due to pain, severe urgency, etc., upon instillation) then the catheter and attached syringe are removed as one unit. In order to maintain strict blinding conditions, a third party (i.e. uninvolved in the study) will empty the remaining solution within the syringe into a measuring container. This volume is recorded as per study protocol. The container, solution, and other materials are then disposed of as per section II.6.

6. The instillation materials are disposed of in a Biohazard container or by alternative suitable measures as determined by local/hospital regulations.
7. The subject's genitalia are washed with antiseptic solution.
8. The subject is repositioned in a comfortable manner as to maximize retention of solution. The subject may be provided with diversionary activities during dwell time while in the clinic. Antispasmodics and other agents may be administered as per protocol to maximize the subject's comfort and dwell time up to 2 hours.

### **III. Post-Instillation**

1. The solution is held intravesically for 2 hours. If the solution is unable to be held for 2 hours, the subject is allowed to void and the total dwell time is recorded as per study protocol.
2. The subject is instructed to void completely into a receptacle (toilet or "hat"). One cup (8 oz.) of bleach or equivalent is spilled into the receptacle after voiding is completed. In the absence of a "hat", the bathroom (toilet area in the clinic) is functionally closed for 15 minutes. After 15 minutes, the mixture is either flushed down the toilet or the "hat" is disposed of appropriately.

If the subject is unable to void at two hours from instillation, a repeat urethral catheterization is performed to empty the bladder.

3. The subject is given standardized instructions regarding the instillation and arrangements are finalized for the next clinic visit and follow-up phone call for the next day.

## 7 Laboratory Procedures & Physical Exam

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

### 7.1 Blood Draw Procedures

Each clinical site will utilize its respective on-site clinical laboratory for serum pregnancy test. This test will be performed at Visit 1 and when a participant has missed one full menstrual cycle (>30 days as indicated on her Voiding Diary). In addition, complete blood count (CBC) with electronic differential, red blood cell count (RBCs) and platelets will be performed at Visit 1 and Week 34 (Visit 15) 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

### 7.2 Physical Examination Procedure

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 Visit 1, (or before Visit 2) and at Week 34 (Visit 15) 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.

### **7.3 Urine Testing Procedure**

#### **7.3.1 *Urine Analysis & Culture***

This test is performed at Visit 1. 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 CRFs include Nitrite, Blood, Hemoglobin and Leukocytes.

Materials needed:

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

#### **7.3.2 *Residual Urine Volume***

This test is performed at Visit 1. 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

#### **7.4 Urine Specimen for Banking - Laboratory Processing Procedure**

Urine specimens for banking will be collected from the patient at the following time points:

- ❑ ***before*** administration of the first treatment (visit 3)
- ❑ ***before*** the administration of the 4<sup>th</sup> treatment (visit 6)
- ❑ ***six to eight hours after*** the 4<sup>th</sup> treatment (visit 6)
- ❑ ***at*** the 34-week clinic visit (visit 15)

Collection of these urine specimens will be obtained as follows:

- ❑ The first and fourth pre-treatment specimen will be collected by bladder catheterization. This collection will be done at the clinic site and the specimen will be processed as soon as possible after collection according to procedure outlined in 7.4.1 through 7.4.4.
- ❑ Six to eight hours after the 4<sup>th</sup> treatment, the patient will collect a clean catch specimen at home as instructed in *Section 6.1.1*, and bring the specimen back to the clinic site at the next visit. The specimen will be processed as soon as possible once received at the clinic site according to procedure outlined in 7.4.5.
- ❑ The 34-week visit specimen will be collected by the clean catch method. This collection will be done at the clinic site and the specimen will be processed as soon as possible after collection according to procedure outlined in 7.4.1 through 7.4.4.

**All specimens will be labeled with the patient's identifier number, initials, and date of collection, except where prohibited by the clinical site Institutional Review Board (IRB).**

All other tracking information of these specimens will be recorded on the visit appropriate administrative Case Report Forms and laboratory specific Urine Sample Tracking Log (**ULOG**) as outlined in Sections 4.5.7, Section 4.5.9, and Section 4.5.10.

##### **7.4.1 Processing Procedure**

**(As shown in Section 7.4.7 Page 1 of procedure diagram)**

1. Collect catheterized urine specimen (*voided specimen is permitted*)
2. Separate urine specimen as follows:
  - a. small portion for Dipstick test: nitrates, hematuria
  - b. 12 ml sample into 15 ml tube for centrifuge
  - c. put remaining urine in refrigerator for processing later that day (see page 2 of diagram)
3. Take the 12 ml sample of urine in 15ml tube (#2b above) and centrifuge the urine for 10 minutes at 1000g
4. Pipette supernatant and discard the pellet
5. Put supernatant into 15 ml tube containing stabilizing agent and protease inhibitor (total volume will be approximately 13 ml)
6. Refrigerate at 4°C (39°F) – ordinary refrigerator temperature.

#### **7.4.2 Processing Procedure**

(As shown in Section 7.4.8 Page 2 of procedure diagram – **STEP I**)

**NOTE:** This step of the procedure can be completed after the patient receives study treatment

1. Take 15ml tube containing supernatant with stabilizing agent and protease inhibitor tablet out of the refrigerator.
2. Into N=10 - 2ml tubes, aliquot a **1.2 ml. amount of urine to each tube.**
3. Freeze @ -70°C.
4. On the clinic site assigned days of each month, send as follows:
  - **Five** - 2ml tubes to University of Iowa Lab on dry ice.
  - **Five** - 2ml tubes to University of Pennsylvania Lab on dry ice.

#### **7.4.3 Processing Procedure**

(As shown in Section 7.4.8. Page 2 of procedure diagram – **STEP II - A**)

1. Take remaining urine (see #2C Section 7.4.1) from refrigerator.
2. Centrifuge 50 ml of remaining urine (in one 50 ml tube or in four 15ml tubes) for 10 minutes at 1000g.
3. Pipette (remove) supernatant and into N=15 – 2ml tubes, aliquot a **1.2 ml amount of urine to each tube.**(Discard remaining urine).
4. Freeze @ -70°C.
5. On the clinic site assigned days of each month, send as follows:
  - **Eight** - 2ml tubes to University of Pennsylvania Lab on dry ice.
  - **Seven** - 2ml tubes to University of Maryland Lab on dry ice.

#### **7.4.4 Processing Procedure Collection of Pellet**

(As shown in Section 7.4.8 Page 2 of procedure diagram – **STEP II B**)

From previous (#2 Section 7.4.3 above) centrifuged 50ml or centrifuged four 15 ml tubes **after** supernatant procedure is completed:

1. Resuspend pellet in **1.0 ml** PBS (Phosphate Buffered Saline).
2. Vortex @ low speed. While vortexing, add 2mls, drop by drop, of 95% ETOH using a 1 ml disposable bulb pipette.
3. Pipette 0.25 ml into **one** 2ml tube (up to first mark on 1 ml disposable bulb pipette).
4. Freeze @ -70°C.
5. On the clinic assigned days of each month, send the (above) **one** - 2ml tubes to the University of Maryland Lab on **dry ice.**
6. Pipette remaining vortexed and fixed cells into **two or more** - 2ml tubes.
7. Store at -20°C (Freezer compartment of ordinary refrigerator).
7. On the clinic assigned days of each month, ship **overnight** the **two or more** 2ml tubes to University of Rochester Lab on **wet ice pack.**

#### **7.4.5 Processing Procedure - Patient Collected Specimen After 4<sup>th</sup> Treatment Visit Six**

**(As shown in Section 7.4.9 Page 3 of procedure diagram)**

Patient collects urine specimen at home after 4<sup>th</sup> treatment Visit 6 (as instructed in Section 6.1.1), and returns the specimen to the clinic at Visit 7.

1. Take the 15 ml tube containing the patient collected specimen and centrifuge at 1000g for 10 minutes.
2. Into N=10 – 1.2 ml tubes, aliquot a **1.2 ml amount of urine to each tube.**
3. Freeze at -70 C.
4. On the clinic assigned days of each month, ship to the University of Iowa on dry ice.

#### **7.4.6 Laboratory Shipping Addresses**

**NOTE:** Prior to shipping, notify lab contact person (indicated by \*) with package shipping numbers, number of packages sent and date of shipping. Pre-printed shipping labels will be used for specimen shipping to the following addresses:

John E. Tomaszewski, M.D./\*Li –Ping Wang – [wangli@dolphin.upenn.edu](mailto:wangli@dolphin.upenn.edu) - Pager 215-401-9765  
University of Pennsylvania  
Department of Pathology, Founders 6.042  
3400 Spruce Street  
Philadelphia, PA 19104

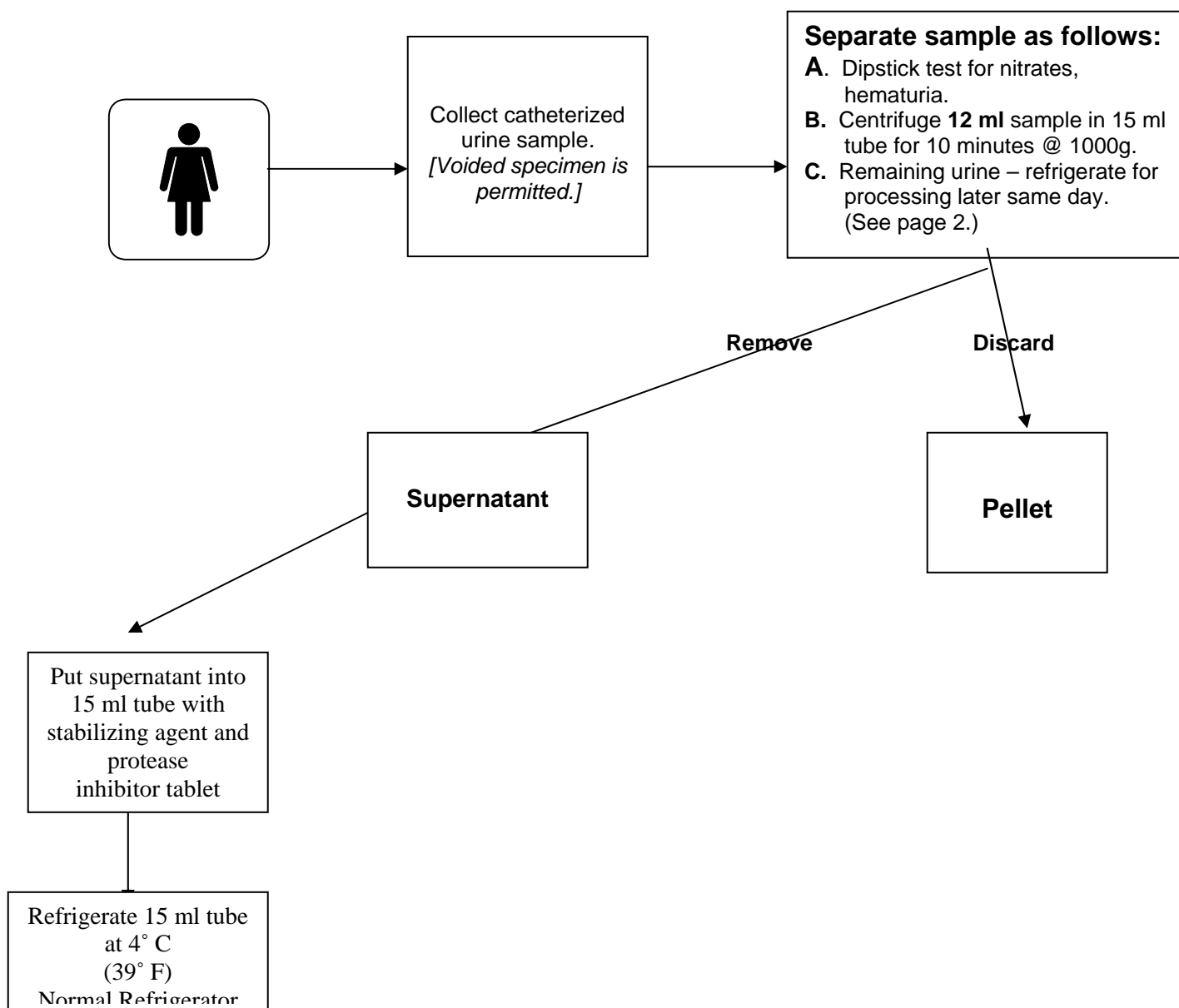
Susan Keay, M.D./\*Kris Koch – [kkoch001@umaryland.edu](mailto:kkoch001@umaryland.edu) - Phone 410-605-7000 x6455  
University of Maryland  
Division of Infectious Diseases  
VAMC-Room 3-B-184  
10 North Greene Street  
Baltimore, MD 21201

Michael O'Donnell, M.D./\*Pat Pollock – Phone 319-384-6040 & e-mail-[michael-a-odonnell@uiowa.edu](mailto:michael-a-odonnell@uiowa.edu)  
University of Iowa Hospitals and Clinic  
Division of Urology #3125 RCP  
200 Hawkins Drive  
Iowa City, Iowa 52242-1089

Jay Reeder, Ph.D./ [\\*Jay Reeder@URMC.Rochester.edu](mailto:Jay.Reeder@URMC.Rochester.edu) - Phone 716-275-1006  
University of Rochester Medical Center  
Department of Pathology, Room 2-6437  
University of Rochester  
575 Elmwood Avenue  
Rochester NY 14642

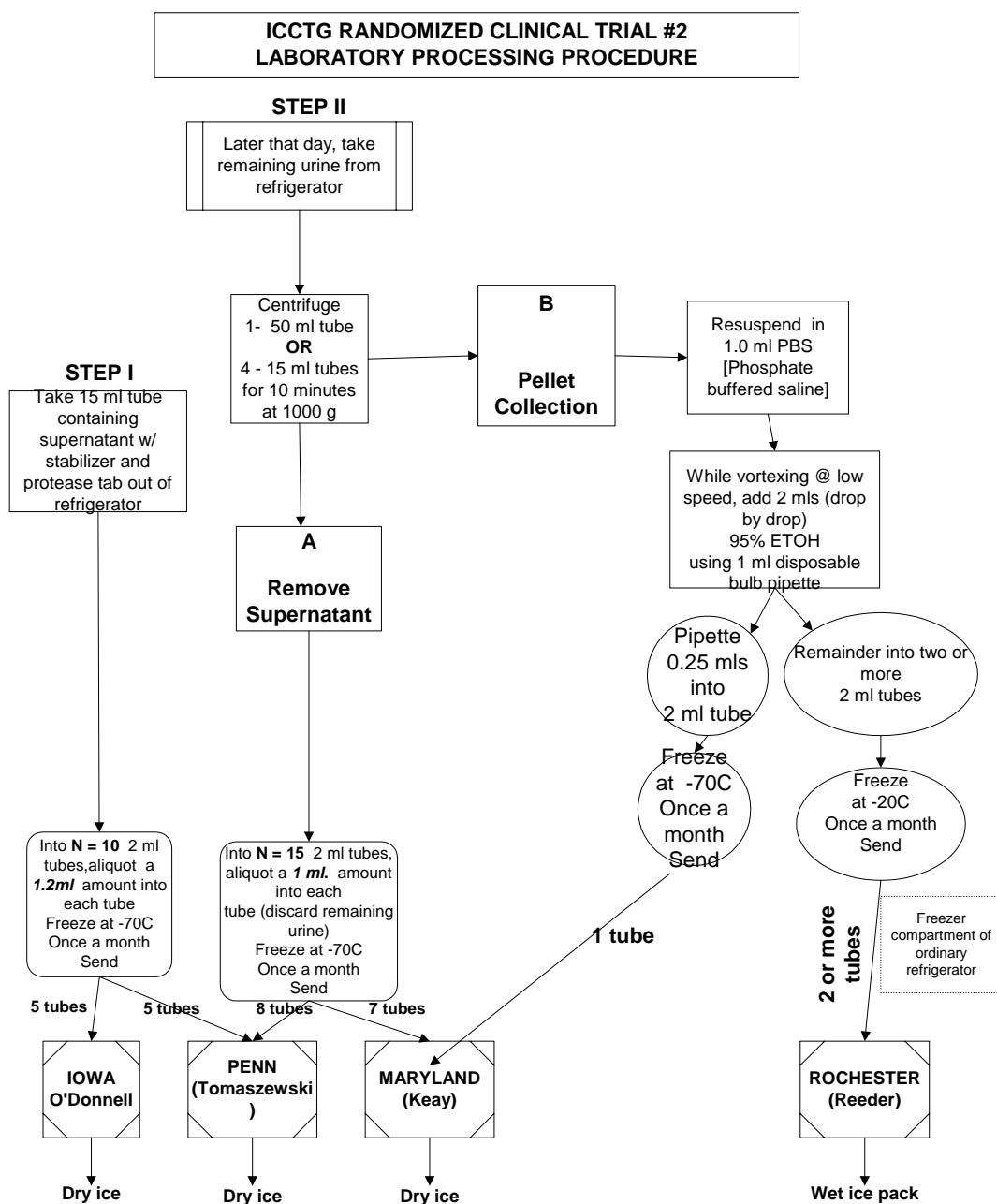
#### 7.4.7 Diagram of Laboratory Processing Procedure – Page ONE

##### ICCTG Randomized Clinical Trial #2 Laboratory Processing Procedure



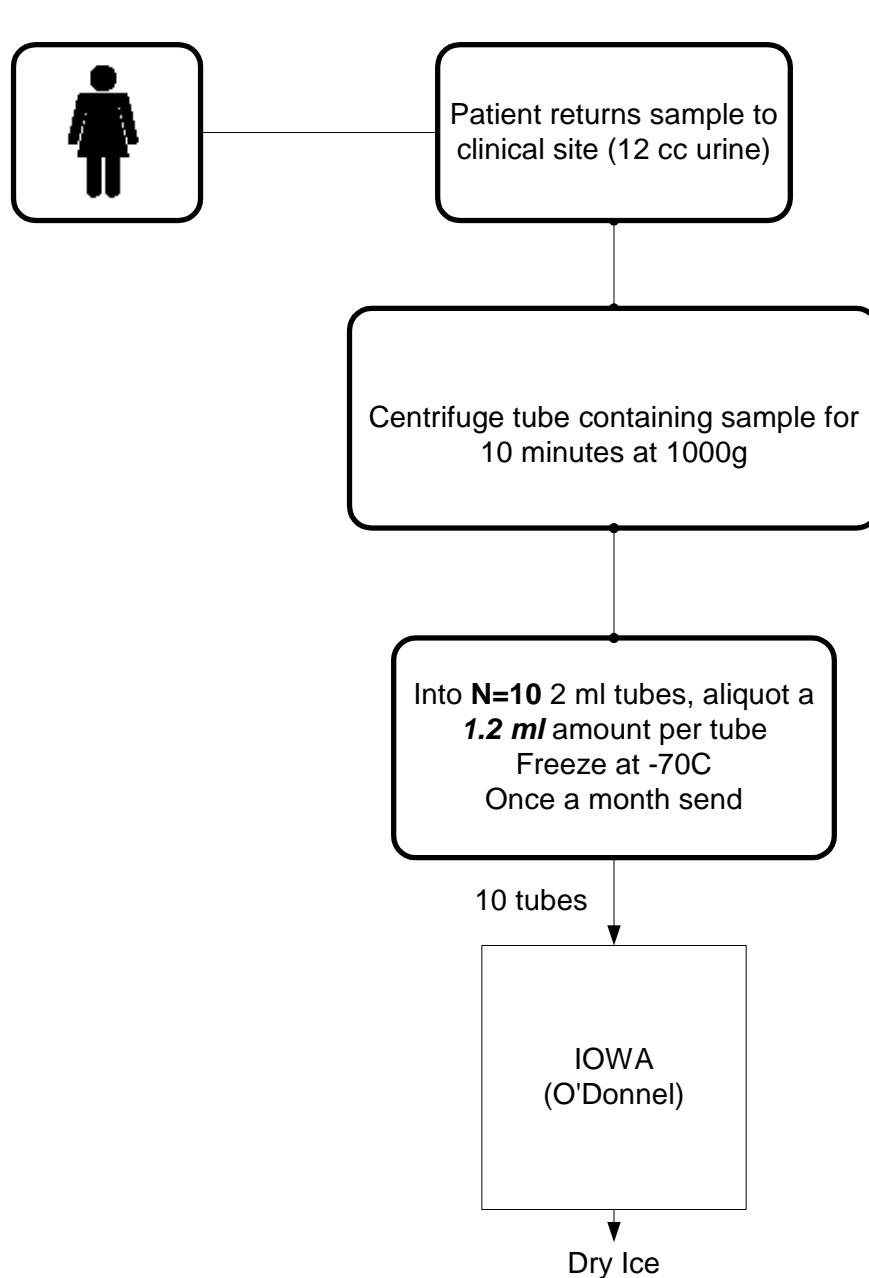


## 7.4.8 Diagram of Laboratory Processing Procedure – Page TWO



#### 7.4.9 Diagram of Laboratory Processing Procedure – Page Three

##### *Patient Urine Specimen Processing Procedure 4th Visit after Treatment*



## **7.5 Instructions for Shipping of Specimens-Shipping Box Preparation**

The *Shipper's Declaration for Dangerous Goods* form will come to you pre-printed, for the most part. Any information you are responsible for filling out on the form must be typed. The *Shipper* box must have the name and address of the person shipping the package. The *Consignee* box must have the name and address of the person the package is being shipped to. Make sure the *Cargo Aircraft Only* box is marked with an "X" through it. The only exception is if you are shipping 75 tube boxes. In this case the *Passenger and Cargo Aircraft* box will have an "X" instead. Also, make sure the *Radioactive* box is marked with an "X" through it. Fill in the amount (in milliliters or kilograms, as appropriate) you are shipping under the *Quantity and type of packaging* box. Finally, fill out your name and title, the city you are shipping from and the date, put down your emergency contact number and sign the form in the bottom right box.

On the outside of the infectious materials box, the following information must be written:

Boxes of urine going to Philadelphia, Baltimore, or Iowa:

- Infectious substance affecting humans (*Bacillus Calmette Guerin* strain of *Mycobacterium bovis*) UN 2814.
- Name and phone number of person responsible for shipping.

Boxes of pellets going to Rochester or Baltimore:

- Ethanol UN 1170.
- Under the UN number write: "Limited Quantity" or "LTD QTY"
- Name and phone number of person responsible for shipping.

You will also need to place the various stickers that come with the infectious shipper container on the outside of the box. Plus "dry ice" sticker, for solid carbon dioxide, or "flammable 3" sticker for ethanol. Because you put a "dry ice" sticker on the box, you do not have to handwrite it on the outside. An orange "Cargo Aircraft Only" sticker is to be placed on all 75 tube shippers.

The *Shipper's Declaration for Dangerous Goods* form is to be placed in a plastic FedEx pouch on the side of the box labeled "*This side for Carrier documents*". Do not seal this pouch. The airbill is to be completed and stuck to either the same side of the box as the SDDG form or on top of the box.

## **8 Data Management System User Guide**

### **8.1 Overview**

#### *Description*

This chapter provides specific instructions on the use of the software application used to enter data into the ICCTG – Protocol 2 Data Management System (DMS).

#### *System Support*

The DCC will provide technical and managerial support for certain aspects of the DMS. Computing support specifically related to the DMS will be provided to the Clinical Center (CC) by the DCC help desk (discussed at the end of this chapter).

### **8.2 ICCTG Main Menu**

**Purpose:** To allow access to ICCTG DMS system CC applications and CRFs.

**Users:** Clinical center personnel:

- Data Management/Data Entry Personnel
- Research Coordinator

#### ***User Actions:***

Open the “ICCTG – Main Menu” using a Web browser. The loading Web page will appear. There are instructions presented on the initial screen, read and follow those instructions.

To access the CRFs for printing press the “Case Report Forms” button and follow the hyperlinks to the appropriate RCT2 CRF. The CRF will open in the Adobe Reader for viewing and printing.

Press the “RCT#2” Button to open the “ICCTG Protocol 2 (RCT#2): Clinical Center Menu”. The database logon dialog box will open.

#### *Log on the database*

1. Enter Username (Assigned by DCC helpdesk support)

2. Enter Password (Assigned by DCC helpdesk support)

NOTE: Do not share USERNAME and PASSWORD information. The DMS tracks user actions based on this access information.

3. Enter Database (ICRCT2)

4. Press “Connect” button
5. The **ICCTG—Protocol 2 (RCT#2)** Menu appears
6. Dialog box displays user name and role
7. Press OK button

### **8.3 ICCTG—Protocol 2 (RCT#2) Clinical Center Menu**

**Purpose:** To allow access to CC DMS applications. These applications allow entry of participant contact data into the DMS located at the DCC and viewing of registered participant status.

**Users:** Clinical center personnel:  
➤ Data Management/Data Entry Personnel  
➤ Research Coordinator

**User Actions:** Choose a menu option:

#### 1. Register Participant

- a. Registers of a Participant into the DMS
- b. Requires Participant ID and Participant Initials

#### 2. Eligibility and Randomization

- a. Allows entry and verification of Participant Screening and Eligibility CRFs.
- b. Requires Participant ID, Participant Initials and Clinical Center.
- c. Requires participant to be eligible for the study.
- d. Requires that all Screening and Eligibility CRFs be entered and verified.
- e. Performs Participant Randomization and issues the Randomization Number.

#### 3. Delete Ineligible Participant

- a. Allow removal of participant information for Ineligible Participants: participants who were determined to be ineligible after they have been registered in to the DMS.
- b. Randomized Participant data **cannot** be deleted from the DMS.
- c. Requires the Participant ID, Participant Initials and Clinical Center.

#### 4. CRF Entry

- a. Allow entry and verification of visit packet CRFs.
- b. Requires a complete visit packet of CRFs for a specific participant and visit.
- c. Allow entry and verification of Study Close-Out [**STCL**], Patient Close-Out [**PTCL**], Study Stop Point Phase I [**SSTOPI**], Study Stop Point Phase II [**SSTOPII**], Treatment Stop Point [**TSTOP**], and Unmasking Record [**UNMASK**] forms.
- d. Requires the Participant ID, Participant Initials, Clinical Center Number, and Visit Number along with the CRFs that are to be entered or verified. Visit Date is also required for STCL, PTCL, SSTOPI, SSTOPII, TSTOP, and UNMASK entry.

#### 5. Entry Status

- a. Allow viewing of the participant status and CRF entry status.
- b. Choose Participant to view participant status.
- c. Choose Form to view CRF entry status.
- d. Enter a Participant ID to view the CRF entry status for a specific participant.
- e. A list box opens to present the appropriate status.

#### 6. Medication Reference

- a. Application that is used to cross-reference drug brand name with their generic equivalents.
- b. Requires Brand name, Generic Name or Code Name of drug.

#### 7. Reports Menu: Opens the Reports Menu Application

#### 8. Cancel: Exits the ICCTG – Protocol 2 (ICCTG RCT#2) Clinical Center Menu

### **8.4 Register Participant**

**Purpose:** To allow registration of a new participant into the DMS. This is required prior to entering participant visit forms.

**Users:** Clinical center personnel:

- Data Management/Data Entry Personnel
- Research Coordinator

### ***User Actions:***

#### **1. Enter the Participant ID**

- a. Participant ID will be 5-numeric characters.
- b. The last three digits will represent the sequence of participant enrollment using the CC number for the first two (2) digits (01001 - 01999 for center one, 02001 - 02999 for center two, etc.).
- c. An error will occur if less than or more than 5 digits are entered or any non-numeric characters are entered.
- d. An error message given for duplicate Participant IDs.

#### **2. Enter the Participant Initials**

- a. Participant Initials must be 2 to 3 uppercase letters.
- b. 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.
- c. Warning message given for duplicate initials.

#### **3. Participant ID and Participant Initials are mandatory fields neither may be left blank.**

#### **4. The entered Participant ID and Participant Initials must be confirmed by re-entering both fields:**

- a. If either field differs from the first entry, an error message is given and the both fields must be re-entered for confirmation.
- b. Each field has the same constraints as indicated above.
- c. After the new Participant ID and Participant Initials are entered and confirmed, repeat the process to register another participant into the DMS or return to the Clinical Center Menu by selecting the Cancel button.

## **8.5 Eligibility and Randomization**

### ***Purpose:***

- Logs the participant Screening, Eligibility, and Randomization CRFs into the DMS.
- Allows entry and verification of Screening and Eligibility CRFs.
- Allows entry of the Randomization form, performs randomization, and issues the Randomization Number.

**Users:** Clinical center personnel:

- Data Management/Data Entry Personnel (**cannot** perform randomization)
- Research Coordinator

***User Actions:***

1. Enter participant ID

- a. The participant initials will be crosschecked with the participant initials for the corresponding Participant ID in the registration table.
- b. 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.

2. Enter Clinical Center Number

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

3. All four fields (Participant ID, Participant Initials, and Clinical Center Number) are mandatory.

4. After entering the mandatory fields, choose:

- a. CRF Type:
  - 1) *Screening*: To enter Screening and Eligibility CRFs.
  - 2) *RAND*: To Randomize the Participant.
- b. For Screening: Choose Entry Type:
  - 1) *Entry*: To perform first entry of the CRFs.
  - 2) *Verification*: To perform the second entry verification of the CRFs.
- c. Proceed: To begin entry of the selected options.
- d. Cancel: To exit the Eligibility and Randomization Application.

5. Screening: After choosing to proceed to Screening Entry or Verification:

- a. The system will open the entry screens for each form in the appropriate order.
- b. 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.
- c. The form entry screens will look like the case report forms.



- d. For all forms, the heading in the upper right hand corner will display the Participant ID, Participant Initials, clinical center number, and the visit week automatically as a standard heading.
  - e. Proceed by entering the visit date in the upper right hand corner. This date is the date the form was completed and must be entered. The range for the date must be between the study date, and the current date.
  - f. Enter the Research Coordinator ID in the upper right hand corner.
  - g. Enter all data on the forms into the appropriate fields.
  - h. The data fields fall into the following categories: alphabetic letter, alphanumeric, categorical, date, numeric, time and free text. There are checkboxes on the Adverse Events/Serious Adverse Events [AE], Concomitant Medication [CMED], and Unmasking [UNMASK] forms. Review the special requirements under navigation. Specifications for these fields are described in the Data Field Specifications. If the entry does not meet the required range or specifications, then an error message is given in the message area at the lower left-hand corner of the application window.
  - i. During First Entry For case reports 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. These buttons are not available during Verification.
  - j. Upon completing data entry for each case report form a Commit button will allow the entries for that form to be saved and moved onto the next. The verification process is completed with an Update button, which updates the data in the DMS.
  - k. The date cannot be changed after it has been saved (committed or updated).
  - l. After the last form has been entered, the entry process can be repeated for the next participant.
  - m. You will have the option of existing the entry process at any time. The data entered on any unsaved forms will be lost.
6. Navigation:
- a. Mouse navigation is limited to use with the buttons and for revisiting lab records.
  - b. Navigation buttons are provided for First Entry.
  - c. Entry is expected to proceed field by field using the tab key or enter key after entering the appropriate field data.

- d. Check box entry can be set with the spacebar or with the mouse if the cursor is on the check box (Note: generally there is a blinking cursor, but on check box fields this is not visible, so a message is presented in the bottom left part of the window and the box is highlighted in red).

7. Verification:

- a. All fields must be entered. Navigation (both keyboard and mouse) is limited.
- b. The data entered for each form field are compared to the data from the first entry.
- c. If it is different a message is given (indicating first entry value, verification entry value, and other, you must choose which entry is correct). If other is chosen, you must enter the new value.
- d. You are not allowed to proceed to the next field without choosing the correct value.

8. Eligibility and Screening Requirements:

- a. The only entry accepted is that which leads to an eligible participant.
- b. If the participant is not eligible, then the entry will not be allowed to proceed.

9. Randomization: After choosing Randomization [**RAND**]

- a. Entry is restricted to only allow data that leads to an eligible participant to be entered.
- b. The randomization number will be issued by the application in the controlled process described below:
  - 1) Instead of providing an entry field for the randomization number, a button (labeled “Randomize Participant”) is provided that causes the application to proceed to the randomization process.
  - 2) After the Randomization [**RAND**] form information has been entered the press the “Randomize Participant” button.
  - 3) The application enters the Participant ID, Participant Initials and the Randomization [**RAND**] form data into the DMS.
  - 4) The application issues the Randomization Number and records this event with the DMS.
  - 5) The user is requested to record the Randomization Number on the Randomization [**RAND**] form and acknowledge this by pressing the Continue button.
  - 6) The application requests that the user re-enter the number for verification.

- 7) If the number is **not** entered correctly, the application displays the correct Randomization Number and request that it be recorded on the Randomization [RAND] form.
- 8) The verification process is repeated until the user enters the correct Randomization Number.
- 9) After the Randomization Number has been properly verified, the application records the verification with the DMS and requests that the Continue button be pressed to complete the Randomization process.

## **8.6 Delete Ineligible Participant**

### ***Purpose:***

- Removes all information for an ineligible from the DMS.
- Participants who have been randomized cannot be deleted.

***Users:*** Clinical center personnel  
Research Coordinator

### ***User Actions:***

1. Enter the Participant ID
  - a. Participant ID has the same requirements as in the Registration Application.
  - b. The Participant ID will be checked against the registration table to verify that the participant does exist.
  - c. If the Participant ID is not registered in the DMS, an error message will be generated and the user will not be allowed to proceed unless the Participant ID is registered.
2. Enter Participant Initials
  - a. The participant initials will be crosschecked with the participant initials for the corresponding Participant ID in the registration table.
  - b. 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.
3. Enter Clinical Center Number
  - a. This number must be the number assigned to the randomization site for the study.
  - b. If the CC number entered is not the same as the assigned to the center, an error message is given.

4. All three fields (Participant ID, Participant Initials and Clinical Center Number) are mandatory.
5. After entering the mandatory fields, choose:
  - a. Proceed to delete the participant, or
  - b. Cancel to exit the Entry Application
6. Acknowledge intent to delete participant
  - a. Dialog Box displays participant identifying information and requires confirmation of intent to delete participant.
  - b. Press OK button to delete participant or Cancel button to return to previous screen.

## **8.7 CRF Entry**

### ***Purpose:***

- Logs the participant visit and participant visit forms into the DMS.
- Allows entry of the participant visit form data into the DMS.

### ***Users:*** Clinical center personnel:

- Data Management/Data Entry Personnel
- Research Coordinators

### ***User Actions:***

1. Enter the participant ID
  - a. Participant ID has the same requirements as in the Registration Application.
  - b. The participant ID will be checked against the registration table to verify that the participant does exist.
  - c. If the Participant ID is not registered for the Clinical Center in the DMS, an error message will be generated and the user will not be allowed to proceed unless the Participant ID registered.
2. Enter participant initials
  - a. The participant initials will be crosschecked with the participant initials for the corresponding participant ID in the registration table.
  - b. 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.

3. Enter Clinical Center Number
  - a. This number must be the number assigned to the Clinical Center for the study.
  - c. If the CC number entered is not the same as that assigned to the center, an error message is given.
4. Enter Visit Number
  - a. The visit number must be 1 to 2 numeric characters.
  - b. An error will occur if visit number is not a valid visit or if you try to enter any other character that is not a number.
  - c. If the visit has already been entered, an error should appear.
  - d. If any previous visits have not yet been entered, an error is given, and will prevent entry of visit forms.
5. All four fields (Participant ID, Participant Initials, Clinical Center Number, and Visit Number) are mandatory. Visit Date is also required for STCL, PTCL, SSTOP1, SSTOP2, TSTOP, and UNMASK.
6. After entering the mandatory fields, choose:
  - a. CRF Type:
    - 1) All visit forms: To enter a visit packet of CRFs.
    - 2) Study Close-Out [STCL], Patient Close-Out [PTCL], Study Stop Point Phase I [SSTOP1], Study Stop Point Phase II [SSTOP2], Treatment Stop Point [TSTOP], or Unmasking Record [UNMASK] to enter one of the as needed forms.
  - b. Entry Type:
    - 1) Entry: To perform first entry of the CRFs.
    - 2) Verification: To perform verification of the CRFs.
  - c. Packet Missing to mark the packet as missing.
  - d. Cancel to exit the CRF Entry Application.
7. After choosing to proceed:
  - a. The system will open the entry screens for each form in the appropriate order.
  - b. 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.

- c. The form entry screens will look like the Case Report Forms.
  - d. 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 can be entered at later time.
  - e. For all forms, the heading in the upper right hand corner will display the participant ID, participant initials, clinical center number, and the visit number automatically as a standard heading.
  - f. 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.
8. Enter the Research Coordinator ID in the upper right hand corner.
- a. Enter all data on the forms into the appropriate fields.
  - b. 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 section.
  - c. For case report forms with multiple pages, the option to either proceed and move forward to next page of the form or move backwards to the preceding page is available (for First Entry not for Verification).
  - d. 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 form.
  - e. The data cannot be changed after it has been saved.
  - f. After the last form has been entered, the entry process can be repeated for the next participant.
9. You will have the option of exiting the entry process at any time. The data entered on any unsaved forms will be lost.
10. Special Requirements for Adverse Events/Serious Adverse Events [**AE**], Concomitant Medication [**CMED**], Clinical Laboratory Results [**LAB**], and Voiding Diary [**VOID**].
- a. The number of records on the form must be entered.
  - b. Only the number of number of records indicated will be allowed. After choosing the number of specimen records to enter, records cannot be deleted (or added). If this number is incorrect or has to be changed, record entry will have to be restarted.
  - d. Any number of records can be entered, but the number has to match the number of records initially indicated.

## 11. Navigation:

- a. Mouse navigation is limited to use with the buttons and for revisiting fields in Concomitant Medication [**CMED**], Adverse Events/Serious Adverse Events [**AE**], Clinical Laboratory Results [**LAB**], and Voiding Diary [**VOID**].
- b. Navigation buttons are provided for First Entry.
- c. Entry is expected to proceed field by field using the tab key or enter key after entering the appropriate field data.
- d. Check box entry can be set with the spacebar or with the mouse if the cursor is on the check box (Note: generally there is a blinking cursor, but on check box field this is not visible, so a message is presented in the bottom left part of the window and the box is highlighted in red).

## 12. Verification:

- a. All fields must be entered. Navigation (both key board and mouse) is limited.
- b. The data entered for each form field are compared to the data from the first entry.
- c. If it is different, a message is given (indicating first entry value, verification entry value, and other, you must choose which entry is correct). If other is chosen, you must enter the new value.
- d. You are not allowed to proceed to the next field without choosing the correct value.
- e. Revisiting entered fields is generally not allowed. The mouse can be used to revisit the record fields in Clinical Laboratory Results [**LAB**], Voiding Diary [**VOID**], Concomitant Medication [**CMED**], and Adverse Events/Serious Adverse Events [**AE**]; but the number of records cannot be changed.
- f. If it is required that an entered field be revisited, generally it will be necessary to exit the verification application and restart verification.

## **8.8 Entry Status**

**Purpose:** Allow viewing the registered participants and the entry status of CRFs.

**Users:** Clinical Center Personnel:

- Data Management/Data Entry Personnel
- Research Coordinator

### ***User Actions:***

1. Select status type (Participant or Forms) to view and enter Participant ID if Forms Status for a specific Participant is desired, then select Proceed to view the list or select Cancel to exit and return to the Clinical Center Menu.
2. Registered Participants: Participant list is presented indicating the:
  - a. *Participant ID*: The participant identifier,
  - b. *Participant Initials*: The participant's initials,
  - c. *Date Registered*: The date the participant was registered into the DMS,
  - d. *Registered By*: The user name/ID of the DMS user that registered the participant into the DMS,
  - e. *Randomization Number*: The 5 digit randomization number assigned to the participant upon successfully randomizing the participant.
  - f. *Date Randomized*: The date that the randomization was completed,
  - g. *Randomized By*: The user name/ID of the person performing randomization,
  - h. *Date Issued*: The date that the randomization number was issued to the person performing randomization for the participant (should be the same as Date Randomized),
  - i. *Issued To*: The user name/ID of the person performing the randomization (should be the same as Randomized By),
  - j. *Date Verified*: The date that the randomization number was verified (should be the same as the Date Randomized), and
  - k. ***Verified By*: The user name/ID of the person verifying the randomization number (should be the same as Randomized By).**
  - j. *Date Deleted*: The date that Screening and Eligibility CRF data was deleted for an ineligible participant. This will only have a date value for participants that have been deleted by the research coordinator using the "Delete Ineligible Participant" option from the RCT#2 Clinical Center Main Menu.
3. Visit Forms: Form Entry Status is presented indicating:
  - a. Participant ID,
  - b. Visit Number,
  - c. Form,
  - d. Missing Status,
  - e. Visit Date,
  - f. Date Logged (into DMS),
  - g. Logged By (generally the first entry person),
  - h. Date Entered,
  - i. Entered By,
  - j. Date Verified, and
  - k. Verified By.



## **8.9 Medication Reference**

**Purpose:** Provide the CCs with a standard cross-reference to convert brand name medications to their generic equivalent and provide a standard medication / drug code.

**Users:** Clinical Center Personnel  
➤ Data Management/Data Entry Personnel  
➤ Research Coordinator

### ***User Actions:***

1. The Medication Reference appears with the following options:
  - Brand Name
  - Generic Name
  - Drug Code
2. Enter Query Criteria:
  - Select Brand Name, Generic Name, or Drug Code then enter the drug name or code in the appropriate box.
  - If you are unsure of the spelling, just enter the first few letters.
3. Change Sort Criteria, if necessary. By default, the list is sorted by Generic Name.
4. After entering the drug name, press enter (or select the “Execute Query” button with the mouse), 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.
5. You can then review the list and choose the appropriate medication code.
6. Choose Cancel when finished, in order to return to the Clinical Center Menu.

## **8.10 Reports**

**Purpose:** To allow the generation of monitoring reports.

**Users:** Clinical Center Personnel:  
➤ Data Management/Data Entry Personnel  
➤ Research Coordinator

## *User Actions:*

### **1. The Report Menu appears with the following options:**

- a. Expected Contacts
- b. Incomplete Entry
- c. Incomplete Verification
- d. Follow-up Schedule
- e. Clinical Center Schedule
- f. Case Report Forms
- g. Cancel

- 2. Choose the desired report or choose Cancel to exit the application and return to the Clinical Center Menu.

## **8.11 Data Field Specifications**

### *Alphabetic Letter Fields*

The participant initials are the only alphabetic letter field in the Case Report Forms. Participant 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.

### *Alpha-numeric Fields*

There are no alphanumeric fields.

### *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 DMS will provide a status message as the lower left of the application window.

### *Check Box*

Check boxes are used on the Adverse Events/Serious Adverse Events [AE], Concomitant Medications [CMED], and Unmasking [UNMASK] forms. A checked value will be recorded as a "1" in the DMS. An unchecked value will be recorded as a NULL with the DMS. The check boxes may be checked using the keyboard space bar or (if the cursor is on the check box) the mouse. When the cursor is on the check box, it may not be readily apparent, so a message will be displayed in the lower left of the application window and the check box will be highlighted in red.

### *Date Fields*

The format for date fields: MM/DD/YYYY. The year always requires four digits. A slash (/) is not needed to separate the number, day, or year; however, a slash is allowed in entry when the date field is recorded.

### 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. Floating-point numbers are formatted with decimal points and the required level of precision.

### 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 colon “:” between the hour and the minutes does not have to be entered. All time fields are in the 24 hours format (00:00-23:59).

### Free Text Fields

The **only free text field** that will be entered is the “Description of Event / Comments” on the Adverse Events/Serious Adverse Events [AE] form. During verification this text will be presented for review and edited, but **will not be verified** by the DMS verification process used to verify all other entry. Since there is no automatic verification process, use caution during the edit and review process to ensure that the text is not deleted or altered by mistake. The editor application (opened by selecting an edit button) allows a full view of the text and allows the edit process to be exited without saving changes.

DMS Entered Descriptive Fields: Adverse Events/Serious Adverse Events [AE] (AE Specify Event (CTC Criteria)) & Concomitant Medications [CMED] (CMED Drug Name)

These fields will not be entered. The DMS will provide the field value (for user review) based on the Adverse Events/Serious Adverse Events [AE] event code (for *Specify Event (CTC Criteria)*) or Concomitant Medications [CMED] drug code (for Drug Name).

## **8.12 Messages**

### Status Messages

- Location: Bottom left part of the application window.
- Required User Action: None, besides viewing the message to assist with application operation.

#### 1. Types of messages

- a. Data entry messages that indicate data types and ranges for field entry.
- b. Messages indicating the status of completing some application processes.
- c. Messages indicating the number of choices in a list box.
- d. Messages indicating the number of records returned from the DMS or number of records available to the application.

### Dialog Boxes

1. *Location:* Messages pop up in dialog boxes.
2. *Required User Action:*
  - User should record all Error Messages indicating problems communicating with the DMS and report these problems to the help desk.
  - User must acknowledge the message by pressing the dialog box Ok button.
3. *Types of Messages:*
  - a. Information Messages:
    - 1) Data entry messages that indicate the status of form entry.
    - 2) Messages indicating the status of completing some application processes.
  - b. Warning Messages:
    - 1) Messages requesting acknowledgement prior to exiting some application processes.
    - 2) Messages requesting acknowledgement prior to deleting data.
  - c. Error Messages:
    - 1) Messages indicating problems committing data to the DMS or receiving data from the DMS. This could be the result of problems with the DMS, application server, or problems with the Internet connection. All problems should be reported to the help desk. If the problem is with the Internet connection, the user may attempt to log off the application and reconnect by:
      - Exit all DMS applications
      - Close all Web browsers.
      - Reconnect and log back on to the DMS.
    - 2) Messages indicating that the user does not have the necessary privileges to access certain applications.
    - 3) Messages indicating that invalid keys were pressed.
    - 4) Messages indicating the status of completing some application processes.

### **8.13 CRCU Software Systems Help Desk**

The CRCU Software Systems Help Desk provides technical support to all study personnel using Data Management System (DMS) software developed and distributed by the CRCU. The help desk will answer questions concerning the operation of the DMS and will assist in resolving any issues that hinder the effective use of the DMS software.

### **8.13.1 Technical Support**

The Help Desk will provide technical support related to problems and issues that may arise when working with the web based Data Management System.

The Help Desk will not be responsible for providing technical support for hardware and/or software that was not provided by the CRCU. For example: word processors, spreadsheets, modems, printers, and ICCTG hardware.

### **8.13.2 Assignment of Database Accounts**

A database account consists of a Username and Password that uniquely identifies a user to the Data Management System. Database accounts are required for a user to gain access to the Data Management System, and are the primary means for ensuring data security and confidentiality. Therefore it is critically important that all database accounts are kept secure and confidential and are not shared with anyone.

In addition to providing data security and confidentiality, database accounts provide a means to trace all database activities to individual user accounts.

To obtain database accounts, a Clinical Center representative should notify the CRCU project manager of the requested user's name and provide a general idea of what functions the user will be performing in the DMS. The CRCU Project Manager will in turn notify the CRCU Software Systems Help Desk of the new user request.

When a database account has been created, the CRCU Software Systems Help Desk will contact the user with his/her account information.

When personnel leave the project, a representative from the Clinical Center should contact the CRCU Project Manager immediately. The CRCU Software Systems helpdesk will then take the necessary actions to deactivate that user's database account.

### **8.13.3 Procedures For Obtaining Help Desk Support**

Study personnel can contact the CRCU Software Systems Help Desk by telephone or e-mail.

### **8.13.3.1 Telephone Support**

**The CRCU Software Systems Help Desk can be contacted at (215) 573-4623.**

When contacting the CRCU Software Systems Help Desk, the caller will need to provide the following information:

- Name
- Study Name (ICCTG)
- Project / Protocol Name (RCT#2)
- Clinical Center Name / Location

If CRCU Help Desk personnel are not available to take the phone call, the caller will be forwarded to voicemail. When leaving a voicemail message, the caller must provide the following information:

- Name
- Study Name (ICCTG)
- Project / Protocol Name (RCT#2)
- Clinical Center Name / Location
- Phone number
- Description of the problem and level of urgency (low, medium, high)

### **8.13.3.2 E-mail Support**

The CRCU Software Systems Help Desk can be e-mailed at: [sshelpdesk@cceb.upenn.edu](mailto:sshelpdesk@cceb.upenn.edu)

When sending e-mail, the following information must be provided:

- Name
- Study Name (ICCTG)
- Project / Protocol Name (RCT#2)
- Clinical Center Name / Location
- Phone number
- Description of the problem and level of urgency (low, medium, high)

### **8.13.4 Help Desk Expected Response Time**

Every effort will be made to respond to voicemail and/or e-mail messages as soon as possible. To facilitate a timely response, help desk personnel are equipped with pagers and will be paged as soon as there is a new voicemail message.

When possible, the CRCU Software Systems Help Desk will attempt to resolve the issue during the initial call. Occasionally, a problem may occur that requires additional interaction between the caller, the help desk, data management, and/or other software systems personnel. Client patience and cooperation is always appreciated during such periods. Our goal is to get the client back to normal operations as quickly as possible.

#### ***8.13.5 Help Desk Availability***

The CRCU Software Systems Help Desk is available during normal business hours (08:00 – 17:00 U.S. Eastern Time).

## **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 participants 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 of 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, unless necessary for monitoring/auditing purposes, in which case copies should not include subject identifiers.

#### ***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 two (2) weeks 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 control (QC) 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 DCCs 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 DCCs Project Manager to coordinate the visit dates.

### **9.7.2 DCC Site Assessment Review**

The site visit team will meet with the DCCs 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 DCCs 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/her designee, and either the DCCs 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 DCCs 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 DCCs 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 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 months of the submission of the initial report.

## **9.10 Maintenance & Disposition of Study Documents, Data & 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 #2.

### ***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 #2. 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 #2.

### **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 & 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 & Materials**

Specimens collected by the randomization sites for storage at designated urine banking laboratories, will be kept for long-term storage until the end of RCT #2. 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 in accordance with their internal standard operating procedures. Clinical sites must maintain all study related materials in accordance to applicable FDA regulations and until receiving written notification from the DCC or Study Sponsor.

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## **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 nonsteroidal antiinflammatory 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 participant'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 participant is eligible, the day/visit in which (s)he 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.

**Blood dyscrasia:** An abnormality of the blood.

**Brompheniramine:** An antihistamine.

**CAE'sarian 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 feeling of illness and weakness.

**Cimetidine (Tagamet):** A histamine H<sub>2</sub> 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 participants 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 that 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 participant is eligible, the day/visit in which (s)he 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 first trimester abortion procedure.

**D&E:** Abbreviation for dilation and evacuation – a second 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 mucosalized 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.

**Enterocoele:** 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 feeling 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 ulcer 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 preceded 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 insensibility 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 participant's immune system attacks his/her own joints.

**SC:** Subcutaneously (beneath the skin).

**Scleroderma:** 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 judgment, they may jeopardize the participant 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.

**Steroids:** 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<sub>2</sub> 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 of 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

**AE** = Adverse Event/ Serious Adverse Event (CRF)

**BCG** = Bacillus Calmette-Guerin

**BPH** = Benign Prostatic Hypertrophy

**BSYM1** = Baseline Symptoms 1 (CRF)

**BSYM2** = Baseline Symptoms 2 (CRF)

**CBC** = Complete Blood Count

**CC** = Clinical Center

**cc** = Cubic Centimeters

**CDM** = Clinical Data Management

**CFR** = Code of Federal Regulations

**CFS** = Chronic Fatigue Syndrome

**CFU** = Colony-forming Unit

**CMED** = Concomitant Medications (CRF)

**COMM** = Comments Sheet

**Co-PI** = Co-Principal Investigator

**CRCU** = Clinical Research Computing Unit

**CRF** = Case Report Form

**CTC** = Common Toxicity Criteria

**CTMC** = Connective Tissue Mast Cell

**CV** = Curriculum Vitae

**DCC** = Data Coordinating Center

**DEMO** = Demographics (CRF)

**DMS** = Data Management System

**DMSO** = Dimethyl Sulfoxide

**DOSE** = Instillation/Dosing Information (CRF)

**ELIG** = Eligibility Confirmation (CRF)

**EST** = Eastern Standard Time

**ETOH** = Ethanol

**EXAM** = Physical Exam (CRF)

**FDA** = Food and Drug Administration  
**FUSYM** = Follow-up Symptoms (CRF)  
**GCP** = Good Clinical Practice  
**IBS** = Irritable Bowel Syndrome  
**IC** = Interstitial Cystitis  
**ICA** = Interstitial Cystitis Association  
**ICCTG** = Interstitial Cystitis Clinical Trials Group  
**ICDB** = Interstitial Cystitis Data Base  
**ICH** = International Conference on Harmonization  
**ID** = Identification  
**IDS** = Investigational Drug Service (University of Pennsylvania)  
**IM** = Intramuscular  
**IND** = Investigational New Drug  
**IRB** = Institutional Review Board  
**IU** = International Unit  
**IV** = Intravenous  
**LAB** = Clinical Laboratory Results (CRF)  
**LFT** = Liver Function Test  
**LLN** = Lower Limits of Normal  
**MED** = Medical History (CRF)  
**mg** = Milligram  
**ml** = Milliliter  
**MOP** = Manual of Procedures  
**MOS** = MOS Sexual Functioning Scale (CRF)  
**N/A** = Not Applicable  
**NCI** = National Cancer Institute  
**NIDDK** = National Institute of Diabetes, Digestive and Kidney Diseases  
**NIH** = National Institute of Health  
**NSAID** = Non-steroidal Anti-Inflammatory Drug  
**NTIS** = National Technical Information Service  
**PDF** = Portable Data Files  
**PDR** = Physician's Desk Reference

**PENN** = University of Pennsylvania

**PHNTP** = Telephone Contact During Treatment Phase (CRF)

**PI** = Principal Investigator

**PID** = Pelvic Inflammatory Disease

**PP&AS** = Publications, Presentations and Ancillary Studies

**PTCL** = Participant Close-out (CRF)

**PTCONT** = Participant Contact Information (CRF)

**PTDIARY** = Participant Daily Medication Diaries

**PTLOG** = Participant Log

**PUTRAC** = Participant Collected Urine Sample Tracking for University of Iowa (CRF)

**QID** = 4 times a day

**RA** = Rheumatoid Arthritis

**RAND** = Randomization (CRF)

**RBC** = Red Blood Cells

**RC** = Research Coordinator

**RCT** = Randomized Clinical Trial

**REF** = Participant Refusal Log (CRF)

**SAE** = Serious Adverse Event

**SAG** = Symptom Assessment Guidelines (CRF)

**SC** = Subcutaneous

**SF-36** = Health Status Questionnaire (CRF)

**SOP** = Standard Operating Procedures

**SSN** = Social Security Number

**SSTOP (I or II)** = Study Stop Point (CRF)

**STCL** = Study Close-out (CRF)

**STVST** = Standard Visit Inventory (CRF)

**SYM** = Interstitial Cystitis Symptom Index and Problem Index (CRF)

**TDD** = Total Daily Dose

**Th2** = T-helper cell type 2

**TID** = Three times a day

**TRANS** = Participant Transfer (CRF)

**TSTOP** = Treatment Stop Point (CRF)



**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  
**ULN** = Upper Limits of Normal  
**ULOGIO** = Urine Sample Tracking Log – University of Iowa (CRF)  
**ULOGMD** = Urine Sample Tracking Log – University of Maryland (CRF)  
**ULOGPA** = Urine Sample Tracking Log – University of Pennsylvania (CRF)  
**ULOGRO** = Urine Sample Tracking Log – University of Rochester (CRF)  
**UNK** = Unknown  
**UNMASK** = Unmasking Record (CRF)  
**URINE** = Urine Screening (CRF)  
**UTI** = Urinary Tract Infection  
**UTRAC** = Urine Sample Tracking (CRF)  
**VOID** = Voiding Diary (CRF)  
**VSTSCH (I and II)** = Study Visit Schedule  
**WBC** = White Blood Cells  
**WIS** = University of Wisconsin Symptom Survey (CRF)

## **MANUAL OF PROCEDURES APPENDICES**

<b><u>APPENDIX A:</u></b>	<b>Exclusionary Medications</b>	<b>(1 page)</b>
<b><u>APPENDIX B:</u></b>	<b>Breakthrough Medications</b>	<b>(1 page)</b>
<b><u>APPENDIX C:</u></b>	<b>Commonly Used Oral Medications in the Treatment of Interstitial Cystitis Symptoms Listed by Therapeutic Category</b>	<b>(4 pages)</b>
<b><u>APPENDIX D:</u></b>	<b>Sample Medication Worksheet for Primary Endpoint</b>	<b>(2 pages)</b>
<b><u>APPENDIX E:</u></b>	<b>Common Toxicity Criteria (CTC)</b>	<b>(34 pages)</b>

## **APPENDIX A**

### **Exclusionary Medications** (ICCTG RCT#2)

During the course of the study, participants **MAY NOT** initiate or otherwise consume any of the following medications or treatments:

- Isoniazid
- Rifampin
- Other antituberculosis therapies (e.g. Ethambutol, Pyrazinamide)
- Anticoagulant therapy (e.g. Coumadin®) with the exception of low dose aspirin therapy.
- Steroids (low dose steroid nasal spray is permitted)
- Intravesical therapies (e.g. DMSO, Clorpactin, Heparin)
- Pentosanpolysulfate (Elmiron®)

## **APPENDIX B**

### **BREAKTHROUGH MEDICATION**

For purposes of this clinical trial, “*breakthrough*” medication is defined as those agents utilized to symptomatically alleviate interstitial cystitis (IC) symptoms of pain, frequency, urgency/pressure.

During the entire treatment and follow-up period (34 weeks), oral medications of the following therapeutic categories will be allowed, on a temporary as needed basis, for use as “*breakthrough*” medication for treating episodes of increase in IC symptoms.

- Narcotic Analgesics
- Urinary Analgesics
- Urinary Antispasmodics
- Analgesics, nonsteroidal anti-inflammatory drugs (NSAIDS)
- Analgesics, salicylate and miscellaneous
- Anticholinergics
- Antibiotics (**except:** Aminoglycosides, Quinolones, Rifampin, Doxycycline, INH)

## **APPENDIX C**

*Commonly used oral medications in the treatment of Interstitial Cystitis symptoms listed by therapeutic category.*

**This list is not to be considered Comprehensive.**

### **❖ Indicates Therapeutic Category for Breakthrough Medication**

<b><i>THERAPEUTIC CATEGORY</i></b>	<b><i>GENERIC NAME</i></b>	<b><i>BRAND NAME ®</i></b>
Antidepressant, Tricyclic	Amitriptyline Amitriptyline & Chlordiazepoxide Amitriptyline & Perphenazine Amoxapine Clomipramine Desipramine Doxepin Imipramine Nortriptyline Protriptyline Trimipramine	Elavil; Enovil Limbitrol Etafron; Triavil Asendin Anafranil Norpramin Sinequan; Adapin Tofranil; Tofranil-PM; Janimine Aventyl; Pamelor Vivactil Surmontil
❖ Narcotic Analgesics	Acetaminophen & Codeine  Alfentanil Aspirin & Codeine Belladonna & Opium Buprenorphine Butorphanol Codeine Dezocine Dihydrocodeine Compound Droperidol & Fentanyl Fentanyl  Hydrocodone & Acetaminophen Hydrocodone & Aspirin Hydrocodone & Ibuprofen Levorphanol	Capital & Codeine; Phenaphen with Codeine; Tylenol with Codeine  Alfenta Empirin with Codeine B&O Suppettes Buprenex Stadol; Stadol NS Codeine Phosphate Dalgan DHC Plus; Synalgos-DC Innovar Duragesic Transdermal; Fentanyl Oralet  Anexsia; Vicodin; Zydone Alor 5/500; Azdone; Damason-P Vicoprofen Levo-Dromoran

<b><i>THERAPEUTIC CATEGORY</i></b>	<b><i>GENERIC NAME</i></b>	<b><i>BRAND NAME ®</i></b>
❖ Narcotic Analgesics (cont'd.)	Meperidine Meperidine & Promethazine  Methadone	Demerol Mepergan  Dolophine
	Morphine Sulfate  Nalbuphine Opium Tincture Oxycodone Oxycodone & Acetaminophen Oxycodone & Aspirin Oxymorphone Paregoric Pentazocine Propoxyphene Propoxyphene & Acetaminophen Propoxyphene & Aspirin  Remifentanyl	Astramorph PF Injection; MSIR Oral Nubain Opium Tincture OxyContin; OxyLR; Percolone Percocet; Roxicet 5/500 Codoxy; Percodan Numorphan Paregoric Talwin; Talwin NX Darvon; Darvon-N; Dolene Darvocet-N; Genagesic; Propacet Bexophene; Darvon Compound-65 Pulvules  Ultiva
Sedating Antihistamines H1 Blocker	Acrivastine & Pseudoephedrine  Azatadine Buclizine Carbinoxamine & Pseudoephedrine  Clemastine Cyproheptadine Dexchlorpheniramine Diphenhydramine  Hydroxyzine  Levocabastine Meclizine Promethazine Tripeleminamine	Semprex-D  Optimine Bucladin-S; Vibazine Biohist-LA; Carbiset; Carbodec; Rondec Tavist; Tavist-1 Periactin Dexchlor; Poladex; Polaramine Benadryl; Banophen; Dormin; Sominex; Nytol Vistaril; Atarax; Anxanil; Atozine; Durrax; Quiness; Rezine Livostin Antivert; Antrizine Anergan; Phenazine; Phenergan PBZ; PBZ-SR; Pyribenzamine
❖ Antispasmodic Agent, Urinary	Flavoxate	Urispas

<b><i>THERAPEUTIC CATEGORY</i></b>	<b><i>GENERIC NAME</i></b>	<b><i>BRAND NAME ®</i></b>
	Oxybutynin	Ditropan; Ditropan XL
❖ Antispasmodic Agent, Urinary (cont'd.)	Propantheline	Pro-Banthine
Anticonvulsant	Carbamazepine Clonazepam Gabapentin Valproic Acid	Epitol; Tegretol Klonopin Neurontin Depakene; Depakote
Alpha <sub>2</sub> -Adrenergic Agonist Agent	Clonidine Tizanidine	Catapres Zanaflex
❖ Analgesic, Urinary	Phenazopyridine  *Pentosan Polysulfate Sodium	Pyridium, Urodine, Urogesic  *Elmiron, PPS-Excluded for use in this study
❖ Analgesic, Nonsteroidal Anti-Inflammatory Drug	Ibuprofen Indomethacin Naproxen Sulindac	Motrin, Advil, Medipren, Midol Indocin Anaprox, Naprosyn Clinoril
❖ Analgesic, Salicylate	Aspirin Choline Magnesium Salicylate Salsalate	Anacin, Ascriptin, Ecotrin Tricosal, Trilisate Argesic-SA, Disalcid, Salflex
❖ Analgesic, Miscellaneous	Tramadol Acetaminophen	Ultram, Tramadol Hcl. Tylenol, Panadol, Aceta, Acephen
❖ Anticholinergic Agent	Anisotropine Benztropine Clidinium and Chlordiazepoxide Glycopyrrolate Hyoscyamine Propantheline Procyclidine Scopolamine Tolterodine Trihexyphenidyl	Valpin 50 Cogentin Librax, Clindex Robinul, Robinul Forte Cystispaz, A-Spas, Levsin Pro-Banthine Kemadrin Scopace Detrol Artane, Trihexy

<b><i>THERAPEUTIC CATEGORY</i></b>	<b><i>GENERIC NAME</i></b>	<b><i>BRAND NAME ®</i></b>
❖ Antibiotic, Miscellaneous	Aztreonam	Azactan
	Methenamine	Urex, Urised, Mandelamine
	Nitrofurantoin	Furadantin, Furan, Macrobid, Macrochantin



## APPENDIX D

### Sample Medication Worksheet For Primary Endpoint Response

**ICCTG  
RCT2**

Participant ID: _____	Participant Initials: _____	Clinical Center: _____
Visit Number: _____	CRF Date: ____/____/____	RC ID: _____

#### Endpoint Worksheet (Sample Worksheet)

##### Administrative

To be completed by the RC to determine participants as Responders/Non-Responders

1. Global Assessment Response (GAR) from Follow-up Symptoms (FUSYM) Question #6 (scale of 1 to 7): 6

If # 1 (GAR) is coded 6 or 7, go to # 2 below. If # 1 (GAR) is coded 1 to 5, skip to #3.

2. For all prescribed IC medications, record:

2A	2B	2C	2D	2E	2F
IC Medication Name	Drug Code (from Medication Reference Tool)	Total Daily Dose (TDD) between Visits 14 and 15 (Weeks 31 and 34) in mgs	Was participant on this TDD at (Baseline) Visit 2? 1 = Yes 0 = No	Total Daily Dose (TDD) at (Baseline) Visit 2, or at start of medication (if prescribed after Visit 2) in mgs	IC medication Status 1 = Responder 2 = Non-Responder
Elavil	1643	50	0	25	2
Catapres	113	100	1	-	1
Meperidine	1687	100	0	50	2
Detrol	18047	0 (medication stopped)	0	6	1

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Page \_\_\_\_ of \_\_\_\_

**ENDPT**

Participant ID: \_\_\_\_  
Visit Number: \_\_\_\_

Participant Initials: \_\_\_\_  
CRF Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

Clinical Center: \_\_\_\_  
RC ID: \_\_\_\_

## Endpoint Worksheet

### Administrative

To be completed by the RC to determine participants as Responders/Non-Responders.

3. Participant status at Visit 15 (see below):

☐ 1 Responder

☒ 2 Non-Responder

Principal Investigator's Signature: \_\_\_\_\_

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_

PI ID: \_\_\_\_\_

### Criteria to define Responders and Non-Responders:

- If # 1 (GAR) is coded 1 to 5, the participant is considered to be a Non-Responder.
- If # 1 (GAR) is coded 6 or 7, the participant is considered to be a:
  - ✓ Responder, only if all prescribed IC medications are coded 1 (Responder) in column 2F
  - ✓ Non-responder, if any of the prescribed IC medications are coded 2 (Non-Responder) in column 2F