

**Chronic Prostatitis Collaborative Research Network
Randomized Clinical Trial #1
(CPCRN RCT#1)**

**Manual of Procedures
(MOP)**

Chronic Prostatitis Collaborative Research Network
Data Coordinating Center
University of Pennsylvania
Philadelphia, PA

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CPCRN RCT#1 Manual of Procedures

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1 Background

Chronic prostatitis (CP) is a disabling condition affecting an untold number of men of all ages and ethnic origins. As early as 1980, the National Ambulatory Care Survey reported 20 office visits/1,000 men/year for symptoms compatible with prostatitis ¹. Although by one estimate, 50% of men will suffer from symptoms of prostatitis at some point in their lives, most symptomatic men do not have bacterial prostatitis, for which the treatment and management is usually successful ². Therefore, as noted by Krieger *et al.* ³, the most common syndromes for men with chronic prostatitis are *idiopathic* (abacterial prostatitis). Depending on the status of the expressed prostatic secretions (EPS), these patients with chronic abacterial prostatitis are classified further as a) nonbacterial prostatitis if the EPS is purulent (leukocyte count elevated) or b) prostatodynia if the EPS is not purulent. To date there is no standardized method of diagnosis and treatment of this condition. As noted recently by Nickel and Sorensen ⁴, the problems and frustrations found in clinical trials investigating therapies for nonbacterial prostatitis are that

"our definition of the syndromes is unclear, the etiology is obscure, the relevance of the only objective finding we have (leukocytosis) is unknown, symptoms are highly variable, the natural history of the disease has not been adequately studied and the numbers in most clinical trials, including ours, are small".

They concluded that "since the symptoms are paramount in these patients, evaluation of response can only be achieved by using reproducible and validated symptom evaluation instruments."

Recognizing the importance of addressing problems in the diagnosis and treatment of prostatitis, a National Institute of Diabetes, Digestive and Kidney (NIDDK) Diseases Workshop on Chronic Prostatitis ⁵ was held in Bethesda, MD on December 7-8, 1995, from which the new consensus working definition and classification of prostatitis syndromes (NIDDK reference standard) for research studies on these diseases and disorders was summarized as follows:

1. *Acute bacterial prostatitis* is an acute infection of the prostate.
2. *Chronic bacterial prostatitis* is a recurrent infection of the prostate.
3. *Chronic nonbacterial prostatitis/chronic pelvic pain syndrome* (CPPS), where there is no demonstrable infection. Subgroups of this class are:
 - 3.1 *Inflammatory chronic pelvic pain syndrome*, where white cells are found in the semen, EPS, or voided bladder urine-3 (VB-3).
 - 3.2 *Non-inflammatory chronic pelvic pain syndrome*, where white cells are NOT found in the semen, EPS, and VB-3.
4. *Asymptomatic inflammatory prostatitis* (AIP), where there are no subjective symptoms but white blood cells are found in prostate secretions or in prostate tissue during an evaluation for other disorders.

Patients in Categories 1-3 are characterized by chronic pain; however, unlike patients in Category 1 & 2, patients with Category 3 prostatitis do not have any detectable infection of the prostate as determined by conventional microbiological techniques. Abnormalities in the EPS are the primary objective features of Category 3 prostatitis and chronic pain is the primary subjective symptom. The majority of patients with chronic prostatitis are Type 3.³

The occurrence and persistence of pain as a primary presenting symptom is an important aspect of both diagnosis and outcome evaluation. In the recent review article in *Pain* by Egan and Krieger⁶, they note that “chronic abacterial prostatitis is remarkably similar to chronic pain syndromes”, and accordingly they make the case for therapy based on multidisciplinary approaches to pain management, rather than the traditional ‘organ system’ approach. Many therapies have been tried for chronic prostatitis, with a primary focus on improving bladder outlet resistance. However, the general consensus among clinical urology research investigators conducting therapy trials involving chronic prostatitis patients is well reflected in the recent summary of Nickel and Sorensen⁴ that

"more research and larger clinical studies in the nonbacterial chronic prostatitis syndromes are urgently required."

In response to these growing concerns about the diagnosis and treatment of Chronic Prostatitis, the NIDDK funded the CPCRn, comprised of seven (7) Clinical Research Centers (CRCs) and a Data Coordinating Center (DCC), effective October 1, 1997. The primary research questions to be addressed by the CPCRn will encompass the diagnosis, etiology, natural history and prognosis, and the development of treatment strategies focused on Chronic Abacterial Prostatitis - Chronic Pelvic Pain Syndrome (CPPS). In support of these broad research goals, the CPCRn developed a longitudinal Chronic Prostatitis Cohort (CPC) Study, to which patients have been accrued and followed. The group also coordinated the development and validation of a symptom severity index for CPPS. This index, known as the National Institute of Health-Chronic Prostatitis Symptom Index (NIH-CPSI), will be used as a primary outcome measure for clinical trials in CP⁷. In parallel with the CPC, a series of clinical trials designed to address specific treatment questions, both etiologic and palliative, will be conducted. This Manual of Procedures (MOP) represents the first multi-center randomized clinical trial (CPCRn RCT#1) to be conducted by the CPCRn.

2 Participant Enrollment

2.1 Participant Recruitment

The most important factor contributing to the success of the CPCRN RCT#1 is the successful recruitment and retention of men with chronic prostatitis. Each clinical center is responsible for recruiting 18-20 participants into the study. Enrollment data will be monitored by the DCC in order to continually assess enrollment rates. Achievement of recruitment goals depends largely on the organizational structure of the individual clinics. Each clinical center will be responsible for determining how best to recruit participants.

2.1.1 Methods of Recruitment

Although most participants will be recruited for CPCRN RCT#1 from the urology practice of the investigator, there are occasions when this is not sufficient or is not the sole source of participant recruitment. The following options are likely sources for participant enrollment:

Investigator's Own Clinical Practice

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

Referral From the Medical Practice of Other Physicians

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

Prostatitis Foundation Home Page on the World Wide Web

The Prostatitis Foundation, which is supported by volunteers and donations, will announce the study on their home page, which will refer interested participants and clinicians to the geographically appropriate investigator.

NIH Sponsored Press Release One Week Prior to the Launch of the Study

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

NIH Home Page on the World Wide Web

After the study has been officially introduced to the media and public, CPCR N RCT#1 will be described on the NIH Home Page, NIDDK division, in the section “What’s New at NIDDK”, and/or “NIDDK Health Information”.

Brochure for Participants

A brochure will be prepared and distributed by the DCC that will address the concerns of the participants. In the brochure (See *Appendix A*), CPCR N RCT#1 is described and the participant study requirements are listed. Clinical centers are encouraged to use these brochures. They should be stamped with the name and contact information of the Research Coordinator (RC) or physician’s office so that participants can contact researchers who can provide study and enrollment information. Also, these brochures may be used at health fairs and other educational and promotional events to advertise the CPCR N Study. These brochures are included in the study protocol and therefore will be IRA approved once the protocol is.

Participant Newsletter

In an effort to keep participants interested in the study, the CPCR N will publish a newsletter every six (6) months for distribution to enrolled participants and potential participants. The newsletter will include information regarding the status of the study, recent medical information on Chronic Prostatitis and perhaps an interview with a study participant or investigator.

Participant Recruitment Video

In addition, a participant recruitment video, which also describes the study and participation requirements, has been developed for us by the ten (10) participating clinical centers. The script to this video has been included in the study protocol; however, your individual IRS may choose to request a copy of the actual video tape.

2.2 Pre-Screening

The first contact with a potential participant will be considered a pre-screening contact and will include an introduction to the study, a review of the eligibility criteria, a description of tests and procedures involved, and a review of the contact schedule. This should be done to ensure not only the participant’s eligibility, but also his willingness

and ability to meet the demands of the study. Potential subjects should **not** be asked to alter any current medications prior to signing the Inform Consent Form.

Pre-screening may be conducted either over the phone or in the clinic. If the initial contact is by phone, the RC placing the call should identify him/herself and inform the potential participant how he was selected. The RC should provide information about the study and answer questions. The potential participant may be given a copy of the informed consent, or if over the phone, a copy can be mailed or faxed. If he is willing, the RC should schedule a time to sign the informed consent and begin the first screening contact visit. If necessary, the RC should schedule a follow-up call to allow the potential participant time to consider the study obligations.

Note: When scheduling the first screening visit, the participant should be informed that he should remain abstinent (without an ejaculation) for two (2) days prior due to the Four-Glass Test Microscopy test.

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). 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 he decides to enroll.
- The participant must be informed of his right to have **questions answered** at any time and of **whom to contact** for answers or in the event of research-related injury.
- The participant must be informed that he will be notified of any safety-related **changes** in the protocol that might affect his willingness to continue in the study.

- 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, and if so, what they consist of.

An informed consent must be obtained from the participant before and study procedures are performed or medications are altered.

2.3.1 Administration of Informed Consent

The participant is screened to confirm his 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 to read a few sentences out loud to ascertain whether the potential participant needs assistance with the written material. If necessary or requested, an impartial witness may read the informed consent(s) to the participant exactly as written. (See *Appendix B: Informed Consent Form*).

This 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. Inform the participant, or parent/legal guardian of participants under 18 years of age, not to sign the informed consent until he has discussed the contents with the RC and all questions have been answered.

If the participant wishes to take the Informed Consent Form home before reaching a decision, then 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 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 signed and personally dated by the participant or his legal representative, or parent/legal guardian of participants under 18 years of age, the person “obtaining consent” and the Principal Investigator (PI). A participant should not be asked to sign the consent statement if he has any doubts about enrolling or if the clinic staff believes he does not understand what his participation would involve. Under *no* circumstance is any study information to be collected or study procedures performed for the specific purpose of CPCR N RCT#1 **before** the participant, or parent/legal guardian of participants under 18 years of age, 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 must be made in each participant’s file that the informed consent process took place prior to any study procedures.

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).

2.3.2 *Withdrawal Consent*

If a participant indicates that he no longer wishes to participate in the study (withdraws consent), the RC will provide a letter on the institution’s letterhead for the participant to sign. This document is mailed to the participant via certified mail, if necessary, and the receipt kept with the participant’s records. The letter should clearly state that the participant has voluntarily withdrawn his consent and no longer wishes to be contacted. Also, the letter may state that confidentiality of records will be maintained and that the participant may continue to receive regular care and treatment at this clinic.

The RC will complete the Study Stop Point [**SSTOP**] form selecting the most representative reason for withdrawal. The RC will also complete the Treatment Stop Point [**TSTOP**] form, if the withdrawal occurs during the treatment phase. The withdrawal request can be made in person or during a phone contact. Participant data folder is clearly marked to indicate withdrawal and is maintained at the clinical center where the participant was recruited and followed. The CPCR N RCT#1 Project Manager is informed of the participant’s withdrawal, so that he can initiate the data archival process at the DCC.

2.4 Circumstances Under Which Withdrawal May Occur

Participants are free to withdraw from the study at any time. Reason(s) for withdrawal will be documented on case report forms and recorded at the DCC.

Participants may withdraw (or be withdrawn) from the study for many reasons including the following:

- Adverse Event/Serious Adverse Event (AE/SAE)
- Significant concurrent illness
- Protocol noncompliance
- Investigator’s discretion
- Withdrawn informed consent
- Relocation

Clarify with the DCC Project Manager if you are uncertain which of the above circumstances require a certified letter of withdrawal consent.

For those participants who withdraw (or are withdrawn) due to AE/SAE, the Adverse Event/Serious Adverse Events [AE] and **Medwatch 3500** forms must be completed and faxed to the DCC as specified in section 3.2.

2.5 Confidentiality

General Information

Extensive efforts will be made to ensure and maintain participant confidentiality, except as may be required by the regulations. All identifying information **must** be maintained in a secure area at all times and **must never** appear on CRF's. Consent form(s) and source documentation **must** be maintained in a separate folder from the CRF's. 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 CRF's 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.

2.6 Assignment of Participant ID

Only after the participant has signed the Informed Consent Form will the participant be logged in the Participant ID Assignment Log [**LOG**] and assigned a Participant ID. Each participant should be assigned the next available participant ID. Once a participant ID has been assigned, it should never, for any reason, be reassigned. (See Participant ID Assignment Log [**LOG**], Section 5.15.2.) The Participant ID Assignment Log [**LOG**] should be stored in a secure, locked filing cabinet.

The 5-digit participant ID is composed of two identifiers. The first two digits indicate the screening site. The last three digits are the sequential ordering of participants. Each clinical center will have a discrete range of ID numbers corresponding to the clinical center number. For example: ID# 0 2 0 0 8 describes Clinical Center #2, Temple University Hospital, participant ID # 008. Clinical centers are numbered as follows:

- 01 = Brigham and Women's Hospital and Massachusetts General Hospital, Boston, MA
- 02 = Temple University Hospital, Philadelphia, PA
- 03 = University of Maryland Medical System, Baltimore, MD
- 04 = Northwestern Memorial Hospital, Chicago, IL
- 05 = Harbor - UCLA Medical Center, Los Angeles, CA
- 06 = Kingston General Hospital, Kingston, Ontario, Canada
- 07 = University of Mississippi Medical Center, Jackson, MI 39216
- 08 = Cleveland Clinic, Fort Lauderdale, FL
- 09 = MLK Drew Medical Center - Los Angeles, California
- 10 = University of Arizona, Tucson Arizona

Participant ID	Participant Initials	Participant Name
02001	JD	John Doe
02002	RS	Robert Smith
02003	MDC	Michael D. Cohen
02004	DW	Doug Weiss

Table 2.6 Participant ID Assignment Log Example

2.7 Participant Eligibility

2.7.1 *Study Eligibility Criteria*

Every participant must meet the required criteria to be eligible to participate in CPCR N RCT#1. The *study eligibility criteria* consist of the following, and are contained in the eligibility checklist (refer to section 5.4.6):

- If the participant meets all of the inclusion criteria, then continue to the exclusion criteria section.
- If the participant meets any of the exclusion criteria, then he is not eligible to participate in CPCR N RCT#1; if he passes the exclusion criteria, he can proceed to the deferral criteria section.
- If the participant meets any of the deferral criteria, the participant is temporarily deferred from enrolling into the CPCR N RCT#1 until such time that the new re-screening date is reached. The RC should flag this form for contact on the appropriate date.

2.7.2 *Inclusion Criteria*

The participant must meet the following criteria in order to be a candidate for CPCR N RCT#1:

- The participant or legal representative must sign and date the appropriate informed consent,
- The participant must be male;
- The participant must have had symptoms of discomfort or pain in the pelvic region for at least a three (3) month period within the last six (6) months.
- The participant must have at least a moderate overall score on the NIH-CPSI [**CPSI**] form (overall score ≥ 15 out of a potential 0-43 points).

Note: Due to the nature of the study, pre-pubertal participants will not be enrolled in the study.

2.7.3 Exclusion Criteria

If the participant meets any of the exclusion criteria, then he is precluded from participating in CPCR N RCT#1:

- Participants with history of prostate, bladder, or urethral cancer.
- Participants with inflammatory bowel disease (such as Crohn's disease or ulcerative colitis, but not irritable bowel syndrome).
- Participants who have undergone pelvic radiation or systemic chemotherapy.
- Participants who have undergone of intravesical chemotherapy.
- Participants who have been treated with intravesical BCG.
- Participants who have been treated for unilateral orchialgia without pelvic symptoms.
- Participants with active urethral stricture.
- Participants with neurological disease or disorder affecting the bladder.
- Participants who have undergone TURP, TUIP, TUIBN, TUMT, TUNA, balloon dilatation of the prostate, open prostatectomy, or any other prostate surgery or treatment such as cryotherapy or thermal therapy.
- Participants who have a neurological impairment or psychiatric disorder preventing his understanding of consent and his ability to comply with the protocol.
- Participants who have liver disease.

- Participants who have a known allergy or sensitivity to ciprofloxacin hydrochloride (CIPRO®), tamulosin hydrochloride (FLOMAX®), or any of their known components (see *Appendix D*).
- Participants who have a history of seizure disorder.
- Participants who are taking theophylline.
- Participants requiring the ongoing use of magnesium, aluminum, or calcium-containing antacids.

2.7.4 Deferral Criteria

If the participant meets any of the deferral criteria, he will be *temporarily* deferred from entering the study. The participant must be free of the condition or off treatment for the below-indicated deferral period before he can enter CPCR N RCT#1. Deferral/Re-entry Criteria:

Deferral Checklist	Re-entry Criteria (Participant deferred until...)
1. If the participant has been treated with tamulosin hydrochloride (Flomax®), doxazosin mesylate (Carura®), terazosin HCL (Hytrin®), or alpha-blockers within the past four (4) weeks, then	Treatment free for four (4) weeks.
2. If the participant has been treated with ciprofloxacin hydrochloride (CIPRO®) in the past four (4) weeks, then	Treatment free for four (4) weeks.
3. If the participant has been treated with antimicrobial agents (oral or intravenous) in the past four (4) weeks, then	Treatment free for four (4) weeks.
4. If the participant has started, stopped, or changed dose level for ANY prostatitis-specific medications within the past four (4) weeks, then	Four (4) weeks from date of medication adjustment.
5. If the participant has had a urinary tract infection, with a urine culture value of >100,000 CFU/ml in the past three (3) months, then	Condition absent for three (3) months.

Deferral Checklist	Re-entry Criteria (Participant deferred until...)
6. If the participant has had clinical evidence of urethritis, e.g. including urethral discharge or positive culture, within the past three (3) weeks, diagnostic of the following sexually transmitted diseases (STDs): gonorrhea, chlamydia, mycoplasma or trichomonas, but not including HIV/AIDS, then	Condition absent for three (3) months.
7. If the participant has had a prostate biopsy in the past three (3) months, then	3 months from date of procedure.
8. If the participant has experienced symptoms of acute or chronic epididymitis within the past three (3) months, then	Condition absent for 3 months.
9. If the participant has begun finasteride (Proscar®) or other androgen hormone inhibitors in the past six (6) months, or stopped finasteride (Proscar®) or other androgen inhibitors within the past six (6) months, then	Treatment stable for six (6) months.
10. If the participant has used bioflavonoid agents in the past two (2) weeks [Example: Quercetin], then	Treatment free for two (2) weeks.
11. If the participant has been diagnosed or treated for symptomatic genital herpes in the past twelve (12) months, then	12 months from date diagnosed, and until they have been symptom free for a 12-month period (asymptomatic for 12 months).
12. If the participant has been taking zinc or iron supplements within the past two (2) weeks, then	Treatment free for two (2) weeks.
13. If the participant has been treated with cimetidine in the past two (2) weeks, then	Treatment free for two (2) weeks.

Unfortunately, participants can be poor historians and/or have a limited understanding of their health problems and associated treatments. It is, therefore, advisable to verify the responses to those questions which have been denoted “as reported by the participant” with their medical record, when possible. If there is a discrepancy, then the information in the participant’s medical record should be considered correct. For

example, if the participant indicated that he has not taken any antimicrobials, but his medical record clearly indicates that he was on an antimicrobial medication approximately two (2) weeks ago, then the medical record should be considered correct. The participant is deferred until he has been off the medication for four (4) weeks.

Participants that are new at a center and for whom there is no medical record available, enrollment criteria will be based on the participant's self-report. However, responses should be verified with the participant's medical record whenever possible.

2.7.5 Screening and Re-Screening Requirements

Every potential participant must complete all of the screening phase requirements indicated in *Chapter 4 - Visit Scheduling and Administration*. If a participant was previously deferred, he must be re-screened to confirm his current eligibility for CPCR N RCT#1. When a participant is re-screened, all screening forms and procedures must be re-done except for the Participant ID Administration Log [LOG]. A re-screened participant has already been assigned a participant ID during Screening Visit #1 and, therefore, should **not** be assigned a new ID number. Re-screened participants should retain their previously assigned ID number. A participant, who was previously excluded, **cannot** be re-screened.

2.7.6 Screening Failures

A participant who does not complete the Screening procedures, for whatever reason, is considered a screening failure and will **not** be randomized to CPCR N RCT#1. For example, a participant who completes, or partially completes, Screening Visit #1 and does not come back for Screening Visit #2 will be considered a screening failure. This does not include participants who have not had a laboratory test performed due to lab error or participant inability to complete a certain procedure despite efforts by the participant and PI. All of the completed screening forms, including informed consent form, for participants who are considered screening failures, should be filed at the center in the CPCR N Confidential Participant File and should not be sent to the DCC.

Note: Participants must be able to provide **at least one** of the following samples: EPS, VB3 or semen, to be included in the study. If the participant is not able to provide at least one of these samples, then he will be considered a screening failure and will **not** be randomized to CPCR N RCT#1.

2.8 Participant Randomization

Only those participants, who have completed the entire screening phase including forms and procedures, will be randomized to CPCR N RCT#1. Participants who fall under the category of Screening Failure will **not** be randomized to CPCR N RCT#1.

Once a participant has completed all of the required screening phase forms and procedures, is confirmed eligible by the Eligibility Checklist **[ELIG]** and the Randomization (**RAND**) form, **and** is randomized to CPCR N RCT#1, study medication will be dispensed. The participant then proceeds to the Treatment Phase of CPCR N RCT#1.

In order to randomize a participant, only the following forms must be data-entered and verified: Screening Visit #1 NIH-CPSI **[CPSI]** and the Eligibility Checklist **[ELIG]**. The score from Screening Visit #2 NIH-CPSI **[CPSI]** is entered on the Randomization **[RAND]** form along with the Highest VB2 culture count and the results of the Chlamydia PCR test. The Randomization **[RAND]** form is only data-entered once and will provide you with a randomization number, which should be recorded at the bottom of the Randomization **[RAND]** form. All other data forms from Screening Visits #1 and #2 should be data-entered and verified within two (2) weeks of Screening Visit #2.

A participant may withdraw from CPCR N RCT#1 at any time. If a participant chooses to withdraw during the Treatment phase of the study, he should be instructed to first notify the RC. The RC should instruct the participant to complete the “Early Stop Treatment” set of forms. Every effort should be made to encourage participants to continue with study visits/contacts even if they stop treatment early.

2.8.1 Back-up Randomization

In the event of a computer failure at the Clinical Center and/or the DCC during randomization, the RC will call the DCC randomization **pager number _____**, which will be available from 0900 to 2000 EST, Monday through Friday.

A member of the DCC team will return the phone call and ask the RC for responses on Visit #1 – NIH/CPSI **[CPSI]**, Eligibility Checklist **[ELIG]**, and Randomization **[RAND]**.

The RC will also be asked about the randomization (drug packet) number of the most recently randomized participant (the last randomization number assigned).

The DCC representative will also ask the RC if data for Visit #1 – NIH/CPSI **[CPSI]** and Eligibility Checklist **[ELIG]** has been entered and verified.

When the DCC representative confirms the participant’s eligibility, the DCC representative will assign the next randomization number. At the earliest possible time, the DCC representative will enter and verify the CRF data into the database and confirm the randomization number generated electronically with the manually assigned number.

The RC will fax copies of the CRFs, needed for manual randomization, for manual audit at the DCC.

When the computer system at the randomization site is operational again, the RC should verify with the DCC that the database has been updated since the telephone randomization was performed, prior to entering data on new participants.

2.9 Participant Transfers

It is possible for a CPCR N RCT#1 participant to transfer to another clinical center during the course of the study. 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 he was enrolled.

2.9.1 Transfer of a Participant During the Screening Phase

It is strongly recommended that participants not be transferred during the screening process. However, if a participant indicates his desire to transfer to another clinical center during the screening phase, then he must be informed of the following:

- Participant must either complete the screening phase at the originating center, **or**
- Participant must suspend all further screening processes at the originating center and undergo the entire screening process from the beginning at the desired center.

2.9.2 Transfer of a Participant During the Treatment/Follow-up Phase

It is important that participants who have been randomized at a particular clinical center retain their **original** participant ID and CPCR N Study File throughout the entire study. If a participant indicates his desire to transfer to another clinical center during the treatment/follow-up phase of CPCR N RCT#1, then the RC must adhere to the following guidelines:

- The RC at the originating clinical center must complete page 1 of the Participant Transfer [**TRANS**] form. This form will contain the participant's ID, initials, next visit number and target date, and indicate the originating and receiving clinical centers.
- The originating RC must provide the participant with contact information for the receiving clinical center, and instruct the participant that it is **his** responsibility to initiate contact with the receiving RC.
- The originating RC should notify the receiving RC and the DCC of the upcoming participant transfer via email or fax of the Participant Transfer [**TRANS**] form.
- The originating RC must send a copy of the participant's CPCR N RCT#1 records to the receiving clinical center.
- The receiving RC must create a new file for the participant's CPCR N RCT#1 records, and for all future follow-up contacts.

- Before any CPCR N RCT#1 forms and procedures are completed at the follow-up contact, the receiving RC must have the participant sign the receiving center's informed consent.
- It will be the joint responsibility of both the originating and receiving RC's to ensure the completeness and accuracy of the participant's CPCR N RCT#1 records.
- The participant should request a transfer of his medical record from the originating center to the receiving center, following the originating center's guidelines for transfer of medical records.

2.10 Study and Participant Documents

Study and participant documents must be made available to the CPCR N RCT #1 Study Group, the licensed product holder(s), NIH, NIDDK, the Food and Drug Administration, and/or any agents/representatives of these parties. These documents should be organized as outlined in binders or files and stored in accordance to FDA security and record retention regulations and until further written notice by the sponsor or the DCC. Each clinical center must maintain the following documents:

Regulatory Binder *(1 per clinical center)*

Contains all essential documents, according to GCP guidelines, required for conducting a clinical trial.

- RCT#1 Protocol/Amendments and Signature Page(s)
- RCT#1 Manual of Procedures and Signature Page
- RCT#1 Case Report Form Templates
- RCT#1 Informed Consent Form Templates
- IRB Documents/Correspondence
- IRB Membership List (current for duration of trial)
- FDA 1572 Forms (HPB3005, Canadian Sites)
- Completed SAE/MEDWATCH Forms
- IND Safety Reports
- Laboratory Certifications/Laboratory Normals (current for duration of trial)
- CVs of all clinic personnel (current within 2 weeks)
- Signature and Delegation of Responsibilities Log
- Study Medication Tracking Log
- Study Medication Shipment Receipts
- Monitoring Log
- Participant Status Log
- Clinic Correspondence – Log and other documentation
- Reports

Note to file: Documents outlined above may be stored in other/additional binders during the course of the study, however a “Note to File” should be placed in any section where this occurs for a monitor’s reference and as a reminder to replace documents at time of study termination

Case Report Form Binder *(1 per study participant)*

Contains all data collection forms and select administrative forms completed during the course of the trial. No participant identifiers other than participant ID number and participant initials should be contained in this binder.

Participant Confidential File *(1 per study participant)*

Contains all documentation collected to support and verify information contained on the data collection forms. This includes the following original source documents: participant signed informed consent, medical records, laboratory results, contact information, administrative forms not contained in Case Report Form Binder, progress notes, and correspondence. In addition, any copies of applicable source documentation should also be stored in this file. Any study documents containing any participant identifiers beyond participant ID number and participant initials should be contained in this file.

Study “Confidential” File *(1 per clinical center)*

Contains Participant ID Assignment Log, a copy of all participant signed informed consents and all financial documents related to the study. Any additional study specific confidential documents should be contained in this file. At the completion of the trial, the Participant Contact Log should be completed and stored in this file. These files must be stored under secure conditions.

3 Participant Safety

3.1 Risks and Benefits

3.1.1 *Risks*

- The RC should inform the participant of potential risks relating to CIPRO® and FLOMAX® prior to instructing the participant on taking the medications. (See *Appendix D*)
- The RC should inform the participant of potential risks relating to venipuncture, before initiating the procedure.

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 learn more about CIPRO® and FLOMAX® and their use in men with Chronic Prostatitis.
- Participants may have access to new clinical trials/therapies.
- Participants will maintain direct contact with Clinical Centers and Research Coordinators.
- Participants will have easy access to medical information.

3.2 Adverse Event

Study participants must be evaluated at each clinic visit and telephone contact for Adverse Events. Please refer to the two (2) main Adverse Event categories below (AEs & 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 this treatment*. An adverse event can therefore be ANY **unfavorable** and **unintended** sign (including an abnormal laboratory finding, for example), symptom or disease temporarily 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 and Reporting Adverse Events (AEs)

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 (if appropriate), according to routine 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);
- Results in a persistent or **significant disability/incapacity** (e.g., the event is a substantial disruption of a person's ability to conduct normal life functions);
- Results in **in-patient hospitalization or prolongation of existing hospitalization;**
- 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 (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 and 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 (completed in accordance with instructions in this MOP). 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 (1) working day of first knowledge, the DCC Project Manager (or their designee) will notify NIH/NIDDK and the University of Pennsylvania IRB of all SAEs. In addition, NIH/NIDDK will promptly notify the two (2) Licensed Product Holders.

Note: Deaths occurring within thirty (30) days of study medication cessation must be reported as above.

3.2.5 IND Safety Reports (21CFR 312.32)

The Sponsor, (NIH/NIDDK), 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 D*). Serving as the sponsor's designee, the DCC shall disseminate these IND safety reports to the investigational sites and licensed product holders. These written notifications shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. The sponsor shall also notify FDA by telephone or by facsimile transmission of unexpected fatal or life-threatening experience *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.

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 CPCR Study Binder.

3.2.6 Current Labeled Side Effects

Like many medications, CIPRO® or FLOMAX® may cause side effects in some participants. The following are lists of the sides effects noted with CIPRO® and FLOMAX®:

CIPRO®:

The most frequently reported events are: nausea, vomiting, diarrhea, abdominal pain/discomfort, rash, headache, and restlessness. Additional adverse events include:

Cardiovascular: palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

CNS: dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reactions, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia.

Gastrointestinal: painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding, and cholestatic jaundice.

Musculoskeletal: arthralgia, or back pain, joint stiffness, achiness, neck and chest pain, flare up of gout.

Renal/Urogenital: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, and acidosis.

Respiratory: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, and pulmonary embolism.

Skin/hypersensitivity: pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, and erythema nodosum. Allergic reactions from urticaria to anaphylactic reactions have been reported.

Special Senses: blurred vision, disturbed vision, decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, and bad taste.

Most of the adverse events were described as only mild or moderate in severity, abated soon after CIPRO® was discontinued and required no treatment.

FLOMAX®:

Hypersensitivity to FLOMAX® can occur and as FLOMAX® is an alpha adrenergic blocker, it can cause lowering of blood pressure. Additional adverse events include:

Body as a whole: headache, infection, asthenia, back pain, and chest pain.

CNS: dizziness, lightheadedness, syncope, somnolence, insomnia, and libido decreased.

Respiratory: rhinitis, pharyngitis, cough increased, and sinusitis.

Digestive System: diarrhea, nausea and tooth disorder.

Urogenital: abnormal ejaculation.

Special Senses: amblyopia

3.3 Unmasking

The University of Pennsylvania Investigational Drug Service (PENN's IDS) will ship treatment kits to each participating site. In addition, PENN IDS will keep a copy of the masking code for each site/participant.

It is anticipated that unmasking will be a very rare occurrence and will only happen under the most critical of situations. Unmasking process should be initiated very carefully and selectively, in a serious or life-threatening situation for the participant only. Each participant should have the pager number of the RC at the onset of the trial, should such an emergency occur later. If the need does arise:

- The RC should instruct the participant to call the RC's pager with unmasking concerns;
- The RC would then contact the on-site Investigator;
- The on-site Investigator would in turn **page Protocol Chair, Dr. Alexander at (410)-460-7838 to discuss if unmasking is warranted. If Dr. Alexander is unavailable, contact Dr. O'Leary at (617) 732-5700 and then when asked for pager number, 12851;**
- If it is determined that the treatment should be unmasked, Drs. Alexander or O'Leary would contact Penn IDS Pharmacist by phone at (215) 349-8817 or pager at 215-960-9565, for the appropriate unmasking information.
- The Penn IDS Pharmacist would then call the on-site investigator (or their designee) regarding which arm of the study (drug) the participant is on.

The on-site investigator/RC should also complete section 1 of the Authorization For Unmasking form [**AUTH**], which will serve as a record of the request/authorization for unmasking, and forward as directed. See section 5.5.2 for information on completing the Authorization For Unmasking [**AUTH**] form. The DCC should be notified via telephone within one (1) working day of the unmasking event, followed by the facsimile copy of the completed (containing all three required signatures) Authorization For Unmasking [**AUTH**] form. If the unmasking occurred as a result of an SAE, the Adverse Event/Serious Adverse Events [**AE**] and **Medwatch 3500** forms must be completed and faxed to the DCC as specified in section 3.2.4.

In addition, the site must send written/dated notification to their IRB, (identifying the participant by study number/initials only), which outlines the *circumstances* for the unmasking, as well as the *medical outcome*. However, it is important to cautiously limit

the knowledge of the unmasked drug to an “as needed to know” basis. A copy of the IRB and DCC notifications must be maintained in the study binder.

4 Visit Scheduling and Administration

4.1 Screening Phase

The screening phase of CPCR N RCT#1 is also known as Visits #1 and #2 of the study. Potential study participants must pass the study eligibility criteria (see *Chapter 2 Participant Enrollment*) before undergoing the rest of the procedures for the screening phase. If it was not possible to obtain the required specimens during Visit #1, an additional visit may need to occur prior to the scheduled Visit #2, in order to obtain these specimens. Visits #1 and #2 must be scheduled no less than seven (7) days and no more than three (3) weeks apart.

4.1.1 Screening Phase Procedures

During the screening phase, each participant must provide the information needed to complete all data forms and laboratory procedures listed in Table 4.1.4. Details on how to complete all data forms are provided in *Chapter 5: Data and Administrative Forms*. Details on how to perform laboratory procedures and specimen handling procedures are provided in *Appendix F: Laboratory Procedures*.

4.1.2 Order of Data Forms and Laboratory Tests

The forms and procedures to be completed during the screening phase should be completed in an order, which is agreeable to both the participant and the clinical center staff. However, the ideal order of these procedures, identified below, has been offered as a way to provide a balance of participant comfort and timeliness. Prior to obtaining a participant's informed consent, potential study participants will be informed of all aspects of the study (including baseline screening procedures, follow-up procedures, assurance of participant confidentiality and any potential risks and benefits to the participant). The subsequent guidelines should be followed.

4.1.3 Screening Visit #1

The first form to be completed is the informed consent, if not signed already. Prior to gathering information or performing any study procedures, the informed consent must be signed in ink and personally dated by the participant or parent/legal guardian of participants under 18 years of age, the person obtaining consent and by the PI.

After the Informed Consent is signed, the next group of forms to be completed in order are: Participant ID Assignment Log [**LOG**], Eligibility Checklists [**ELIG**], NIH-CPSI [**CPSI**] and the Participant Contact Information [**CONTACT**]. Once the participant has been assigned a Participant ID, and if the participant meets the eligibility criteria, he can proceed with the screening phase. The participant's medical history should be collected and recorded on the Medical History [**MED**] form.

The physical exam and the four-glass test must be performed by the physician at the first screening visit. In addition, the Physical Exam **[EXAM]** form should be completed during the exam. The Four-Glass Test Microscopy **[FGTM]** form and the Four-Glass Test Specimen Cultures **[FGTC]** form should be completed as soon as the lab reports are available. The RC should remind the participant that he should remain abstinent (without an ejaculation) for two (2) days prior to the Four-Glass Test Microscopy test. However, the sample may be collected even if the participant has not been abstinent.

Note: If the participant is not willing to undergo the rectal exam that forms part of the physical exam, the participant will not be allowed to participate in the study.

A one-day Voiding Log **[VOID]** form will be given to the participant during Screening Visit #1 to be returned during Screening Visit #2. The RC is responsible for explaining the log and distributing instructions to the participant.

Screening Visit #1 Closeout

At the end of the first screening visit, the RC should instruct the participant to bring in all over-the-counter and prescribed medications that he is currently taking to his next screening visit. This will help the RC to complete the Concomitant Medications **[CMED]** form during Screening Visit #2.

The RC should instruct the participant on the use of the Voiding Log **[VOID]** form, which has to be completed and brought to the next screening visit.

The RC should explain to the participant that he must remain abstinent (without an ejaculation) for two (2) days prior to Screening Visit #2, in order to provide the required semen sample.

The RC will review the visit checklist **[VISIT1]** form to ensure that all required forms and procedures were completed. The RC should complete the Participant Status Log **[STATUS]** form and schedule Screening Visit #2 according to the conventions noted in section 4.6.1.

4.1.4 Screening Visit #2

The RC will review the eligibility checklist **[ELIG]** form with the participant to ensure that all responses from Visit #1 remain accurate. The participant will be given a NIH-CPSI questionnaire to complete and the score will be recorded on the Randomization **[RAND]** form. The completed Randomization form will be entered into the database and the RC will be provided with a randomization number. This number will directly correspond to a study medication kit that will be dispensed to the participant at this visit. The dispensing log **[DISP]** form and Study Medication Tracking Log **[TRACK]** form should be completed at this time. While the RC is performing the randomization, the participant should be instructed to complete the following questionnaires/data forms: SF-12 **[SF12]**, Follow-up symptoms **[SYM]**, and Demographics **[DEMO]**.

The RC will collect the Voiding Log [**VOID**] form from the participant and will review it for completeness.

The RC will review all over-the-counter and prescribed medications that the participant is currently taking, and transcribe them on the medication diary [**DIARY**] form, and will complete the Concomitant Medications [**CMED**] form.

The uroflow and PVR test procedures should be performed and the Uroflow [**URO**] form completed after the test.

The semen sample must be collected at Screening Visit #2. The Semen Sample [**SEMEN**] form should be completed as soon as the lab report is available. It is preferred that the participant be abstinent (without an ejaculation) for two (2) days prior to providing this sample. However, the sample may be collected even if the participant has not been abstinent. If the participant says he is unable to provide the semen sample in the office, he will be given a sterile urine cup and will be asked to obtain the sample at home. Once the sample is obtained, it should be kept at room temperature for 30 minutes, then placed on ice, and brought to the clinic within one hour of obtaining the semen sample.

Once the semen sample culture report is available, the RC should complete the Uropathogens Localized to Semen Worksheet [**UCAL**] form to determine if the participant will be required to provide an additional semen sample at Visit #4 (week 6) clinic visit.

Note: A participant can refuse to provide a semen sample. However, the RC must inform the participant that in order to be eligible for the CPCR N RCT#1 at least one of the following: EPS, VB3 or a semen sample **must** be obtained. If none of these tests are obtained, the participant will be considered a screening failure and cannot be included in the study.

Screening Visit #2 Closeout

The RC should provide the participant with two (2) sets of the following forms: NIH-CPSI [**CPSI**], SF-12 [**SF12**] and Follow-up symptoms [**SYM**] forms. The first set is to be completed by the participant at the time of Visit #3. The second set is to be completed in the event that the participant discontinues study treatment prematurely.

The participant will also be given another one-day Voiding Log [**VOID**] form. The RC should instruct the participant to complete just prior to Visit #4.

The RC will provide the participant with comprehensive instructions on the use of the Medication Diary [**DIARY**] form and the Exclusionary Meds [**EMEDS**] form.

The RC will review the Visit #2 checklist [**VISIT2**] form to ensure that all required forms and procedures were completed. The RC should update the Participant Status Log [**STATUS**] form and schedule Visit #3 according to the participant's follow-up contact schedule.

Table 4.1.4 Data and Administrative Forms for Screening Phase

Screening Phase
<p><u>Screening Visit #1:</u></p> <ul style="list-style-type: none"> • Informed Consent • Eligibility Checklist [ELIG] • NIH-CPSI [CPSI] • Medical History [MED] • Physical Exam [EXAM] • Four Glass Test Microscopy [FGTM] • Four Glass Test Specimen Culture [FGTC] • Participant Contact Information [CONTACT] • Visit Checklist [VISIT1] • Participant Status Log [STATUS] • Participant ID Assignment Log [LOG] • Forms distributed to participant: <ul style="list-style-type: none"> 1. Voiding Log [VOID] <p><u>Screening Visit #2:</u></p> <ul style="list-style-type: none"> • NIH-CPSI [CPSI] • Randomization [RAND] • SF-12 [SF-12] • Follow-up symptoms [SYM] • Demographics [DEMO] • Dispensing Log [DISP] • Concomitant Medications [CMED] • Semen Sample [SEMEN] • Uroflow Study [URO] • Voiding Log [VOID] • Visit Checklist [VISIT2] • Study Medication Tracking Log [TRACK] • Participant Status Log [STATUS] • Forms distributed to participant: <ul style="list-style-type: none"> 1. Voiding Log [VOID] 2. Medication Diary [DIARY] 3. 2-NIH-CPSI [CPSI] 4. 2-SF-12 [SF12] 5. 2-Follow-up symptoms [SYM]

4.2 Treatment/Follow-up Phase

All eligible participants who have completed the screening phase and were successfully randomized will proceed to the Treatment/Follow-up Phase of CPCR N RCT#1. The treatment phase is comprised of one telephone contact Visit #3 (week 3) and one clinic visit, Visit #4 (week 6). The Follow-up phase is comprised of 2 telephone contacts: Visit #5 and Visit #6 (weeks 9 and 12).

4.2.1 Telephone Contact (Visits #3, #5 and #6)

TELEPHONE CONTACT
<u>Contact Visit #3, #5 and #6:</u>
<ul style="list-style-type: none">• NIH-CPSI [CPSI]• SF-12 [SF12]• Follow-up symptoms [SYM]• Follow-up Contacts [FUP]• Adverse Event/Serious Adverse Event [AE]• Study Stop Form [SSTOP] <i>Week #12 only</i>• Visit Checklist [VISIT3], [VISIT5], or [VISIT6]• Participant Status Log [STATUS]

Table 4.2.1: Data and Administrative Forms for Telephone Contact.

Forms Requirements

Table 4.2.1 identifies the forms that should be completed for the Visit #3, #5, and #6 Telephone Contact.

Reminder to RC: Review the Participant Contact Information [**CONTACT**] at each contact to insure that each participant's information has not changed since previous contacts.

Completion of Data and Administrative Forms

Details on completing all data and administrative forms are provided in *Chapter 5: Data and Administrative Forms*.

Ideally, the telephone contact will consist of the RC reminding the participant that it is time for him to complete the NIH-CPSI [**CPSI**], SF-12 [**SF12**] and Follow-up symptoms [**SYM**] forms and mail them to the clinic, if he has not already done so. In the event that the participant is not able to complete the forms himself, for whatever reason, the RC will interview the participant and the RC will complete the forms.

Additionally, the RC will question the participants about any adverse events or serious adverse events the participant may be experiencing and record this information on the Adverse Event/Serious Adverse Event [AE] form.

Additionally at Visit #6 (week 12) only, the RC will complete the study stop [SSTOP] form.

Telephone Contact Closeout

The RC will review the visit checklist [VISIT3], [VISIT5] or [VISIT6] form to ensure that all required forms were completed. The RC will schedule the next participant contact according to the Participant Follow-up Contact Schedule. **Note:** *there will be no further study contacts/follow-up beyond Visit #6 (week 12) study visit.*

4.2.2 Visit #4 Clinic Contact (Week 6)

Each participant will complete a Visit #4 (week 6) Clinic Contact. This visit concludes the treatment phase.

CLINIC CONTACT	
<u>Contact Visit #4:</u>	
•	NIH-CPSI [CPSI]
•	SF-12 [SF12]
•	Follow-up symptoms [SYM]
•	Concomitant Medications [CMED]
•	Follow-up Contacts [FUP]
•	Adverse Event/Serious Adverse Event [AE]
•	Physical Exam [EXAM]
•	Four Glass Test Microscopy [FGTM]
•	Four Glass Test Specimen Culture [FGTC]
•	Semen Sample [SEMEN]
•	Uroflow [URO]
•	Voiding Log [VOID]
•	Treatment Stop [TSTOP]
•	Visit Checklist [VISIT4]
•	Study Medication Tracking Log [TRACK]
•	Forms distributed to participant:
1.	3-NIH-CPSI [CPSI]
2.	3-SF-12 [SF12]
3.	3-Follow-up symptoms [SYM]
4.	Rescue Treatment Event [RMED]

Table 4.2.2: Data and Administrative Forms for Week 6 Clinic Contact.

Forms Requirements

Table 4.2.2 contains the list of forms and procedures that must be completed for each participant undergoing the Visit #4 (week 6) Clinic Contact.

Completion of Data and Administrative Forms and Laboratory Procedures

Details on completing all required forms are provided in *Chapter 5: Data and Administrative Forms* and *Appendix F: Laboratory Procedures*.

The RC will collect the following forms from the participant: Voiding Log [**VOID**] form and Medication Diary [**DIARY**] form. They should also collect the study medication bottles and any unused study medication. The Treatment Stop [**TSTOP**] form should be completed.

The physical exam and the four-glass test must be performed by the physician at the Visit #4 (week 6) clinic visit. In addition, the Physical Exam [**EXAM**] form should be completed during the exam. The Four-Glass Test Microscopy [**FGTM**] form and the Four-Glass Test Specimen Cultures [**FGTC**] form should be completed as soon as the lab reports are available. The RC should remind the participant that he should remain abstinent (without an ejaculation) for two (2) days prior to Four-Glass Test Microscopy test. However, the sample may be collected even if the participant has not been abstinent.

Reminder to the RC: the four-glass test and semen sample cannot be done during the same visit. It is recommended that these two procedures be scheduled one (1) week apart, however, a minimum of three (3) days apart is acceptable, based on participant availability.

The Semen Sample [**SEMEN**] form should be completed as soon as the lab report is available. It is preferred that the participant be abstinent (without an ejaculation) for two (2) days prior to providing this sample. However, the sample may be collected even if the participant has not been abstinent. If the participant says he is unable to provide the semen sample in the office, he will be given a sterile urine cup and will be asked to obtain the sample at home. Once the sample is obtained, it should be kept at room temperature for 30 minutes, then placed on ice, and brought to the clinic within one (1) hour of obtaining the semen sample.

At the Visit #4 (week 6) clinic visit, only the PVR test procedure should be performed and the Uroflow [**URO**] form completed after the test.

Visit #4 (Week 6) Clinic Contact Closeout

The RC will review the Visit #4 checklist form to ensure that all required forms were completed. The RC should provide the participant with three (3) sets of the following forms: NIH-CPSI [**CPSI**], SF-12 [**SF-12**] and Follow-up symptoms [**SYM**]. The first two sets are to be completed by the participant at the time of Visits #5 and #6. The third set is to be completed at the first occurrence of the participant initiating a rescue medication/treatment, in addition to the Rescue Treatment Event [**RMED**] form.

The RC will schedule the next participant contact according to the Participant Follow-up Contact Schedule provided for each individual participant. If the participant has forgotten to bring in his Voiding Log [**VOID**] or Medication Diary [**DIARY**], the RC will remind the participant to mail the form to the clinic as soon as possible.

4.3 Additional Contacts

4.3.1 *Early Stop Treatment*

Any participant who discontinues study treatment early (prior to the Visit #4 clinic visit), for any reason, should have an Early Stop Treatment Contact. The RC should instruct participants at the time of randomization to contact the clinical center immediately if they stop taking their study medications for any circumstance.

EARLY STOP TREATMENT CONTACT	
<ul style="list-style-type: none">• NIH-CPSI [CPSI]• SF-12 [SF12]• Follow-up symptoms [SYM]• Treatment Stop [TSTOP]• Visit Checklist [VISIT98]• Study Medication Tracking Log [TRACK]	

Table 4.3.1: Data and Administrative Forms for Early Stop Treatment Contact.

Forms Requirements

Table 4.3.1 contains the list of forms that must be completed for each participant undergoing the Early Stop Treatment Contact.

Completion of Data and Administrative Forms

Details on completing all required forms are provided in *Chapter 5: Data and Administrative Forms*.

The RC should make every effort to collect complete data on all participants, regardless of the reason the study medication was discontinued. **Reminder to the RC:** If a participant stops taking one of the study medications, he must discontinue both. Participants who decide to discontinue study medication prematurely should be encouraged to complete the remainder of the study contacts. The Treatment Stop Point [TSTOP] form should be completed at this time, along with the Study Stop Point [SSTOP] form if applicable.

Early Stop Treatment Contact Closeout

The RC will review the Visit #98 checklist [VISIT98] form to ensure that all required forms were completed. The RC will schedule the next participant contact according to the Participant Follow-up Contact Schedule, if the participant is willing to continue with the study. If the participant is not willing to continue with the study, the RC should instruct the participant to return all study related materials (study medication bottles, unused study medication, Medication Diary [DIARY], Voiding Log [VOID], etc.)

4.4 Rescue Treatment Event

Any participant, who initiates new medication or treatment for symptoms of prostatitis or pelvic pain, **after** the Visit # 4 (week 6) clinic contact and **before** the Visit #6 (week 12) phone contact, should have a Rescue Treatment Event Contact. The RC should instruct participants at the Visit #4 (week 6) clinic contact to notify the clinical center immediately if they begin taking any medications for prostatitis or pelvic pain.

RESCUE TREATMENT EVENT CONTACT	
•	NIH-CPSI [CPSI]
•	SF-12 [SF-12]
•	Follow-up symptoms [SYM]
•	Rescue Treatment Event [RMED]
•	Visit Checklist [VISIT99]

Table 4.4: Data and Administrative Forms for Rescue Treatment Event Contact.

Forms Requirements

Table 4.4 contains the list of forms and procedures that must be completed for each participant undergoing the Rescue Treatment Event Contact.

Completion of Data and Administrative Forms

Details on completing all required forms are provided in *Chapter 5: Data and Administrative Forms*.

Participants who decide to initiate rescue medication or treatment prior to the Visit #6 (week 12) phone contact should be encouraged to complete the remainder of the study contacts. If, however, a participant elects not to continue with the study, then the Study Stop Point [**SSTOP**] form should be completed at this time.

4.5 Rescue Treatment Event Contact Closeout

The RC will review the Visit #99 checklist [**VISIT99**] form to ensure that all required forms were completed. The RC will schedule the next participant contact according to the Participant Follow-up Contact Schedule, if the participant is willing to continue with the study. If the participant is not willing to continue with the study, the RC should instruct the participant to return all study-related materials (Rescue Treatment Event [**RMED**] form, questionnaires, etc.).

4.6 Scheduling of Contacts

The RC will explain the three different types of follow-up contacts to the participant, the different forms and procedures required for each contact and the approximate length of time that should be allotted for each type of contact.

4.6.1 *Screening Visits*

At the completion of Screening Visit #1, the RC should schedule the participant for Screening Visit #2. If it was not possible to obtain the required specimens during Visit #1, an additional visit may need to occur prior to scheduled Visit #2, in order to obtain these specimens. Visits #1 and #2 must be scheduled no less than seven (7) days and no more than three (3) weeks apart

At the end of the final screening visit, the RC will schedule the participant's Visit #3 (week 3) Telephone Contact. The RC should not wait to generate the Participant Follow-up Contact Schedule before scheduling the Visit #3 (week 3) Telephone Contact.

4.6.2 *Treatment/Follow-up Phase Contacts*

A Participant Follow-Up Contact Schedule will be generated for each individual participant according to the date of his randomization. This schedule indicates the sequence of follow-up contacts, target dates for each contact, and time windows in which the contact must be completed.

At the close of each contact, the RC will schedule the next contact, whether it is a telephone or clinic contact, by referencing the Participant Follow-up Contact Schedule.

Note: The RC should inform the participant that he should remain abstinent (without an ejaculation) for two (2) days prior to the Visit #4 (6 week) Clinic Contact.

4.7 Determination of the Participant Follow-Up Contact Schedule

The target date for any follow-up contact is calculated by adding the correct number of days to the date of the participant's randomization visit. The correct number of days is calculated by the number of weeks, based on a 30.4 day month, after the participant's randomization visit in which the follow-up contact should occur.

The *time window* for any follow-up contact is the time frame in which the contact should be completed. The time window for all contacts for CPCR N RCT#1 is defined as the interval of time starting seven (7) days before and ending seven (7) days after the target date of the contact. All dates are determined from the date of the randomization, without regard to whether they fall on a weekend or a holiday.

4.8 Participant Follow-Up Contact Schedule

This schedule is generated to aid the RC in scheduling all follow-up contacts for participants. When the RC generates the Participant Follow-up Contact Schedule from the database, it should be placed in the participant's study file. At the conclusion of a participant contact, the RC should refer to the schedule in order to schedule the next contact. The RC should document the completed contact date under the column titled "Actual Contact Date", and refer to the next line to determine the type and appropriate date of the next contact.

Scheduling contact dates within permissible time windows will be based on the participant's pattern of adherence to scheduled contacts. When contact dates are adhered to, the contact should be scheduled as close as possible to the target date. Rescheduling of contacts should be discouraged. When rescheduling contacts, the next contact should be scheduled as early as possible within the permissible time window in order to increase the chances of rescheduled contacts falling within the window. If the RC or the participant is not sure when to schedule the next contact, it should be set as early as possible within the time window.

If a participant has to reschedule a contact, the RC should attempt to reschedule the appointment within the remaining time window. If the contact cannot be planned within the time window, the contact should be scheduled and completed before the first possible date of the next contact window. If this is not possible, it will be considered a "missed" contact.

A Sample Participant Follow-up Contact Schedule is shown below.

Participant Follow-Up Contact Schedule				
Participant ID: 03016				
Participant Initials: ____				
Randomization Date: 05/31/2001				
The indicated contacts should be done within the time window specified and as close to the target date as possible.				
TIME WINDOW				
Type of Contact	Target Date	First Possible Date	Last Possible Date	Actual Contact Date
Visit #3 (Week 3) Phone	06/23/01	06/16/01	06/30/01	
Visit #4 (Week 6) Clinic	07/16/01	07/09/01	07/23/01	
Visit #5 (Week 9) Phone	08/07/01	07/31/01	08/14/01	
Visit #6 (Week 12) Phone	08/30/01	08/27/01	09/06/01	

Table 4.8: Sample Participant Follow-Up Contact Schedule

4.8.1 Missed Study Contacts

If a follow-up contact cannot be completed within the time window allowed, the contact should be scheduled and completed before the window date of the next study contact. If the contact cannot be completed before the window date of the next contact, the contact must be considered missed, and the visit should be marked as missed in the database.

When a participant misses a follow-up contact, the RC should stress to the participant the importance of collecting follow-up data. When a participant misses multiple follow-up contacts, the PI may consider withdrawing the participant from the study.

4.9 Contact Reminders

The RC should contact the participant at least three (3) days prior to the Visit #4 to remind them a) remain abstinent for 48 hours, b) complete void log, c) bring study medication bottles, void log and medication diary with them.

5 Data and Administrative Forms Procedures

5.1 Acquisition of Forms from the DCC

The CRFs are provided to the Clinical Centers in electronic format as **.pdf** (portable document format) files. The Clinical Center is responsible for printing all data and administrative forms. The forms necessary for each contact are grouped together, in order to streamline the printing process. Each CRF has a code name located in **bold** at the bottom right of the page. Each form is dated at the bottom left corner to identify the version of the CRF. This is important should a form be revised at a later date.

5.2 General Instructions for the Completion of CRFs

The following guidelines are applicable to all CRFs being completed for CPCR N RCT#1:

Two types of forms are used in this study: Data Forms and Administrative Forms:

- Data Forms contain participant data that is entered into the database.
- Administrative Forms are used for processing Data Forms, tracking data flow and in scheduling study procedures and appointments. Administrative Form data is not entered into the database.

The RC should always verify the forms in a packet against the corresponding Visit Checklist to confirm that all forms are available before the participant arrives for a clinic visit, or before a telephone contact is made. The RC will be able to print a copy of any missing forms from the .pdf file. The DCC will make the current version available within the application files.

All CRFs should be completed in **black** ink. Do not use pencil or blue or red ink. Always use participant's initials, not full name. **Print** legibly and clearly. All questions must be answered (all fields completed). Be concise, however, avoid using abbreviations and symbols. **UNK** should be written in any space left unanswered. When the participant is not sure of an answer, he should use his "**best estimate**" rather than leave the question unanswered. It is important that the RC complete the CRF Master Heading **before** continuing with the form to insure easy identification in case of separated pages. Master headings are at the top of each CRF page. The Master Heading elements include: the Participant ID Number, the Participant's Initials, Clinical Center code, Visit Number and Visit Date, and the RC's Identification number. The RC ID number may be completed following form review. Do not write comments in the margins or on the reverse side of the forms. A legible source document **must** exist for all data recorded on the CRF.

Errors should be corrected on the CRFs by crossing out the error with a single line and entering the correct information. *Always* initial and date the change. Circle the correct answer for clarification, if necessary. **Never** use correction fluid.

The RC is responsible for reviewing all of the completed forms. All personal identifying information must be removed from lab or procedure reports prior to forwarding copies to the DCC. All source documentation sent to the DCC must have all personal identifying information obliterated (“blacked out”) and the study identifying information (Participant ID and Participant Initials) should be recorded. Making a photocopy after blacking out the name assures complete confidentiality.

5.3 Time Frame for Completion and Data Entry of CRFs

The time frame for completion and data entry of CRFs is **two (2) weeks** from the date of collection. In the event of a Serious Adverse Event (SAE), all CRFs must be completed and data entered in a timely manner.

5.3.1 *Forms Completion*

In general, the RC completes all CRFs, unless otherwise specified on the form. Upon completion and review of the forms, RC ID will be recorded in the Master Heading, located in the top right-hand corner of each CRF page. The RC should review all forms for legibility, accuracy, and completeness *before* they are entered into the database. The Visit Checklists will assist in documenting the review, entry, and verification process. If the RC identifies an error while reviewing the forms, the error should be corrected on the current form by crossing out the error with a single line in black ink, entering the correct information and initialing and dating the change. The RC should circle the correct answer for clarification, if necessary.

5.3.2 *Participant Completed Forms*

For those forms completed by the participant, the RC will instruct the participant in form use and completion. The RC should be readily available to assist the participant with any questions. If the RC believes that the participant may have difficulty reading the forms, the RC may interview the participant to complete the forms. Since the participant may find some of the information on the forms to be sensitive, whenever possible, the participant should be encouraged to complete the forms alone.

Following careful review of participant completed forms, the RC will complete the RC ID line in the top right corner of the Master Heading. The RC should review the form for completeness and legibility before the participant leaves the clinic, in case additional information or clarification is required.

5.3.3 *Participant Interview Completed Forms*

For those forms completed by the RC through Participant Interview, the RC will collect and record information obtained from direct interview.

In completing the forms, the RC clarifies any participant answer that is unclear or incomplete. The interviewer should have the participant elaborate or reconsider an incomplete or inappropriate answer without leading the participant or influencing the content of the answer; thereby, creating possible bias in his answer.

Some questions addressed in the CRFs are personal and may be considered very sensitive by the participant. When a participant shows reluctance in answering a question, the interviewer should reassure the participant regarding the confidentiality of the response and explain the importance of the question.

5.3.4 Research Coordinator Completed and Principal Investigator Completed Forms

PI completed forms should be completed by the PI or designee. All forms that are completed by the RC or the PI should be completed during the contact unless awaiting a necessary lab report.

The RC should review those forms completed by the PI for completeness and legibility, and complete the RC ID line in the upper right hand corner of the form. The PI should initial the form documenting his/her review.

5.4 Specific Instructions for Completing CRFs

This section provides specific instructions on how to complete each CRF. **Please note the forms are listed alphabetically in their respective categories, either data entry forms or administrative forms.** If, after consulting this section, you are still unsure of how to complete a form, please contact Clinical Data Management at the DCC

Case Report Forms – Data Entry Forms (in alphabetical order by Form Name)	
Form Name	Form Code
Adverse Events and Serious Adverse Events	AE
Concomitant Medication	CMED
NIH – Chronic Prostatitis Symptom Index	CPSI
Demographics	DEMO
Dispensing Log	DISP
Eligibility Checklist	ELIG
Physical Exam	EXAM
Four Glass Test – Cultures	FGTC
Four Glass Test – Microscopy	FGTM
Follow-Up Contacts	FUP
Medical History	MED
Randomization	RAND
Rescue Treatment Event	RMED
Semen Sample	SEMEN
SF – 12	SF12
Study Stop Point	SSTOP

Case Report Forms – Data Entry Forms (in alphabetical order by Form Name)	
Form Name	Form Code
Follow-Up Symptoms	SYM
Treatment Stop Point	TSTOP
Unmasking Record	UNMASK
Uroflow	URO
Voiding Log	VOID

5.4.1 Adverse Events and Serious Adverse Events [AE]

Purpose: To collect information concerning any adverse event(s) (AE) or Serious Adverse Event(s) (SAE) that the participant experiences during the course of the trial.

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

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

When: Visit #3, #4, #5, and #6.
The RC completes a form each time a participant experiences an AE/SAE, either reported during a Phone Contact or Clinic Visit, or if the participant contacts the study personnel to report an AE/SAE, between Phone Contacts or Clinic Visits. A new form is used at each contact/visit. Multiple AE/SAEs can be documented on the same form during a single Phone Contact or a Clinic Visit.

General Directions

The following items are listed in the same order in which they appear on the form. When completing the form, please refer to the answer key on page two of the form.

The **Visit Number** in the top right corner (in the master heading) 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 form is completed between Visit #3 and Visit #4, the Visit Number would be 4).

Adverse Event Number (AE#): This is a sequential number which begins with '001', '002', '003', etc. This number only repeats during the study if the event being recorded is a continuation of an event previously recorded.

Event Code: Identify the Event Code number by referring to the coded list of CTC.

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 a condition that began prior to study entry, mark (X) in the box.

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.

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

Frequency: Using the code provided in the column, record the frequency of the episodes.

Relationship to Study Drugs: The PI will determine, whether the AE/SAE was related to the study medications, using the codes provided in the column.

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

Outcome: Record the outcome using the codes provided in the column based on the details of the AE/SAE. Codes with an asterisk to the left of the number are SAEs. Please follow the instructions in *Participant Safety section 3.2.4* for recording and reporting SAEs.

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 has not yet been resolved, mark (X) in the box, instead of entering a date.

Was the Event Serious?: If the *Outcome* meets the SAE criteria (as outlined in section 3.2.3) and is marked with an asterisk, the event is serious. 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 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 “ ”.

When recording a new AE/SAE, complete the entire 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.

**C
P
C
R
N** **Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

List all adverse events that have newly occurred, changed, or resolved.

ii. Were there any new adverse events, or follow-ups to adverse events from this previous visit, reported by the patient at this visit? <input type="checkbox"/> Yes <input type="checkbox"/> No												
If YES, list the number of (S)AEs to be recorded at this visit: _____												
Adverse Event Number	Event Code	Date of Onset <small>Mark box if AE is continuing from a previous visit</small>	Grade	Duration	Frequency	Relationship to Study Drug?	Actions taken regarding study drug?	Treatment for event?	Outcome	Date of Resolution <small>Enter date OR check box if AE is continuing</small>	Was this event serious?	
AE #	From CTX List	mm/dd/yyyy	record one	record one	record one	record one	record one	record one	record one	record one or appropriate	mm/dd/yyyy	record one
_____	_____	____/____/____									____/____/____	
Specify Break (CTC Criteria)					Description of Event/Comments							
_____	_____	____/____/____									____/____/____	
Specify Break (CTC Criteria)					Description of Event/Comments							
_____	_____	____/____/____									____/____/____	
Specify Break (CTC Criteria)					Description of Event/Comments							
_____	_____	____/____/____									____/____/____	
Specify Break (CTC Criteria)					Description of Event/Comments							
_____	_____	____/____/____									____/____/____	
Specify Break (CTC Criteria)					Description of Event/Comments							

Investigator's Signature: _____

Date of Signature: ____/____/____ PI ID: _____

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AE

**C
P
C
R
N** **Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

Key:

<u>Grade:</u>	<u>Duration:</u>	<u>Frequency:</u>	<u>Relationship to subject?</u>	<u>Action taken concerning study drug?</u>	<u>Treatment for system?</u>	<u>Outcome:</u>	<u>Was the event serious?</u>
0= None	1= Minutes	1= Once	1= Not Related	0= None	1= Yes	1= Resolved/No follow-up needed	1= Yes
1= Mild	2= Hours	2= 2 or 3 Episodes	2= Possibly Related	1= Drug Interrupted	0= No	2= On-going treatment continued	0= No
2= Moderate	3= Days	3= 4 or more Episodes	3= Definitely Related	2= Drug Discontinued		3= ER Visit/prolonged hospitalization	
3= Severe	BB= UNK	4= Daily	BB= Unknown*	BB= N/A		4= Resulted in persistent or significant disability/incapacity	
4= Life-threatening or Disabling						5= Congenital anomaly	
5= Fatal						6= Life-threatening	
BB= UNK						7= Fatal	

*Indicates Serious Adverse Events
Outcome of Serious is based on PI's judgement

SAE Contact Information: (Notify the following within 24 hours of knowledge of event)

1. On-Site Investigator
2. Clinical Center IRB
3. DCC -- Phone: (215) 573-6318
Fax: (215) 573-6262

5.4.1.1 Continuing Adverse Events

All continuing AE's should be recorded at each visit until they are resolved.

When reporting an ongoing recorded event, use the same 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 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 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. The description should indicate this is a resolution of a previously recorded AE/SAE, along with any other information the RC believes is critical.

If a previously recorded event still exists, but has changed in grade, the event should be treated as a new event, and the original event should be resolved.

5.4.1.2 Serious Adverse Events Notification Procedure

For all Serious Adverse Events, the RC will notify the On-Site Investigator who will assess and confirm adverse event seriousness according to Outcomes Categories 3 through 7.

The On-Site Investigator will notify his/her local IRB, according to established procedures, as well as the DCC at The University of Pennsylvania (UPenn) within twenty-four (24) hours of first knowledge.

The telephone and fax numbers for the DCC contacts are listed on the Adverse Events/Serious Adverse Events [AE] form.

In addition to completing/faxing the Adverse Events/Serious Adverse Events [AE] form to the DCC, the RC will also complete and fax a **MedWatch 3500** form.

5.4.1.3 MedWatch 3500 Form

MedWatch 3500 forms are provided by the FDA to facilitate Serious Adverse Event reporting. The **MedWatch 3500** form copy included in *Appendix H* may be duplicated for event reporting purposes. Further information about the **MedWatch 3500** form and Serious Adverse Event reporting is available on-line at <http://www.fda.gov/medwatch/report/desk/advevnt.htm>. Hard copies may also be printed from the web site for eventual completion and submission to the DCC.

A **MedWatch 3500** form must be completed and faxed to the DCC within twenty-four (24) hours of the RC or Investigator's first knowledge of the serious adverse event. This means that two forms are to be completed when a Serious Adverse Event has occurred: the Adverse Events/Serious Adverse Events [AE] form and the **MedWatch 3500** form.

5.4.2 Concomitant Medication [CMED]

Purpose: Concomitant refers to other medications/supplements/vitamins that are taken concurrently or at the same time as the study drug. This form will document and track all medications taken at entry and during the course of the study. Medication refers to any prescription or non-prescription drugs, any over-the-counter (OTC) drugs, vitamins and nutritional supplements or herbal remedies. Document the names, dosages and frequencies of other medications the participant is taking and include them in your listing.

Who: The RC completes this form based on the participant's interview and the participant's completed Medication Diary [DAIRY] form.

When: Visit #2 and #4

General Directions

The information on this form is obtained from the participant's interview and the participant's completed Medication Diary [DAIRY] form and is used to track all concomitant medications being used during the course of the study. Starting at Visit #2, the participant records all medications being used, any new medications started, dosage changes and any medications stopped at any time up to Visit #4.

Line #: This is a sequential number which begins with '001', '002', '003', etc. This number only repeats during the study if the medication being recorded is a continuation of a medication previously recorded.

Drug Code#: This is the code that has been obtained from the Medication Reference Tool in the database system.

Drug Name: The drug name, as recorded on the Medication Diary [DAIRY].

Total Daily Dose: Using the Medication Diary [DAIRY], the RC should multiply the *Strength of each dose* by the *Total Number of Doses per 24 Hours*.

Unit: Select the *most specific response* possible, based on the information obtained from the DAIRY.

Route: Select the *most specific response* possible, based on the information obtained from the DAIRY.

5.4.3 NIH-CPSI [CPSI]

Purpose: To collect information regarding the participant's symptoms of chronic prostatitis.

Who: Participant completed after RC explains purpose and how to complete form.

When: Visits #1, #2, #3, #4, #5 and #6, and at time of first rescue medication event or early treatment discontinuation, if applicable.

General Directions

Participant completes questions #1 through #9. The RC calculates overall score based on patient's responses and records at the bottom of page 2.

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Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

NIH - CHRONIC PROSTATITIS SYMPTOM INDEX

Today's Date: ____/____/____

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?
 - a. Area between rectum and testicles (perineum) ☐₁ Yes ☐₀ No
 - b. Testicles ☐₁ Yes ☐₀ No
 - c. Tip of the penis (not related to urination) ☐₁ Yes ☐₀ No
 - d. Below your waist, in your pubic or bladder area ☐₁ Yes ☐₀ No

2. In the last week, have you experienced:
 - a. Pain or burning during urination? ☐₁ Yes ☐₀ No
 - b. Pain or discomfort during or after sexual climax (ejaculation)? ☐₁ Yes ☐₀ No

3. How often have you had pain or discomfort in any of these areas over the last week?

☐₀ Never
☐₁ Rarely
☐₂ Sometimes
☐₃ Often
☐₄ Usually
☐₅ Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

☐₀ ☐₁ ☐₂ ☐₃ ☐₄ ☐₅ ☐₆ ☐₇ ☐₈ ☐₉ ☐₁₀

No Pain Pain as bad as you can imagine

**C
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Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____ / ____ / ____
RC ID: _____

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?
- ☐ 0 Not at all
☐ 1 Less than 1 time in 5
☐ 2 Less than half the time
☐ 3 About half the time
☐ 4 More than half the time
☐ 5 Almost always
6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?
- ☐ 0 Not at all
☐ 1 Less than 1 time in 5
☐ 2 Less than half the time
☐ 3 About half the time
☐ 4 More than half the time
☐ 5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?
- ☐ 0 None
☐ 1 Only a little
☐ 2 Some
☐ 3 A lot
8. How much did you think about your symptoms, over the last week?
- ☐ 0 None
☐ 1 Only a little
☐ 2 Some
☐ 3 A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?
- ☐ 0 Delighted
☐ 1 Pleased
☐ 2 Mostly satisfied
☐ 3 Mixed (about equally satisfied and dissatisfied)
☐ 4 Mostly dissatisfied
☐ 5 Unhappy
☐ 6 Terrible

To be completed by the RC:

Overall Score: _____
(Sum of #1 - 9)

5.4.4 Demographics [DEMO]

Purpose: To collect demographic data on a participant

Who: Participant and RC completed

When: Visit #2 – second screening visit

General Directions

Participant should complete questions #1 through #7; RC should complete question #8.

Qx #4: A partner can be someone of the same sex.

Qx #8: To be completed by the RC to allow the CPCRn RCT#1 data to be linked to the CPC data.

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/_____
RC ID: _____

DEMOGRAPHICS

To be completed by the study participant...

1. What is your date of birth? _____ / _____ / _____
2. How do you describe yourself?
 - ☐ ₁ Asian or Pacific Islander
 - ☐ ₂ Black/African-American (not Latino/Hispanic)
 - ☐ ₃ Latino/Hispanic/Mexican-American
 - ☐ ₄ Native American
 - ☐ ₅ White/Caucasian (not Latino/Hispanic)
 - ☐ ₆ Multiracial
 - ☐ ₇ Other
3. What is the highest educational level you have attained?
 - ☐ ₁ Less than high school
 - ☐ ₂ High school or GED
 - ☐ ₃ Some college/university
 - ☐ ₄ Graduated from college/university
 - ☐ ₅ Graduate or professional school after college/university
4. Are you currently living with a spouse or partner?
 - ☐ ₁ Yes
 - ☐ ₀ No
5. What is your current employment status?
 - ☐ ₁ Employed
 - ☐ ₂ Unemployed
 - ☐ ₃ Retired
 - ☐ ₄ Disabled
 - ☐ ₅ Homemaker
6. What is your ZIP (US) or Postal (Canadian) code?
 - a. ZIP Code (for US Residents) _____
 - b. Postal Code (for Canadian Residents) _____

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

7. How were you referred to the CPCR clinical trial?
- ☐ ₁ Urologist for this study
☐ ₂ Other urologist
☐ ₃ Other non-urology physician
☐ ₄ Newspaper
☐ ₅ Internet
☐ ₆ Other

To be completed by the RC...

8. Is the participant enrolled in the Chronic Prostatitis Cohort (CPC) Study?
If **Yes**,
- a. Participant's CPC Patient ID _____
- b. Participant's initials _____
- ☐ ₁ Yes
☐ ₀ No

5.4.5 Dispensing Log [DISP]

Purpose: To record study medications dispensed to a participant

Who: RC completed

When: Visit #2 – second screening visit

General Directions

The number of pills dispensed for both study medications should correspond to the number recorded on the Study Medication Tracking Log [**TRACK**] form.

The labels from both bottles of study medications should be removed from the bottles and affixed to the appropriate place on the form. The RC dispensing the medications should sign both labels.

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

DISPENSING LOG

1. Date *CIPRO*® capsules dispensed: ____/____/____
2. Total number of *CIPRO*® capsules dispensed: _____
(Record on Study Medication Tracking Log)

Affix and sign the drug label for the *CIPRO*® capsules here
Record on Study Medication Tracking Log

-
-
3. Date *Flomax*® capsules dispensed: ____/____/____
 4. Total number of *Flomax*® capsules dispensed: _____
(Record on Study Medication Tracking Log)

Affix and sign the drug label for the *Flomax*® capsules here
Record on Study Medication Tracking Log

NOTE: By signing the labels here, you are confirming that you have:

1. checked the label on the bottle with the randomization number on the Randomization form, and
2. confirmed that the drug is being given to the participant with the ID number written on this form.

5.4.6 Eligibility Checklist [ELIG]

Purpose: This four-page form establishes Participant eligibility. All Inclusion Criteria responses must be “Yes” to be eligible for enrollment. All exclusion/deferral responses must be “No” for the participant to be eligible for enrollment.

Who: RC completed

When: Visit #1 – first screening visit

General Directions

The RC can review these criteria with a potential participant prior to screening to prevent him from making an unnecessary trip to the clinic.

All information should be verified by reviewing the participant’s medical records.

If any Deferral criteria are answered “YES”, indicate the date the participant will be eligible for re-screening on page 4.

Qx #4: This question is obtained from the NIH-CPSI [**CPSI**] form completed by participant. The participant should **not** be told what the specific criteria are for pain and overall scores for eligibility.

Qx #6: Irritable bowel disease is not an exclusion criterion.

Qx #11: A urethral stricture is judged to be active if the participant has had a urethral dilatation in the past six months.

Qx #16: see *Appendix D Drug Product Insert*.

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

ELIGIBILITY CHECKLIST

Inclusion Criteria

1. ***Participant has signed and dated the appropriate Informed Consent document.*** ☐₁ Yes ☐₀ No
 a. If **Yes**, record the date the form was signed. ____/____/____
2. Participant is a male. ☐₁ Yes ☐₀ No
3. Participant must have had symptoms of discomfort or pain in the pelvic region for at least a three (3) month period within the last six (6) months. ☐₁ Yes ☐₀ No
4. Participant has at least a moderate overall score on the NIH-CPSI (overall score ≥ 15 out of a potential of 0 - 43 points). ☐₁ Yes ☐₀ No

ALL INCLUSION CRITERIA RESPONSES MUST BE "YES" FOR THE PARTICIPANT TO BE ELIGIBLE FOR ENROLLMENT

Exclusion Criteria

5. Participant has a history of prostate, bladder, or urethral cancer. ☐₁ Yes ☐₀ No
6. Participant has inflammatory bowel disease (such as Crohn's disease or ulcerative colitis, but not irritable bowel syndrome). ☐₁ Yes ☐₀ No
7. Participant has undergone pelvic radiation or systemic chemotherapy. ☐₁ Yes ☐₀ No
8. Participant has undergone intravesical chemotherapy. ☐₁ Yes ☐₀ No
9. Participant has been treated with intravesical BCG. ☐₁ Yes ☐₀ No

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

- | | | |
|-----|---|--|
| 10. | Participant has been treated for unilateral orchialgia without pelvic symptoms. | <input type="checkbox"/> ₁ Yes <input type="checkbox"/> ₀ No |
| 11. | Participant has an active urethral stricture. | <input type="checkbox"/> ₁ Yes <input type="checkbox"/> ₀ No |
| 12. | Participant has a neurological disease or disorder affecting the bladder. | <input type="checkbox"/> ₁ Yes <input type="checkbox"/> ₀ No |
| 13. | Participant has undergone TURP, TUIP, TUIBN, TUMT, TUNA, balloon dilatation of the prostate, open prostatectomy, or any other prostate surgery or treatment such as cryotherapy or thermal therapy. | <input type="checkbox"/> ₁ Yes <input type="checkbox"/> ₀ No |
| 14. | Participant has a neurological impairment or psychiatric disorder preventing his understanding of consent and his ability to comply with the protocol. | <input type="checkbox"/> ₁ Yes <input type="checkbox"/> ₀ No |
| 15. | Participant has liver disease. | <input type="checkbox"/> ₁ Yes <input type="checkbox"/> ₀ No |
| 16. | Participant has a known allergy or sensitivity to ciprofloxacin hydrochloride (CIPRO®), tamsulosin hydrochloride (Flomax®), or any of their known components. | <input type="checkbox"/> ₁ Yes <input type="checkbox"/> ₀ No |
| 17. | Participant has a history of seizure disorder. | <input type="checkbox"/> ₁ Yes <input type="checkbox"/> ₀ No |
| 18. | Participant is taking theophylline. | <input type="checkbox"/> ₁ Yes <input type="checkbox"/> ₀ No |
| 19. | Participant requires ongoing use of magnesium, aluminum, or calcium-containing antacids. | <input type="checkbox"/> ₁ Yes <input type="checkbox"/> ₀ No |

<p>ALL EXCLUSION CRITERIA RESPONSES MUST BE "<u>NO</u>" FOR THE PARTICIPANT TO BE ELIGIBLE FOR ENROLLMENT</p>
--

**Randomized
Clinical
Trial #1**Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____**Deferral Criteria**

20. Participant has been treated with tamsulosin hydrochloride (Flomax®), doxazosin mesylate (Cardura®), terazosin HCL (Hytrin®), or alpha-blockers in the past four (4) weeks. ☐₁ Yes ☐₀ No
21. Participant has been treated with ciprofloxacin hydrochloride (CIPRO®) in the past four (4) weeks. ☐₁ Yes ☐₀ No
22. Participant has been treated with antimicrobial agents (oral or parenteral) in the past four (4) weeks. ☐₁ Yes ☐₀ No
23. Participant has started, stopped, or changed dose level for **ANY** prostatitis-specific medications within the past four (4) weeks. ☐₁ Yes ☐₀ No
24. Participant has had a urinary tract infection, with a urine culture value of >100,000 CFU/ml in the past three (3) months. ☐₁ Yes ☐₀ No
25. Participant has had clinical evidence of urethritis, e.g. including urethral discharge or positive culture, within the past three (3) months, diagnostic of the following sexually transmitted diseases (STDs): gonorrhea, chlamydia, mycoplasma or trichomonas, but not including HIV/AIDS. ☐₁ Yes ☐₀ No
26. Participant has had a prostate biopsy in the past three (3) months. ☐₁ Yes ☐₀ No
27. Participant has experienced symptoms of acute or chronic epididymitis within the past three (3) months. ☐₁ Yes ☐₀ No
28. Participant has begun finasteride (Proscar®) or other androgen hormone inhibitors in the past six (6) months, or stopped finasteride (Proscar®) or other androgen hormone inhibitors within the past six (6) months. ☐₁ Yes ☐₀ No
29. Participant has used bioflavonoid agents in the past two (2) weeks. [Example: Quercetin] ☐₁ Yes ☐₀ No

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/_____
RC ID: _____

30. Participant has been diagnosed with or treated for symptomatic genital herpes in the past twelve (12) months. ☐ Yes ☐ No
31. Participant has been taking zinc or iron supplements within the past two (2) weeks. ☐ Yes ☐ No
32. Participant has been treated with cimetidine in the past two (2) weeks. ☐ Yes ☐ No

⇒ **ALL DEFERRAL CRITERIA RESPONSES MUST BE "NO" FOR THE PARTICIPANT TO BE ELIGIBLE FOR ENROLLMENT.**

⇒ **IF ANY RESPONSES TO THE DEFERRAL CRITERIA ARE "YES" INDICATE DATE PARTICIPANT WILL BECOME ELIGIBLE FOR RE-SCREENING.**

DATE: ____/____/____ (mm/dd/yyyy)

5.4.7 Physical Exam [EXAM]

Purpose: To obtain information about the participant's study specific health status through a physical examination of abdominal and genitourinary systems.

Who: Investigator completed or his/her approved designee. The PI (or designee) performing the examination **must** sign and date the Physical Exam form. Prior to data entry, the RC should review this form for completeness.

When: Visit #1 – first screening visit and Visit #4 clinic visit.

General Directions

Qx #1: Height is only completed at Visit #1.

Qx #1 and #2: It is *preferable* that height and weight be measured without shoes.

**Randomized
Clinical
Trial #1**Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

PHYSICAL EXAM

1. Height *(to be completed at screening only)*
Enter either inches or cm. _____ . ____ inches
_____ . ____ cm
2. Weight
Enter either lbs. or kgs. _____ . ____ lbs
_____ . ____ kgs
3. Blood Pressure
_____ systolic (mmHg)
_____ diastolic (mmHg)
4. Abdomen
☐₁ Normal
☐₂ Mass
☐₃ Organomegaly
a. Abdominal tenderness ☐₁ Yes ☐₀ No
5. Flanks
☐₁ Normal
☐₂ Mass
a. Flank tenderness ☐₁ Yes ☐₀ No
6. Varicocele
☐₀ Absent
☐₁ Present
a. Varicocele tenderness ☐₁ Yes ☐₀ No
7. Hydrocele
☐₀ Absent
☐₁ Present
a. Hydrocele tenderness ☐₁ Yes ☐₀ No
8. Inguinal Hernia
☐₀ Absent
☐₁ Present
a. Inguinal hernial tenderness ☐₁ Yes ☐₀ No

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Clinical
Trial #1**

Participant ID: _____
 Participant Initials: _____
 Clinical Center: _____
 Visit Number: _____
 Visit Date: ____/____/_____
 RC ID: _____

Genitalia

14. Foreskin ☐₀ Absent
☐₁ Normal
☐₂ Abnormal
15. Glans ☐₁ Normal
☐₂ Abnormal
16. Epididymes ☐₁ Normal
☐₂ Abnormal
- a. Epididymal tenderness ☐₁ Yes ☐₀ No
17. Testes ☐₁ Normal
☐₂ Abnormal
- a. Testicular tenderness ☐₁ Yes ☐₀ No

Examiner's Signature: _____

Date of Signature: ____/____/_____
 PI ID: _____

**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

9. Is there any tenderness in the following areas?

- | | | |
|---------------------------------------|---|--|
| a. Coccyx | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| b. Pubis | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| c. Suprapubic area | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| d. External pelvic floor (perineum) | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| e. Internal pelvic floor (side walls) | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| f. Cord/inguinal area | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |

Prostate Exam

- | | |
|--|---|
| 10. Size | <input type="checkbox"/> ₁ Normal
<input type="checkbox"/> ₂ Enlarged
<input type="checkbox"/> _{gg} Not done |
| 11. Consistency | <input type="checkbox"/> ₁ Normal
<input type="checkbox"/> ₂ Firm
<input type="checkbox"/> ₃ Soft
<input type="checkbox"/> _{gg} Not done |
| 12. Nodularity, irregularity, or asymmetry | <input type="checkbox"/> ₁ Yes <input type="checkbox"/> ₀ No
<input type="checkbox"/> _{gg} Not done |
| 13. Prostatic tenderness | <input type="checkbox"/> ₁ Yes <input type="checkbox"/> ₀ No
<input type="checkbox"/> _{gg} Not done |

5.4.8 Four Glass Test – Cultures [FGTC]

Purpose: To collect culture data on the four samples taken during the four glass test (VB1, VB2, EPS, and VB3).

Who: RC completed, based on lab reports

When: Visit #1 – first screening visit and Visit #4 clinic visit

General Directions

The participant should be reminded to remain abstinent for 48 hours prior to the four-glass test.

The RC will complete this form based on availability of the clinic's lab report. The VB2 sample culture is measured at 48 hours and 5 days. All other four-glass test sample cultures are measured at 5 days. The culture count is measured in CFU/mL.

Species Code table: This table contains the codes for each species to be identified in the lab report.

Was there any growth?: For each four glass test sample (i.e. VB1, etc.), if 'No growth' is indicated, the culture data does not need to be completed. (Note: for EPS sample, mark 'Not done' if a sample was collected, but there was not enough for the culture after the microscopy.)

Culture count tables: If growth was identified, enter the total number of different species you are reporting and complete the culture count table as follows:

- *Species code:* to be taken from the Species Code table. Each species identified on the lab report should be recorded separately.
- *<100,000 or ≥ 100,000 CFU/mL:* check the appropriate box according to the count listed on the lab report.
- *If <100,000, please enter actual count:* If the count is less than 100,000 CFU/mL, then enter the exact count as it is listed on the lab report.

NOTE: For VB2, if there is any culture count $\geq 100,000$ CFU/mL, the participant is ineligible.

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/_____
RC ID: _____

FOUR GLASS TEST - CULTURES

1. Date of participant's Four Glass Test ____/____/____

The table below lists the species to be identified in each sample, and each species's appropriate code. Use these codes when completing the tables for the culture count for each four glass test sample.

Species	Species Code
Staphylococcus Epidermidis	01
Staphylococcus Aureus	02
Staphylococcus Other	03
Streptococcus Viridans	04
Staphylococcus Hemolyticus	05
Streptococcus Other	06
Enterococcus Fecalis	07
Corynebacterium	08
Escherichia Coli	09
Klebsiella	10
Pseudomonas	11
Proteus	12
Other	13

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Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/_____
RC ID: _____

48 Hour Culture Count

2. Date of 48 hour count _____/_____/_____

VB2 - 48 hours

3. Was there any growth? ☐ Yes ☐ No

If **Yes**, please complete the chart below, indicating what specimens were present, and the culture count measured in CFU/ml: **Enter total number of species recorded:** ____

Species Code	< 100,000 OR ≥ 100,000	If < 100,000, please enter actual count
_____	<input type="checkbox"/> <100,000 <input type="checkbox"/> ≥100,000	_____, _____ CFU/ml
_____	<input type="checkbox"/> <100,000 <input type="checkbox"/> ≥100,000	_____, _____ CFU/ml
_____	<input type="checkbox"/> <100,000 <input type="checkbox"/> ≥100,000	_____, _____ CFU/ml
_____	<input type="checkbox"/> <100,000 <input type="checkbox"/> ≥100,000	_____, _____ CFU/ml

5 Days Culture Count

4. Date of 5 day count _____/_____/_____

VB1 - 5 Days

5. Was there any growth? ☐ Yes ☐ No

If **Yes**, please complete the chart below, indicating what species were present, and the culture count measured in CFU/ml: **Enter total number of species recorded:** ____

Species Code	< 100,000 OR ≥ 100,000	If < 100,000, please enter actual count
_____	<input type="checkbox"/> <100,000 <input type="checkbox"/> ≥100,000	_____, _____ CFU/ml
_____	<input type="checkbox"/> <100,000 <input type="checkbox"/> ≥100,000	_____, _____ CFU/ml
_____	<input type="checkbox"/> <100,000 <input type="checkbox"/> ≥100,000	_____, _____ CFU/ml
_____	<input type="checkbox"/> <100,000 <input type="checkbox"/> ≥100,000	_____, _____ CFU/ml

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Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/_____
RC ID: _____

VB2 - 5 Days

6. Was there any growth? ☐₁ Yes ☐₀ No

If **Yes**, please complete the chart below, indicating what species were present, and the culture count measured in CFU/ml: **Enter total number of species recorded:** ____

Species Code	< 100,000 OR ≥ 100,000	If < 100,000, please enter actual count
_____	<input type="checkbox"/> ₀ <100,000 <input type="checkbox"/> ₁ ≥100,000	_____, _____ CFU/ml
_____	<input type="checkbox"/> ₀ <100,000 <input type="checkbox"/> ₁ ≥100,000	_____, _____ CFU/ml
_____	<input type="checkbox"/> ₀ <100,000 <input type="checkbox"/> ₁ ≥100,000	_____, _____ CFU/ml
_____	<input type="checkbox"/> ₀ <100,000 <input type="checkbox"/> ₁ ≥100,000	_____, _____ CFU/ml

NOTE: If there is a culture count ≥100,000 for VB2, the participant is ineligible for this CPRN trial.

EPS - 5 Days

7. Was the participant able to provide an EPS sample? ☐₁ Yes ☐₀ No

If **Yes**, continue on to question #8.
If **No**, go to question #9.

8. Was there any growth? ☐₁ Yes ☐₀ No ☐₉₉ Not done

If **Yes**, please complete the chart below, indicating what species were present, and the culture count measured in CFU/ml: **Enter total number of species recorded:** ____

Species Code	< 100,000 OR ≥ 100,000	If < 100,000, please enter actual count
_____	<input type="checkbox"/> ₀ <100,000 <input type="checkbox"/> ₁ ≥100,000	_____, _____ CFU/ml
_____	<input type="checkbox"/> ₀ <100,000 <input type="checkbox"/> ₁ ≥100,000	_____, _____ CFU/ml
_____	<input type="checkbox"/> ₀ <100,000 <input type="checkbox"/> ₁ ≥100,000	_____, _____ CFU/ml
_____	<input type="checkbox"/> ₀ <100,000 <input type="checkbox"/> ₁ ≥100,000	_____, _____ CFU/ml

**C
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Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

VB3 - 5 Days

9. Was a VB3 sample collected? ☐ _L Yes ☐ _G No

If **Yes**, continue on to question #10.

10. Was there any growth? ☐ _L Yes ☐ _G No

If **Yes**, please complete the chart below, indicating what species were present, and the culture count measured in CFU/ml: **Enter total number of species recorded:** ____

Species Code	< 100,000 OR ≥ 100,000	If < 100,000, please enter actual count
_____	<input type="checkbox"/> _G <100,000 <input type="checkbox"/> _L ≥100,000	____, ____ CFU/ml
_____	<input type="checkbox"/> _G <100,000 <input type="checkbox"/> _L ≥100,000	____, ____ CFU/ml
_____	<input type="checkbox"/> _G <100,000 <input type="checkbox"/> _L ≥100,000	____, ____ CFU/ml
_____	<input type="checkbox"/> _G <100,000 <input type="checkbox"/> _L ≥100,000	____, ____ CFU/ml

5.4.9 Four Glass Test – Microscopy [FGTM]

Purpose: To collect microscopy data on the four samples taken during the four glass test (VB1, VB2, EPS, and VB3).

Who: RC completed, based on lab reports

When: Visit #1 – first screening visit and Visit #4 clinic visit.

General Directions

The participant should be reminded to remain abstinent for 48 hours prior to the four-glass test.

The RC will complete this form based on the clinic's lab report. If reported cell counts are less than 25, indicate actual count.

Qx #9 through #11 are obtained from the dipstick.

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

FOUR GLASS TEST - MICROSCOPY

1. Date of participant's Four Glass Test ____/____/____
 2. Has the participant remained abstinent for the past 48 hours? ☐ Yes ☐ No
-

VB1

3. White Blood Cell Count (/hpf)
☐ ≤ 25
☐ > 25
If ≤ 25 , give actual count ____ /hpf
4. Red Blood Cell Count (/hpf)
☐ ≤ 25
☐ > 25
If ≤ 25 , give actual count ____ /hpf
5. Yeast
☐ Absent
☐ Present

**C
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Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

VB2

- | | | |
|-----|-------------------------------|---|
| 6. | White Blood Cell Count (/hpf) | <input type="checkbox"/> ₀ ≤ 25
<input type="checkbox"/> ₁ > 25

If ≤ 25 , give actual count _____ /hpf |
| 7. | Red Blood Cell Count (/hpf) | <input type="checkbox"/> ₀ ≤ 25
<input type="checkbox"/> ₁ > 25

If ≤ 25 , give actual count _____ /hpf |
| 8. | Yeast | <input type="checkbox"/> ₀ Absent
<input type="checkbox"/> ₁ Present |
| 9. | pH | <input type="checkbox"/> ₁ 5.0
<input type="checkbox"/> ₂ 5.5
<input type="checkbox"/> ₃ 6.0
<input type="checkbox"/> ₄ 6.5
<input type="checkbox"/> ₅ 7.0
<input type="checkbox"/> ₆ 7.5
<input type="checkbox"/> ₇ 8.0 |
| 10. | Glucose (mg/dl) | <input type="checkbox"/> ₁ 0
<input type="checkbox"/> ₂ 100
<input type="checkbox"/> ₃ 250
<input type="checkbox"/> ₄ 500
<input type="checkbox"/> ₅ 1000
<input type="checkbox"/> ₆ 2000 |
| 11. | Protein (mg/dl) | <input type="checkbox"/> ₁ Negative
<input type="checkbox"/> ₂ Trace
<input type="checkbox"/> ₃ 30 (+)
<input type="checkbox"/> ₄ 100 (++)
<input type="checkbox"/> ₅ 300 (+++)
<input type="checkbox"/> ₆ ≥ 2000 (+++++) |

**Randomized
Clinical
Trial #1**Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/_____
RC ID: _____**EPS**

12. Estimated volume of EPS sample

☐₁ None
☐₂ 1 to 2 drops
☐₃ 3 or more dropsIf **None**, go directly to question #20.

13. White Blood Cell Count (/hpf)

☐₁ ≤ 25
☐₂ 26 - 50
☐₃ 51-75
☐₄ 76-100
☐₅ >100
____ /hpfIf ≤ **25**, give actual count

14. Macrophage

☐₀ Absent
☐₁ Present
____ /hpfIf **Present**, give actual count

15. Red Blood Cells

☐₀ Absent
☐₁ Present

16. Yeast

☐₀ Absent
☐₁ Present

17. Sperm

☐₀ Absent
☐₁ Present

18. Was there any remaining EPS sample sent to lab for storage?

☐₁ Yes ☐₀ NoIf **Yes**, date EPS sample sent to lab for storage ____/____/____

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

VB3

19. Was a VB3 sample collected? ☐₁ Yes ☐₀ No
If **Yes**, continue,
20. White Blood Cell Count (/hpf) ☐₀ ≤ 25
☐₁ > 25
If ≤ **25**, give actual count _____ /hpf
21. Red Blood Cell Count (/hpf) ☐₀ ≤ 25
☐₁ > 25
If ≤ **25**, give actual count _____ /hpf
22. Yeast ☐₀ Absent
☐₁ Present
23. Prostate fluid form elements (e.g. fat bodies) ☐₀ Absent
☐₁ Present

5.4.10 Follow-Up Contacts [FUP]

Purpose: To collect information through telephone or clinic contact regarding study treatment, adverse events or changes in non-study medications.

To report the new onset of symptoms and/or changes in previously reported symptoms. To elicit information about unexpected or untoward experiences; noting that any serious or non-serious adverse drug event will be documented on the appropriate Adverse Events/Serious Adverse Events [AE] (and **MedWatch 3500** form, if applicable) form.

To discuss the participant's medication diary noting any changes and/or additions to the medication regimen including prescription and non-prescription drugs, vitamins and/or herbal/food supplements that are currently being taken or have been started since last contact (document on the Concomitant Medication [CMED] form).

To collect information regarding study medication usage and to compute a percentage representing compliance.

Who: RC completed form with information received from the participant.

When: Visit #3, #4, #5 and #6

General Directions

- Visit 3 – three week telephone call: complete question #1 only.
- Visit 4 – six week clinic visit: complete questions #1 through #4
- Visit 5 – nine week telephone call: complete question #1 only.
- Visit 6 – twelve week telephone call: complete question #1 only.

Qx #1: This question prompts the participant to communicate any adverse events or other medical problems that have occurred since the last visit. If the response is **Yes**, then AE/SAE must be recorded on the Adverse Events/Serious Adverse Events [AE] form.

Qx #3: This question prompts the RC to review any non-study medication the participant may have taken since their last contact. If the response is **Yes**, then the medication must be recorded on the Concomitant Medications [CMED] form. If the patient reports the use of an exclusionary medication, then they should be discontinued from the study immediately.

Qx. #4: *This question is completed at Visit #4 only.*

- In box A, document the amount of the drug dispensed.

- In box B, the amount returned; and, in box C, the amount reported lost or destroyed.
- In box D, document the amount used ($A - (B + C) = D$).
- *Note that by adding the amounts in boxes B and C and subtracting that total from the amount in box A you will have the answer for box D.
- In box E, document the amount that should have been used.
- In box F, calculate percent compliance by dividing the amount in box D by the amount in Box E and multiplying that result by 100.

**C
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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

FOLLOW-UP CONTACTS

To be completed at all visits (all phone contacts and clinic visits):

1. Since your last contact, have you had any medical problems? ☐ ₁ Yes ☐ ₀ No
(Includes adverse experiences, abnormal laboratory values, hospitalizations, discontinued medications due to adverse events, other complications, or pre-existing conditions that have worsened)

⇒ If **Yes**, an Adverse Event must be reported/recorded on the EVENT form

To be completed at Visit 4 (6 week clinic visit):

2. Are you still taking the study medications? ☐ ₁ Yes ☐ ₀ No
3. Since your last contact, have you taken any concomitant medications? ☐ ₁ Yes ☐ ₀ No

⇒ If **Yes**, the medication must be reported/recorded on the Concomitant Medications form. (Refer to the Exclusionary Medication list in the MOP. Patients who have taken exclusionary meds must be taken off of the study medication.)

4. Compliance:

Capsules dispensed at the last visit (A)	Amount Returned (B)	Amount lost/destroyed (C)	Capsules Used A-(B+C) (D)	Amount that should have been used (E)	Percent Compliance (D/E) x 100 (F)
<i>CIPRO</i> ® Capules: _____	_____	_____	_____	_____	_____
<i>Flomax</i> ® Capules: _____	_____	_____	_____	_____	_____

5.4.11 Medical History [MED]

Purpose: To obtain information about the participant's history of prostatitis and general medical history.

Who: RC completes form with information obtained from participant interview

When: Visit #1 – first screening visit

General Directions

Qx #1 and #2: If the participant does not recall the exact month, ask the participant to make a best guess.

**C
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Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/_____
RC ID: _____

MEDICAL HISTORY

Prostatitis History

1. Do you know when your first episode of prostatitis was diagnosed? ☐ ₁ Yes ☐ ₀ No
If **Yes**, when was it diagnosed? ____/____/_____
(month / year)
2. Do you know when your current episode of prostatitis was diagnosed? ☐ ₁ Yes ☐ ₀ No
If **Yes**, when was it diagnosed? ____/____/_____
(month / year)
3. Have you ever had a prostate biopsy? ☐ ₁ Yes ☐ ₀ No ☐ ₈₈ Unknown
4. Have you ever had a bladder biopsy? ☐ ₁ Yes ☐ ₀ No ☐ ₈₈ Unknown

General Medical History

Have you ever had, or do you currently have a history of any of the following?

5. Cardiovascular disease ☐ ₁ Yes ☐ ₀ No ☐ ₈₈ Unknown
6. Gastrointestinal disease
 - a. Irritable bowel syndrome ☐ ₁ Yes ☐ ₀ No ☐ ₈₈ Unknown
 - b. Spastic colon ☐ ₁ Yes ☐ ₀ No ☐ ₈₈ Unknown
 - c. Diverticulitis ☐ ₁ Yes ☐ ₀ No ☐ ₈₈ Unknown
 - d. Other gastrointestinal disease ☐ ₁ Yes ☐ ₀ No ☐ ₈₈ Unknown

**Randomized
Clinical
Trial #1**Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

7. Genitourinary disease

- | | | | | |
|----|-----------------------------|---------------------------------|--------------------------------|--------------------------------------|
| a. | Childhood bladder problems | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| b. | Urinary stones | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| c. | Incontinence | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| d. | Interstitial cystitis | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| e. | Urinary tract infection | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| f. | Balanitis | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| g. | Peyronie's disease | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| h. | Erectile dysfunction | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| i. | Other genitourinary disease | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |

8. Musculoskeletal, rheumatologic, or connective tissue disease

- | | | | | |
|----|--|---------------------------------|--------------------------------|--------------------------------------|
| a. | Arthritis | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| b. | Fibromyalgia | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| c. | Reiter's syndrome | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| d. | Other musculoskeletal, rheumatologic, or connective tissue disease | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |

9. Neurologic disease

- | | | | | |
|----|-----------------------------------|---------------------------------|--------------------------------|--------------------------------------|
| a. | Migraine headaches | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| b. | Vertebral disc disease or surgery | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| c. | Numbness or tingling in limbs | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| d. | Other neurologic disease | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |

**Randomized
Clinical
Trial #1**Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

10. Endocrine or metabolic disease

- | | | | | |
|----|--------------------------------------|---|--|--|
| a. | Hypothyroid disease | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No | <input type="checkbox"/> ₈₈ Unknown |
| b. | Hyperthyroid disease | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No | <input type="checkbox"/> ₈₈ Unknown |
| c. | Diabetes | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No | <input type="checkbox"/> ₈₈ Unknown |
| d. | Other endocrine or metabolic disease | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No | <input type="checkbox"/> ₈₈ Unknown |

11. Hematopoietic, lymphatic, or infectious disease

- | | | | | |
|----|---|---|--|--|
| a. | Sinusitis | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No | <input type="checkbox"/> ₈₈ Unknown |
| b. | Frequent upper respiratory infection | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No | <input type="checkbox"/> ₈₈ Unknown |
| c. | Epstein-Barr virus | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No | <input type="checkbox"/> ₈₈ Unknown |
| d. | Chronic fatigue syndrome | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No | <input type="checkbox"/> ₈₈ Unknown |
| e. | Tuberculosis | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No | <input type="checkbox"/> ₈₈ Unknown |
| f. | HIV/AIDS | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No | <input type="checkbox"/> ₈₈ Unknown |
| g. | Genital herpes | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No | <input type="checkbox"/> ₈₈ Unknown |
| h. | Other hematopoietic, lymphatic, or infectious disease | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No | <input type="checkbox"/> ₈₈ Unknown |

12. Dermatologic disease

- | | | | | |
|----|----------------------------|---|--|--|
| a. | Psoriasis | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No | <input type="checkbox"/> ₈₈ Unknown |
| b. | Other dermatologic disease | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No | <input type="checkbox"/> ₈₈ Unknown |

**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/_____
RC ID: _____

13. Psychiatric disease
- | | | | |
|------------------------------|---------------------------------|--------------------------------|--------------------------------------|
| a. Depression | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| b. Eating disorder | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| c. Anxiety/panic attacks | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| d. Suicide attempt | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| e. Other psychiatric disease | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
14. Urological surgery
- | | | | |
|-----------------------------|---------------------------------|--------------------------------|--------------------------------------|
| a. Inguinal hernia repair | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| b. Scrotal surgery | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| c. Vasectomy | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| d. Other urological surgery | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
15. Allergies
- | | | | |
|---------------------------------|---------------------------------|--------------------------------|--------------------------------------|
| a. Food allergies | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| b. Hay fever/seasonal allergies | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| c. Asthma | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| d. Latex allergy | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| e. Medical Allergies | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |
| f. Other allergies | <input type="checkbox"/> _1 Yes | <input type="checkbox"/> _0 No | <input type="checkbox"/> _88 Unknown |

5.4.12 Randomization [RAND]

Purpose: To ensure that a potential participant is eligible for CPCR N RCT#1 and to document the randomization process.

Who: RC completed

When: Visit #2 – second screening visit

General Directions

Qx #1 and #2: The participant must be eligible based on the inclusion, exclusion, and deferral criteria at both Visit #1 and Visit #2.

Qx #3: The RC should record the overall score from the NIH-CPSI [**CPSI**] administered at Screening Visit #2.

Qx #4: See Qx #4 on the Four-Glass Test – Cultures [**FGTC**] form. If any of the species identified for VB2 has a culture count $\geq 100,000$ CFU/mL, the participant is ineligible. Check box to indicate whether culture count is less than or greater than or equal to 100,000 CFU/mL.

Qx #5: A valid PI (or designee) must sign the Randomization form prior to randomizing a participant. The database system will not accept an invalid ID, and will not allow randomization.

Qx #6: A valid RC must sign the Randomization form after randomizing a participant. The database system will not accept an invalid ID.

Qx #7: Record the Randomization number supplied by the database system during on-line randomization.

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/_____
RC ID: _____

RANDOMIZATION

1. Did the participant meet all of the eligibility criteria at the first baseline visit? ☐₁ Yes ☐₀ No

2. Does the participant still meet all of the eligibility criteria at the second baseline visit? ☐₁ Yes ☐₀ No

3. Baseline 2 (Visit 2) NIH-CPSI

a. Overall Score: _____
⇒ Must be initialed by the RC

4. Highest VB2 Culture count (from FGTC form) ☐₀ <100,000
☐₁ ≥100,000

5. PCR Test Results ☐₁ Negative
☐₂ Positive

⇒ **By initialing above and signing below, you are confirming that all the information contained on this form is correct to the best of your knowledge, and that this participant is eligible to participate in this study.**

6. Investigator's Signature: _____

Date of Signature: ____/____/____ PI ID: _____

7. Signature of RC performing randomization: _____

Date of Signature: ____/____/____ RC ID: _____

8. Perform computer randomization and record randomization number _____

5.4.13 Rescue Treatment Event [RMED]

Purpose: To collect information regarding any rescue medication or treatment a participant may initiate during the follow up phase of the trial.

Who: Participant and RC completed

When: At the first instance of a participant initiating rescue treatment during the follow up phase (weeks 6 through week 12)

General Instructions

Report medication and/or treatment the participant reports they initiated for prostatitis or pelvic pain symptoms during the follow up phase. Do not report any medications that participant's were either taking prior to beginning the trial or during the treatment phase of the trial. This form is completed at the time of the first incidence of rescue treatment only.

Q#22-24: Instruct participant to indicate medication/treatment not listed. RC should complete corresponding drug code from the medication reference tool, if applicable.

RESCUE TREATMENT EVENT

1. Date you started rescue medication or treatment: ____/____/____

We are interested in learning how long the effect of treatment lasts after you stop taking the study drugs. Please indicate any of the following medications or treatments you are presently taking for your prostatitis or pelvic pain that you were not already taking prior to beginning the study. That is, record only those prostatitis medications/treatments that you have started since stopping the study medications. If you are unsure what category the medication/treatment falls into, please contact your RC for assistance.

	<u>Yes</u>	<u>No</u>
2. Antibiotics or antimicrobials (oral or intravenous)	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
3. Anticholinergics or antispasmodics	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
4. Anticonvulsants	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
5. Antidepressants	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
6. Anti-inflammatory medications	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
7. Anti-anxiety medications	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
8. Alpha blockers	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
9. 5-alpha reductase inhibitors	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
10. Narcotics	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
11. Steroids	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
12. Urinary tract analgesics	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
13. Allopurinol	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
14. Plant extracts or herbs	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
15. Zinc	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀
16. Acupuncture or acupressure	<input type="checkbox"/> ₁	<input type="checkbox"/> ₀

**Randomized
Clinical
Trial #1**Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

- | | <u>Yes</u> | <u>No</u> |
|---|---------------------------------------|---------------------------------------|
| 17. Biofeedback | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₀ |
| 18. Electrical stimulation | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₀ |
| 19. Prostate massage | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₀ |
| 20. Special diet or nutritional supplements | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₀ |
| 21. Stress reduction techniques | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₀ |
| 22. Other | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₀ |
| Please specify, _____ | | |
| Drug Code: _____ (to be completed by RC) | | |
| 23. Other | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₀ |
| Please specify, _____ | | |
| Drug Code: _____ (to be completed by RC) | | |
| 24. Other | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₀ |
| Please specify, _____ | | |
| Drug Code: _____ (to be completed by RC) | | |

5.4.14 Semen Sample [SEMEN]

Purpose: To collect culture and microscopy data on participant semen samples

Who: RC completed, based on lab reports

When: Visit #2 – second screening visit and if required at Visit #4 clinic visit.

General Directions

The participant should be reminded to remain abstinent for 48 hours prior to the specimen collection.

Second semen sample collection will only occur if uropathogens are localized to semen at Visit #2-second screening visit (see Uropathogens Localized to Semen Calculations [UCAL] worksheet).

The RC will complete this form based on the clinic's lab report. If reported cell count is less than 25, indicate actual count.

Semen sample cultures are measured at 5 days. The culture count is measured in CFU/mL.

Species Code table: This table contains the codes for each species to be identified in the lab report.

Was there any growth? If 'No growth' is indicated, the culture data does not need to be completed.

Culture count tables: If growth was identified, enter the total number of different species you are reporting and complete the culture count table as follows:

- *Species Code:* to be taken from the Species Code table. Each species identified on the lab report should be recorded separately.
- *<100,000 or ≥ 100,000 CFU/mL:* check the appropriate box according to the count listed on the lab report.
- *If <100,000, please enter actual count:* If the count is less than 100,000 CFU/mL, then enter the exact count as it is listed on the lab report.

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

SEMEN SAMPLE

1. Did the participant have uropathogens localized to semen at the screening visit? ☐₁ Yes ☐₀ No

NOTE: If the answer to #1 is "NO" at Visit 4, do not continue.

2. Has the patient remained abstinent for the past 48 hours? ☐₁ Yes ☐₀ No
3. Was the patient able to provide a semen sample? ☐₁ Yes
☐₂ No, refused
☐₃ No, unable
- If **Yes**, please continue

Semen Microscopy

4. Volume of semen sample _____ . _____ ml
5. White Blood Cell Count (/hpf) ☐₁ ≤ 25
☐₂ 26 - 50
☐₃ 51-75
☐₄ 76-100
☐₅ >100
- If < 25, give actual count _____ /hpf
6. Number of seminal plasma aliquots sent to lab for storage _____

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Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

The table below lists the species to be identified in each sample, and each species' appropriate code. Use these codes when completing the tables for the culture count for each species.

Species	Species Code
Staphylococcus Epidermidis	01
Staphylococcus Aureus	02
Staphylococcus Other	03
Streptococcus Viridans	04
Staphylococcus Hemolyticus	05
Streptococcus Other	06
Enterococcus Faecalis	07
Corynebacterium	08
Escherichia Coli	09
Klebsiella	10
Pseudomonas	11
Proteus	12
Other	13

5 Day Culture Count

7. Date of 5 day count _____ / _____ / _____
month day year

8. Was there any growth? ☐ Yes ☐ No

If **Yes**, please complete the chart below, indicating what species were present, and the culture count measured in CFU/ml: **Enter total number of species recorded:** ____

Species Code	< 100,000 OR ≥ 100,000	If < 100,000, please enter actual count
____	<input type="checkbox"/> <100,000 <input type="checkbox"/> ≥100,000	_____ CFU/ml
____	<input type="checkbox"/> <100,000 <input type="checkbox"/> ≥100,000	_____ CFU/ml
____	<input type="checkbox"/> <100,000 <input type="checkbox"/> ≥100,000	_____ CFU/ml
____	<input type="checkbox"/> <100,000 <input type="checkbox"/> ≥100,000	_____ CFU/ml
____	<input type="checkbox"/> <100,000 <input type="checkbox"/> ≥100,000	_____ CFU/ml

5.4.15 SF-12 [SF12]

Purpose: To collect information regarding the participant's change in quality of life during trial.

Who: Participant completed after RC explains purpose and how to complete form

When: Visits #1, #2, #3, #4, #5 and #6, and at time of first rescue treatment event or early treatment discontinuation, if applicable.

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Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

SF-12

Today's Date: ____/____/____

This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer every question by marking *one* box. If you are unsure about how to answer, please give the best answer you can.

1. In general, would you say your health is:
- ☐₁ Excellent
☐₂ Very good
☐₃ Good
☐₄ Fair
☐₅ Poor

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

2. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
- ☐₁ Yes, limited a lot
☐₂ Yes, limited a little
☐₃ No, not limited at all
3. Climbing **several** flights of stairs
- ☐₁ Yes, limited a lot
☐₂ Yes, limited a little
☐₃ No, not limited at all

During the *past 4 weeks*, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

4. **Accomplished less** than you would like
- ☐₁ Yes
☐₀ No
5. Were limited in the **kind** of work or other activities
- ☐₁ Yes
☐₀ No

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Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

6. **Accomplished less** than you would like ☐₁ Yes
☐₀ No
7. Didn't do work or other activities as **carefully** as usual ☐₁ Yes
☐₀ No
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? ☐₁ Not at all
☐₂ A little bit
☐₃ Moderately
☐₄ Quite a bit
☐₅ Extremely

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the *one* answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks:

- | | All of
the time | Most of
the time | A good bit
of the time | A little of
the time | None of
the time |
|---|---|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| 9. Have you felt calm and peaceful? | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ | <input type="checkbox"/> ₄ | <input type="checkbox"/> ₅ |
| 10. Did you have a lot of energy? | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ | <input type="checkbox"/> ₄ | <input type="checkbox"/> ₅ |
| 11. Have you felt downhearted and blue? | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ | <input type="checkbox"/> ₄ | <input type="checkbox"/> ₅ |
| 12. During the <u>past 4 weeks</u> , how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)? | <input type="checkbox"/> ₁ All of the time
<input type="checkbox"/> ₂ Most of the time
<input type="checkbox"/> ₃ A good bit of the time
<input type="checkbox"/> ₄ A little of the time
<input type="checkbox"/> ₅ None of the time | | | | |

5.4.16 Study Stop Point [SSTOP]

Purpose: To document the point at which the participant completed the trial.

Who: RC and PI completed

When: Visit #6, or at time of early study withdrawal

General Directions

If a participant withdraws from the study early, the Study Stop Point [**SSTOP**] form is completed at the time of withdrawal. Otherwise, it is completed at the end of Visit #6, the last study contact.

Qx #1: Indicate if the participant has successfully completed the trial. Reasons for not successfully completing the trial include, but are not limited to:

- Poor compliance in taking study medication (< 80%)
- Missed clinic visits or phone contacts
- Missing lab tests (Four-Glass Test Culture [**FGTC**], etc.)

Qx #2 and #3: The PI and the RC **must** sign and date the Study Stop Point [**SSTOP**] form.

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

STUDY STOP POINT

1. Has the participant successfully completed the study? ☐₁ Yes ☐₀ No

If **No**, please indicate the reason

- a. Low compliance (below 80%) ☐₁ Yes ☐₀ No
b. Missing visits/contacts ☐₁ Yes ☐₀ No
c. Missing tests ☐₁ Yes ☐₀ No
d. Other ☐₁ Yes ☐₀ No

Please specify: _____

Signatures:

I verify that all information collected on the CPCR N RCT#1 data collection forms for this participant is correct to the best of my knowledge and was collected in accordance with the procedures outlined in the CPCR N RCT#1 Protocol and Manual of Procedures.

2. Principal Investigator's Signature: _____

Date of Signature: ____/____/____ PI ID: _____

3. Research Coordinator's Signature: _____

Date of Signature: ____/____/____ RC ID: _____

4. Physician Comments (optional):

5.4.17 Follow-Up Symptoms [SYM]

- Purpose:** To collect information regarding the participant's change in prostatitis symptoms during the trial.
- Who:** Participant completed after RC explains purpose and how to complete form
- When:** Visits #1, #2, #3, #4, #5 and #6, and at time of first rescue treatment event or early treatment discontinuation, if applicable.

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Clinical
Trial #1**

Participant ID: _____
 Participant Initials: _____
 Clinical Center: _____
 Visit Number: _____
 Visit Date: ____/____/_____
 RC ID: _____

FOLLOW-UP SYMPTOMS

Today's Date: ____/____/____

1. As compared to when you started the study, how would you rate your overall symptoms now?

<input type="checkbox"/> ₀	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆
Markedly worsened	Moderately worsened	Slightly worsened	No change	Slightly improved	Moderately improved	Markedly improved

5.4.18 Treatment Stop Point [TSTOP]

Purpose: To document the point at which the participant discontinued the study medications and why.

Who: RC completed

When: Visit #4, or at time of early treatment discontinuation

General Directions

Qx #1 and #2: If a participant stops taking one of the study medications, he must discontinue both.

Qx #3a: If a participant is discontinuing study medications early due to an unacceptable concomitant medication, the RC must verify that this is also recorded on the Concomitant Medications [**CMED**].

Qx #3b: Adverse Event, *as determined by the PI* – if the PI has decided that, due to an adverse event, the participant should not continue to take the study medications, the RC should ensure that this is also recorded on the Adverse Event/Serious Adverse Events [**AE**] form.

Qx #3c: Adverse Event, *as determined by the participant* – if the participant has decided that, due to an adverse event, he no longer wishes to take the study medications, the RC should ensure that this is also recorded on the Adverse Events/Serious Adverse Events [**AE**] form.

**Randomized
Clinical
Trial #1**Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/_____
RC ID: _____

TREATMENT STOP POINT

1. Date participant took final dose of *CIPRO*® medication: ____/____/____
2. Date participant took final dose of *Flomax*® medication: ____/____/____
3. Has the participant stopped treatment early? ☐₁ Yes ☐₀ No
If **Yes**, please state the reason for early withdrawal
 - a. Use of unacceptable medication ☐₁ Yes ☐₀ No
Listed on Concomitant Medications as Line #: _____
 - b. Adverse Event, *as determined by the PI* ☐₁ Yes ☐₀ No
Listed on Adverse Event form as AE #: _____
Date of onset: ____/____/_____
Please specify: _____
 - c. Adverse Event, *as determined by the participant* ☐₁ Yes ☐₀ No
Listed on Adverse Event form as AE #: _____
Date of onset: ____/____/_____
Please specify: _____
 - d. Participant dissatisfied with treatment ☐₁ Yes ☐₀ No
Please specify: _____
 - e. Participant no longer interested in participating ☐₁ Yes ☐₀ No
Please specify reason: _____
 - f. Other ☐₁ Yes ☐₀ No
Please specify reason: _____

5.4.19 Unmasking Record [UNMASK]

Purpose: To record the unmasking of the study drug randomization assignment due to unforeseen circumstances such as Serious Adverse Events, or Hospitalization. This form will be completed after unmasking has actually occurred. Dr. Richard Alexander or Dr. Michael O'Leary will make all unmasking determinations in collaboration with the site investigator.

Participants who have been unmasked will be medically followed until the study is completed as scheduled. Related procedures, such as specimen collection, will be discontinued.

Note that the administrative form **Authorization for Unmasking [AUTH]** is a record of the unmasking process and precedes the completion of this form. See Authorization for Unmasking [AUTH] for a detailed description of the unmasking process.

Who: RC completed in collaboration with the PI.

When: Following Unmasking

Completing the Form

Note the date and time of the unmasking. Attach a copy of the Unmasking Authorization [AUTH] form. Be sure to contact the DCC within one (1) working day of the unmasking event documenting the name of the DCC contact person on the form. If the DCC was not contacted, state the reason. Indicate the reason for unmasking. In the case of a SAE, the Adverse Events/Serious Adverse Events [AE] and **MedWatch 3500** forms must be completed and faxed to the DCC, as specified in the AE/SAE section. Include any related information, such as hospitalization, laboratory test results and outcome.

Once completed, a copy of this form must be faxed to the DCC at 215-573-4790. **Remember to attach a copy of the original Unmasking Authorization [AUTH] form containing all three (3) signatures.** You will receive the original Unmasking Authorization [AUTH] form, documenting the process, from the UPenn IDS Pharmacist via mail. This copy will not reveal the treatment assignment to the DCC staff. Only the faxed copy, which remains at the Clinical Center, contains that information.

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/_____
RC ID: _____

UNMASKING RECORD

1. Date of unmasking: ____/____/____
2. Time of unmasking: ____:____ (24-hour)
3. Randomization Number: _____
4. Unmasking authorization attached? ☐ Yes ☐ No
5. Was the DCC contacted within 72 hours of unmasking? ☐ Yes ☐ No
 - a. If **Yes**, name of person contacted: _____
 - b. If **No**, state the reason: _____
6. Why was the drug unmasked?
 - a. Serious Adverse Event ☐ Yes ☐ No
Listed on Adverse Event form as AE # _____
 - b. Other hospitalization ☐ Yes ☐ No
 - c. Other ☐ Yes ☐ No
Please specify: _____

DIRECTIONS: Fax this form to the DCC at (215) 573-6262. Please include original **AUTH**; **DO NOT** send **AUTH** copy revealing treatment assignment.

5.4.20 Uroflow [URO]

Purpose: To collect data from the participant's uroflow analysis

Who: RC completed, based on lab reports

When: Visit #2 – second screening visit and Visit #4 clinic visit.

General Directions

The RC will complete this form based on availability of the clinic's lab report.

Qx #1, #2, #3: Only completed at Visit #2

Qx #4: The post-void residual is completed at Visit #2 after the uroflow and at Visit #4 after the four-glass test.

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

UROFLOW

1. Total voided volume _____ ml
2. Peak flow _____ ml/sec
3. Average flow _____ ml/sec
4. Post-void residual _____ ml

Note: At Visit 4 (week 6), complete Post-Void Residual **ONLY**.

5.4.21 Voiding Log [VOID]

Purpose: To collect information on a participant's voiding pattern over a 24-hour period of time.

Who: Participant completed after RC explains purpose and how to complete form

When: Visit #2 – second screening visit and Visit #4 clinic visit.

General Directions

Participants should be instructed to record no more than 24 hours worth of data and to record all times using military time.

The RC should complete the first column by numbering each entry sequentially and indicate the total number of voids recorded at the top of page 2.

Visit #2: The RC should distribute the Voiding Log at Visit #1 for the participant to complete and return at Visit #2. The participant should complete the log as close to Visit #2 as possible.

Visit #4: The RC should distribute the Voiding Log at Visit #2 for the participant to complete and return at Visit #4. The participant should complete the log as close to Visit #4 as possible.

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/_____
RC ID: _____

VOIDING LOG

1. Beginning date and time of log _____ / _____ / _____
_____ : _____ (military time)
2. Ending date and time of log _____ / _____ / _____
_____ : _____ (military time)
3. What time did you go to bed? _____ : _____ (military time)
4. What time did you get up for the day? _____ : _____ (military time)

5. Which number best describes your AVERAGE pain or discomfort on this day?

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
No Pain								Pain as bad as you can imagine		

Randomized Clinical Trial #1

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

[illegible]

5.5 Administrative Forms – Specific Instructions

Case Report Forms – Administrative Forms (in alphabetical order by Form Name)	
Form Name	Form Code
Clinical Site Staff “Signature and Delegation of Responsibilities” Log	SITELOG
Authorization to Unmask	AUTH
Clinic Correspondence Log	CCORRESP
Exclusionary Medications	EMEDS
Forms Administration Schedule	SCHEDULE
How To Complete Your Voiding Log	HOWTO
Lab Tracking Log	LAB
Medication Diary	DIARY
Monitoring Log	MONITOR
Participant Contact Information	CONTACT
Participant Correspondence Log	PCORRESP
Participant ID Assignment Log	LOG
Participant Status Log	STATUS
Participant Transfer	TRANS
Progress Notes	PROGRESS
Study Medication Tracking Log	TRACK
Uropathogens Worksheet	UCAL
Visit 1 Checklist	VISIT1
Visit 2 Checklist	VISIT2
Visit 3 Checklist	VISIT3
Visit 4 Checklist	VISIT4
Visit 5 Checklist	VISIT5
Visit 6 Checklist	VISIT6
Visit 98 Checklist	VISIT98
Visit 99 Checklist	VISIT99

5.5.1 *Clinical Site Staff “Signature and Delegation of Responsibilities” Log* **[SITELOG]**

Binder: Clinic Regulatory Binder

All personnel working on the CPCR N RCT#1 must sign the Clinical Site Staff “Signature and Delegation of Responsibilities” Log **[SITELOG]**.

The PI should indicate delegation of study responsibilities by initialing in the column associated with the task he is delegating and signing and dating each row. This form should be updated regularly as new staff is added.

Investigator's Name: _____

Site Number: _____

CLINICAL SITE STAFF "SIGNATURE AND DELEGATION OF RESPONSIBILITIES" LOG

The Site Investigator must designate which tasks each study person is qualified & designated to perform on by initialing each of the applicable boxes and signing/dating each row.									
Personnel: Write Printed Name and Corresponding Signature of Clinical Site Personnel	Initials	Role in Study (e.g., RC) & Credentials if applicable	Administering Informed Consent	Dispensing Study Drug(s)	Blood Draws & Laboratory Tests	Vital Signs & Basic Study Procedures Assessments	Physical Exams "Integrit"	Data Entry & Query Resolution	Investigator's Signature and Date of Approval
PI:		On-Site Investigator							

5.5.2 Authorization to Unmask [AUTH]

Binder: Participant Study File

The purpose of this form is to document the chain of communication from the On-site Investigator to the CPRN RCT#1 PI requesting authorization to unmask. The PI and/or RC complete this form. This form will be filled out in case of a serious adverse event occurrence, or other clinical circumstance necessitating unmasking.

General Directions

The form is completed in three parts: 1) the On-site Investigator request, 2) the PI authorization and 3) the University of Pennsylvania IDS Pharmacist release of treatment assignment information. The IDS Pharmacist will fax this completed form to the On-site Investigator. It will be filed in the participant's chart as the source document. The U Penn Pharmacist will also mail the original signed copy to the site. Attach the original to the fax copy.

It is important that treatment assignment information remain **strictly confidential**. Only those clinicians who are directly involved with the participant's care should have access to the information. The faxed information should be received at a fax machine that is reserved for CPCR N RCT#1 study-specific documents only. It should be located in a secure and private area. Treatment assignment information should be promptly filed in a secured location.

In the event that the on-site investigator, authorizing PI or IDS pharmacist is unable to fax at the time of the unmasking request, information/authorization may be provided by phone. The Authorization for Unmasking **[AUTH]** form should be completed and faxed/mailed as described above at first opportunity.

Unmasking Process

1. The On-site Investigator (or designee) will contact Dr. Richard Alexander, PI (Pager 410-460-7838). If unavailable, contact Dr. Michael O'Leary (Pager 617-732-6325) by telephone. He will complete Section 1 of the Authorization to Unmask **[AUTH]** form and fax it to the authorizing PI. The original form will be placed in the participant's record.
2. Once the PI determines that unmasking is indicated, he will sign the Authorization to Unmask **[AUTH]** form and fax it to the UPenn IDS Pharmacist at 215-349-5132. They will also forward their original signature document to the UPenn IDS. Additionally, the PI may respond by telephone to both the On-site Investigator and IDS Pharmacist.
3. The IDS Pharmacist will document the treatment assignment on the form and sign it.
4. He will then fax the completed Authorization to Unmask **[AUTH]** form to the On-site Investigator at the number provided in section 1. This faxed form will serve as the source document.
5. The Pharmacist will mail the original form to the On-site Investigator. It will contain the PI and Pharmacist signatures but **not** the treatment assignment. Attach the original Authorization to Unmask **[AUTH]** form to the faxed Authorization to Unmask **[AUTH]** form and file it in the participant's record.

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**Randomized
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Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

AUTHORIZATION FOR UNMASKING

1. **Request to Unmask Study Medication:**

Specify reason for unmasking: _____

Site Investigator's Signature: _____ Date: _____

Site Investigator's Phone and Beeper #: _____

Site Investigator's Fax #: _____

- Instructions:**
1. Notify **Richard Alexander, M.D.** (410) 460-7838, if unable to contact, then notify **Michael O'leary, M.D., M.P.H.** (617) 732-6325
 2. Fax this form to the authorizing PI
 3. File the original in the participant's chart.

2. **Authorization:**

I authorize / do not authorize [**CIRCLE ONE**] the Penn Investigational Drug Service (IDS) to reveal treatment code for the above listed study participant.

Authorizing PI's Signature: _____

Date: _____

- Instructions:**
1. Fax to IDS Pharmacist (215) 349-5132.
 2. Forward the original signature document to the Penn IDS.

3. **Investigational Drug Service:**

Pharmacist's Signature: _____

Date: _____

- Instructions:**
1. Identify treatment assignment below.
 2. Fax to the Site Investigator listed in section 1.
 3. Treatment assignment _____

NOTE: If unable to fax/complete form at time of unmasking, information/authorization may be provided by phone. AUTH form should be completed and faxed/mailed as instructed at first opportunity.

5.5.3 Clinic Correspondence Log [CCORRESP]

Binder: Clinic Regulatory Binder

All correspondence between the clinic and the DCC should be recorded on the Clinic Correspondence Log. Refer to the Correspondence Type codes listed at the bottom of each page for the type. From and To should indicate the names of the persons involved in the correspondence. Refer to the Status Codes listed at the bottom of each page for the status, and update the status as appropriate.

CPCRN *Randomized Clinical Trial #1*

[illegible]

Codes:

Correspondence Type: F = Fax, E = Email, L = Letter, T = Telephone

Status Codes: O = Ongoing, RC F = Received and Files, RS = Resolved, P = Pending

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Page of

CCORRESP

5.5.4 Exclusionary Medication [EMEDS]

Binder: None

The Exclusionary Medications form should be distributed to each participant in the CPCRn RCT#1 to remind him of the medications he should not take while participating in the study. The generic names and common examples of brand names are listed for each medication for easy reference.

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EXCLUSIONARY MEDICATIONS

The following medications **may not** be taken during the time you are participating in this clinical trial:

Product List	Generic Name	Selected Brand Names
Flomax®) (other than the study drug)	Tamulosin hydrochloride	Flomax®)
Cipro®)(other than the study drug)	Ciprofloxacin hydrochloride	Cirpo®)
COX-2 Inhibitor (including aspirin*)	Rofecoxib	VIOXX®
Non-steroidal Anti-Inflammatory Drugs (NSAIDs)	Ibuprofen Ibuprofen Naproxen	Motrin® Aleve® Naprosyn®
Anti-microbial agents	antibiotics	
5-Alpha Reductase Inhibitors	Finasteride	Proscar® Propecia®
Narcotics		
Anticoagulants	Warfarin	Coumadin®
Cimetidine	Cimetidine	Tagamet®)
Alpha Blocker	Terazosin HCL Doxazosin Mesylate	Hytrin® Cardura®
Antacids		Maalox® Mylanta®
Zinc Supplements		
Bioflavonoid	Quercetin	

* Participants taking aspirin daily for cardiac reasons may continue to do so at a maximum daily dose of 325 mg a day.

5.5.5 Forms Administration Schedule [SCHEDULE]

Binder: Clinic Regulatory Binder

The Forms Administration Schedule [**SCHEDULE**] should be utilized by the RC as a reference or reminder, along with the visit checklists, as to which forms are completed at each contact.

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FORMS ADMINISTRATION SCHEDULE

	Screening		+3 weeks	+6 weeks	+9 weeks	+12 weeks	Early Stop Treatment	Rescue Event
Form	Visit 1 (clinic)	Visit 2 (clinic)	Visit 3 (phone)	Visit 4 (clinic)	Visit 5 (phone)	Visit 6 (phone)	Visit 98 (PRN)	Visit 99 (PRN)
Eligibility Checklist (ELIG)	X							
NIH-CPSI (CPSI)	X	X	X	X	X	X	X	X
Randomization (RAND)		X						
SF-12 (SF12), Follow-Up Symptoms (SYM)		X	X	X	X	X	X	X
Demographics (DEMO)		X						
Dispensing Log (DISP)		X						
Concomitant Medication (CMED)		X		X				
Follow-Up Contacts (FUP)			X	X	X	X		
Adverse Events/Serious Adverse Events (AE)			X	X	X	X		
Medical History (MED)	X							
Physical Exam (EXAM)	X			X				
Four Glass Test Microscopy (FGTM)	X			X				
Four Glass Test Cultures (FGTC)	X			X				
Semen Sample (SEMEN)		X		X				
Uroflow and PVR (URO)		X		X*				
Voiding Log (VOID)		X		X				
Treatment Stop (TSTOP)				X			X	
Study Stop (SSTOP)						X		
Rescue Treatment Event (RMED)								X
Unmasking** (UNMASK)								
Patient Contact Information	X							
Visit Checklist	X	X	X	X	X	X	X	X
Study Medication Tracking Log		X		X			X	
Participant Status Log	X	X				X		
Participant ID Assignment Log	X							
* PVR Only. ** This form is completed only when clinically needed.								

5.5.6 How To Complete Your Voiding Log [HOWTO]

Binder: None

The How To Complete Your Voiding Log [HOWTO] form provides the participant with detailed instructions for completing his Voiding Log [VOID] form. The RC should distribute this handout each time with the Voiding Log [VOID] form.

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HOW TO COMPLETE YOUR VOIDING LOG

The Voiding Log must be completed for screening clinic visit #2, as well as Visit 4, the 6-week clinic visit, according to the following guidelines:

1. Just before the scheduled clinic visit, record the times and amounts of each urination for a 24-hour period.
2. On the first page, enter the date and the time when you started keeping track of each urination.
3. The date and time you ended the log should be 24 hours after the start time. It is important to ensure you have collected a full 24-hour's worth of data.
4. The first column of the log, Void Number, is to be completed by the RC, after the Voiding Log is complete, when you have turned it back in.
5. For each urination, measure the amount in CC's.
6. If you woke up because you had to urinate, then indicate so by answering "Yes" to the question "Did you wake to void?".
7. Please use **black or blue** ink.

Example:

Void Number (completed by the RC)	Time of void (military time)	Amount voided (CC's)	Did you wake to void?
___	___ 8 : 3 0	100	<input checked="" type="checkbox"/> ₁ Yes <input type="checkbox"/> ₀ No
___	1 1 : 0 5	130	<input type="checkbox"/> ₁ Yes <input checked="" type="checkbox"/> ₀ No
___	1 3 : 5 0	80	<input type="checkbox"/> ₁ Yes <input checked="" type="checkbox"/> ₀ No

5.5.7 Lab Tracking Log [LAB]

Binder: Clinic Regulatory Binder

All specimens that are collected and stored as part of the CPCR N RCT#1 should be documented on this log.

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[illegible]

LAB

5.5.8 Medication Diary [DIARY]

Binder: Participant Study Binder

The Medication Diary **[DIARY]** form is to be completed by the participant beginning with Visit #1 and ending with Visit #4. The information collected on the Medication Diary **[DIARY]** is to be used to complete the Concomitant Medication **[CMED]** form.

At Visit #1, the first screening visit, the participant will be instructed to bring to Visit #2 all of the medications he is currently taking. The RC will review the medications with the participant, and list each medication on the Medication Diary [**DIARY**], including the

start date, the strength and form per dose, the route, and the total number of doses per 24 hours.

The RC will review the Exclusionary Medications [**EMEDS**] form and the instructions on the first page of the Medication Diary [**DIARY**] with the participant. The participant will take the Medication Diary [**DIARY**] form home after Visit #2 and update it according to the instructions.

At Visit #4, the participant should bring the Medication Diary [**DIARY**] with him to the clinic visit. The RC will review the diary for completeness. The original will be collected and used to complete the Concomitant Medications [**CMED**] form, and then filed in the participant's study binder.

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MEDICATION DIARY

Patient Initials: _____

RC Name: _____

Date of Visit 2 - Second Screening Clinic Contact: ____ / ____ / _____

Scheduled date of Visit 4 - Week 6 Clinic Contact: ____ / ____ / _____

Instructions for completing this form (Medication Diary):

This diary is to be completed during the time period between your Visit 2 and Visit 4 clinic contacts (the dates listed above). At Visit 2, the RC will review with you all the medications you are currently taking. These medications will be listed on the table on page 2.

Please record all **changes** in your medications as follows:

Starting a new medication that is continuing: On the next available line, record the name of the medication and the date you started the new medication. The stop date will be left blank, since you are still taking the medication. Then complete the strength and form, the route, and the total number of doses in a 24 hour timeframe.

Stopping a previous listed medication: Find the line where the medication is already listed. Complete the stop date.

Starting and stopping a medication (i.g. medication only taken for one day): On the next available line, record the name of the medication, the date you started the new medication, the date you stopped the medication, the strength and form, the route, and the total number of doses in a 24 hour timeframe.

Recording changes in a previously listed medication (e.g. changing dose): Find the line where the medication is already listed. Complete the stop date by recording the last date you took that medication at that dosage. On the next available line, record the name of the medication, the date you started the medication at the new dosage, the date you stopped (if not continuing), the strength and form, the route, and the total number of doses in a 24 hour timeframe, with the appropriate modifications.

Please record **all** medications you are taking, including both prescription and over-the-counter medications, as well as your study medications. If you are unsure as to the amount you take, use your best estimate or ask your doctor or pharmacist.

If you have any questions about completing this diary, please call your Research Coordinator.

Patient Initials: _____

*tablet - includes caplets and gelcaps

** intravesical - instilled into the urinary bladder

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Patient Initials: _____

[illegible]

*tablet - includes caplets and gelcaps

** intravesical - instilled into the urinary bladder

5.5.9 Monitoring Log [MONITOR]

Binder: Clinic Regulatory Binder

The Monitoring Log [MONITOR} is to be completed at the time of a site visit by the DCC to the clinical center. The DCC monitor is responsible for completing this log.

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MONITORING LOG			
Date of Visit	Reason for Visit	DCC Representatives	CC Representatives

5.5.10 Participant Contact Information [CONTACT]

Binder: Participant's confidential files

The Participant Contact Information [CONTACT] form should be completed by the participant at Visit #1 and is strictly confidential. This form should never be forwarded to the DCC. If a participant's information changes throughout the course of the study, he should complete a new form.

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Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

PARTICIPANT CONTACT INFORMATION

This form contains **confidential** information, and is for Clinical Center use *only*. **DO NOT** forward to the DCC.

1. Patient Name: _____
Last, First, MI
2. Address: _____
Street Address

City, State, Zip Code
3. Mailing Address, if different than above: _____
Street Address

City, State, Zip Code
4. Home Phone Number: _____
(_____) _____ - _____
(area code)
5. Work Phone Number: _____
(_____) _____ - _____
(area code)
6. FAX Number: _____
(_____) _____ - _____
(area code)
7. Email Address: _____
8. What is the best way to contact you?

9. When is the best time to contact you?

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Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

10. Who is your usual doctor or primary care physician?
Name: _____

Last, First, MI

Address: _____

Street Address

City, State, Zip Code

Phone Number: _____

(____) _____ - _____
(area code)

Other Contacts (people at a different address we can contact if we are unable to reach you)

11. Name: _____

Last, First, MI

Address: _____

Street Address

City, State, Zip Code

Phone Number: _____

(____) _____ - _____
(area code)

Relationship to you: _____

12. Name: _____

Last, First, MI

Address: _____

Street Address

City, State, Zip Code

Phone Number: _____

(____) _____ - _____
(area code)

Relationship to you: _____

CONFIDENTIAL

5.5.11 Participant Correspondence Log [PCORRESP]

Binder: Participant Study Binder

All correspondence between the clinic and the participant *must* be tracked on the Participant Correspondence Log [**PCORRESP**] form. Any communication, no matter how insignificant it may seem, should be recorded on this log.

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PARTICIPANT CORRESPONDENCE LOG

Participant ID: _____

Date: ____/____/____

Date: ____/____/____

Date: ____/____/____

Date: ____/____/____

5.5.12 Participant ID Assignment Log [LOG]

Binder: Part of the Clinic Regulatory Binder, but stored separately

The Participant ID Assignment Log [**LOG**] contains a list of all the participant ID's and identifies the name and initials of the participant assigned to each ID. This log is strictly confidential and must be kept in a secure location.

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PARTICIPANT ID ASSIGNMENT LOG

[illegible]

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PARTICIPANT ID ASSIGNMENT LOG

[illegible]

5.5.13 Participant Status Log [STATUS]

Binder: Clinic Regulatory Binder

The Participant Status Log [**STATUS**] tracks each participant and potential participant and his status with respect to the study. This form **must** be updated regularly and faxed to the DCC on the first Monday of every month. The DCC will send a reminder e-mail to the sites.

- Participant Number: Each potential participant contacted about participation in CPCR N RCT#1 should be listed on this log, and numbered sequentially.
- Participant ID: If an ID is assigned, and a participant is enrolled in the study, enter his assigned ID.
- Participant Initials: Enter the initials of the potential participant.
- Date of Informed Consent: Once a participant signs the informed consent, enter the date
- First Screening Date: Enter the date of the participant's Visit #1.
- Participant Randomized: Enter **Y** once the participant is randomized. If the participant cannot be randomized, for whatever reason, enter **N**.
- If No, Reason*: If the participant cannot be randomized, enter the reason, using the codes listed at the bottom of the form.
- Date Randomized: If the participant is randomized, enter the date.
- Randomization Number: If the participant is randomized, enter his randomization number.
- Completed/Dropped: Enter **C** once the participant completed the study (reaches Visit #6). If the participant does not complete the study, withdraws early, etc., enter **D**.
- If Dropped, Reason**: If the participant withdraws early, enter the reason, using the codes listed at the bottom of the form.
- Date Study Stopped: Enter the date of last study contact.

PARTICIPANT STATUS LOG

[illegible]

* Reasons for non-randomization:

DNMEC - Did not meet eligibility criteria, give form name and qx. number
PDecline - Participant declined
FDecline - Family member or participant representative declined
Other - Specify

**** Reasons for dropout:**

AE/SAE - Adverse Event or Serious Adverse Event
 PDecline - Participant declined
 FDecline - Family member or participant representative declined
 LTFU - Lost to Follow-Up
 NC - Non-compliant
 Other - Specify

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Figure of

STATUS

5.5.14 Participant Transfer [TRANS]

Binder: Participant Study Binder

The Participant Transfer [TRANS] form tracks the transfer of patient information and CRF's between clinic sites in the event that a participant relocates to another CPCRNI site. The participant will retain his original ID number throughout the course of the trial

- Page one: Should be completed by the RC at the site from which the participant is being transferred. The completed form should be faxed to the DCC and the Receiving Site.
- Provide the Participant with contact information for the Receiving Site.
- The participant's study file and CRF's should be shipped to the Receiving Site via FEDEX or other trackable courier.
- Page two: Should be completed by the RC at the site to which the participant is transferring. The completed form should be faxed to the DCC and the Originating Site.
- A new consent must be signed by the participant

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Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

PATIENT TRANSFER *ORIGINATING* CENTER

(Research Coordinator completed whenever a patient transfers to another participating site.)

Originating Center (Completed by the Originating Center)

NOTE: photocopies of this form to be sent to the DCC and the Receiving Center.

1. Indicate date and month number of last patient visit (at originating center). Date: ____/____/____
month day year
Visit #: ____
2. Date and month number of next scheduled visit (at receiving center). Date: ____/____/____
month day year
Visit #: ____
3. Date case report forms copied and sent to receiving center. Date: ____/____/____
month day year
4. Please indicate receiving study center I.D. number: ____
5. Date receiving center contacted. Date: ____/____/____
month day year
6. Name of Research Coordinator contacted at receiving center. _____
7. Indicate reason for transfer: _____

A transfer is considered complete when the receiving center has received all required materials from the originating center (a copy of the patient's study record, and an informed consent is signed at the receiving center.

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Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

PATIENT TRANSFER *RECEIVING* CENTER

(Research Coordinator completed whenever a patient transfers to another participating site.)

Receiving Center (Completed by the Receiving Center)

NOTE: Photocopies of this form to be sent to the DCC and the Originating Center.

1. Indicate the date of copy of study record was received from originating center. Date: ____/____/____
month day year
2. Indicate the date the receiving center was contacted by the patient or the originating center. Date: ____/____/____
month day year
3. Indicate date and month number of patient's first scheduled visit (at receiving center). Date: ____/____/____
month day year
Visit #: ____
4. Date patient signed informed consent. Date: ____/____/____
month day year

A transfer is considered complete when the receiving center has received all required materials from the originating center (a copy of the patient's study record, and an informed consent is signed at the receiving center.

5. Date transfer completed: Date: ____/____/____
month day year
6. Indicate receiving physician I.D. #: _____
7. Comments (optional): _____

5.5.15 Progress Notes [PROGRESS]

Binder: Participant's confidential files

The Progress Notes [PROGRESS] form should be used to track the participant's clinic visits and phone calls, and as source documentation for the study data. Any notes made by the RC or PI must be signed by the person writing the note.

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PROGRESS NOTES

Participant Name/ID: _____ / _____

Date: ____ / ____ / ____

[illegible]

5.5.16 Study Medication Tracking Log [TRACK]

Binder: Clinic Regulatory Binder

The Study Medication Tracking Log [TRACK] form tracks all study medications dispensed and collected during the course of the CPCR N RCT#1. This form should correspond to the Dispensing Log [DISP] form and the Visit #4 Follow-Up Contacts [FUP] form for each participant. Each participant randomized should be listed on this log when he receives and when he returns his study medications.

- Participant ID: When dispensing the study medications, enter the Participant ID.
- Participant Initials: When dispensing the study medications, enter the participant's initials.
- Randomization Number: When dispensing the study medications, enter the randomization number assigned by the database system. The number **must** match the number on the drug kit being dispensed.
- Date Dispensed: When dispensing the study medications, enter the date.
- # of Capsules Dispensed: When dispensing the study medications, enter the number of capsules in the bottle being distributed to the participant.
- Dispensed By: When dispensing the study medications, enter the initials of the clinic personnel distributing the study medications. This person must have been designated by the PI to perform this function (as indicated on the Clinical Site Staff "Signature and Delegation of Responsibilities" Log [SITELOG] form).
- Date Returned: When collecting the study medications from the participant, enter the date.
- # of Capsules Returned: When collecting the study medications from the participant, enter the number of capsules in the bottle the participant is turning in.
- Returned To: When collecting the study medications from the participant, enter the initials of the clinic personnel collecting the study medications. This person must have been designated by the PI to perform this function (as indicated on the Clinical Site Staff "Signature and Delegation of Responsibilities" Log [SITELOG] form).
- Amount Lost: When collecting the study medications from the participant, enter the number of capsules the participant reports as having been lost or destroyed.

STUDY MEDICATION TRACKING LOG

[illegible]

TRACK

5.5.17 Uropathogens Localized to Semen Calculations [UCAL]

Binder: Participant's Study Binder

This form will aid in the calculations required to determine if the participant has uropathogens localized to semen. Participants found to be positive will be required to provide an additional semen specimen at the completion of the treatment portion of the trial. Participants will be asked to return to the clinic a few days after Visit #4 to provide an additional semen specimen since it is not recommended that the Four-Glass Test and semen specimen collection occur on the same day. There is space provided on page two to record the participants various culture counts and complete the calculations.

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Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

UROPATHOGENS LOCALIZED TO SEMEN CALCULATIONS

Participants are considered to have uropathogens localized to semen when one of the following situations exists:

1. There are pathogens* identified in the semen that are not present in either the VB1 or VB2 cultures.

OR

2. The same pathogens* are identified in the semen and the VB1 or VB2 cultures, but a greater amount (at least a 2 log difference) in the semen.

*Only the following pathogens will be considered **uropathogens** and need be included in any calculations:

Species	Species Code
Staphylococcus Aureus	02
Enterococcus Fecalis	07
Escherichia Coli	09
Klebsiella	10
Pseudomonas	11
Proteus	12

To determine if the participant has uropathogens localized to semen, first identify which pathogens from the above list were isolated in both semen and VB1 or VB2 cultures.

Next, determine in which range the VB1 or VB2 culture count fits using the following codes:

0=0-9
1=10-99
2=100-999
3=1,000-9,999
4=10,000-99,999
5=100,000 and higher

Now, determine in which range the semen culture count fits using the same codes.

**Randomized
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Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

Subtract the VB1 or VB2 culture count code number from the semen culture count code number. If the answer is 2 or greater, then the uropathogens are localized to semen. The participant will be required to provide another semen specimen at Visit 4.

Sample calculations: Proteus culture count for semen = 10,000 4
Proteus culture count for VB2 = 100 2
4-2=2, so the uropathogen **is** localized to semen

OR

Proteus culture count for semen = 10,000 4
Proteus culture count for VB2 = 1,000 3
4-3=1, so the uropathogen **is not** localized to semen

		A		B	A-B
Species Code	Semen Culture Count	Count Code	Maximum of VB1/VB2 Culture Count	VB1/VB2 Count Code	Difference in Culture Count
02					
07					
09					
10					
11					
12					

5.5.18 Visit 1 Checklist [VISIT1]

Binder: Participant's Study Binder

The Visit #1 Checklist [**VISIT1**] form lists all the forms and tests to be completed for Visit #1, the first screening visit. This form *must* be completed for every participant, and filed in the participant's study binder.

Any forms marked **No** must have an explanation provided in the comment section.

The review, first entry, and verification section *must* be initialed and dated.

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Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

VISIT 1 CHECKLIST - FIRST SCREENING CLINIC CONTACT

- | | | | |
|-----|---|---|--|
| 1. | Acquire informed consent | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 2. | Assign Participant ID number | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 3. | Eligibility Checklist (ELIG) (Inclusion, Exclusion, and Deferral Criteria) | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 4. | NIH-CPSI (CPSI) | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 5. | Medical History (MED) | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 6. | Physical Exam (EXAM) | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 7. | Four Glass Test Microscopy (FGTM) and Cultures (FGTC) | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 8. | Participant Contact Information (CONTACT) | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 9. | Distribute Voiding Log (VOID) | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 10. | Complete Participant Status Log (STATUS) | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 11. | Instruct participant to bring his current medications to Visit 2 | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 12. | Schedule Visit 2 - second screening clinic contact | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |

If **No** for any of the above, please comment: _____

Review Completed forms (initial and date): _____

First Entry (initial and date): _____

Verification (initial and date): _____

5.5.19 Visit 2 Checklist [VISIT2]

Binder: Participant's Study Binder

The Visit #2 Checklist [VISIT2] lists all the forms and tests to be completed for Visit #2, the second screening visit. This form *must* be completed for every participant, and filed in the participant's study binder.

Any forms marked **No** must have an explanation provided in the comment section.

The review, first entry, and verification section *must* be initialed and dated.

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

VISIT 2 CHECKLIST - SECOND SCREENING CLINIC CONTACT

- | | | | |
|-----|--|------------------------------|-----------------------------|
| 1. | NIH-CPSI (CPSI) | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 2. | Randomize participant and complete the Randomization (RAND) form | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 3. | SF-12 (SF12) and Follow-Up Symptoms (SYM) | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 4. | Demographics (DEMO) | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 5. | Review Medication Diary (DIARY)/complete Concomitant Medication (CMED) | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 6. | Semen Sample (SEMEN) and Uropathogens Localized to Semen Calculations (UCAL) | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 7. | Uroflow and PVR (URO) | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 8. | Collect Voiding Log (VOID) | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 9. | Update Participant Status Log (STATUS) | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 10. | Dispense study medications and complete the Dispensing Log (DISP) and the Study Medication Tracking Log (TRACK) | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 11. | Distribute <i>one</i> copy of DIARY , EMEDS , VOID , and distribute <i>two</i> copies of CPSI , SYM and SF12 . | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| 12. | Schedule Visit 3 - Week 3 phone contact | <input type="checkbox"/> Yes | <input type="checkbox"/> No |

If **No** for any of the above, please comment: _____

Review Completed forms (initial and date): _____
First Entry (initial and date): _____
Verification (initial and date): _____

5.5.20 Visit 3 Checklist [VISIT3]

Binder: Participant's Study Binder

The Visit #3 Checklist [**VISIT3**] form lists all the forms and tests to be completed for Visit #3 telephone contact. This form *must* be completed for every participant, and filed in the participant's study binder.

Any forms marked **No** must have an explanation provided in the comment section.

The review, first entry, and verification section *must* be initialed and dated.

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

VISIT 3 CHECKLIST - WEEK 3 PHONE CONTACT

- | | | | |
|----|--|---|--|
| 1. | Follow-Up Contacts (FUP) | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 2. | Adverse Events and Serious Adverse Events (AE) | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 3. | Instruct participant to complete and mail the NIH-CPSI, the SF-12 and the Follow-Up Symptoms | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 4. | Schedule next visit | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 5. | Receive the NIH-CPSI, the SF-12, and the Follow-Up Symptoms in the mail | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |

If **No** for any of the above, please comment: _____

Review Completed forms (initial and date): _____

First Entry (initial and date): _____

Verification (initial and date): _____

5.5.21 Visit 4 Checklist [VISIT4]

Binder: Participant's Study Binder

The Visit #4 Checklist [VISIT4] form lists all the forms and tests to be completed for Visit #4 clinic visit. This form *must* be completed for every participant, and filed in the participant's study binder.

Any forms marked **No** must have an explanation provided in the comment section.

The review, first entry, and verification section *must* be initialed and dated.

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**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: _____ / _____ / _____
RC ID: _____

VISIT 4 CHECKLIST - WEEK 6 CLINIC CONTACT

1. NIH-CPSI (**CPSI**), SF-12 (**SF12**), and Follow-Up Symptoms (**SYM**) ☐₁ Yes ☐₀ No
2. Collect Medication Diary (**DIARY**)/complete Concomitant Medication (**CMED**) ☐₁ Yes ☐₀ No
3. Collect study medications and complete Follow Up Contacts (**FUP**) and the Study Medication Tracking Log (**TRACK**) ☐₁ Yes ☐₀ No
4. Adverse Events/Serious Adverse Events (**AE**) ☐₁ Yes ☐₀ No
5. Physical Exam (**EXAM**) ☐₁ Yes ☐₀ No
6. Four Glass Test Microscopy (**FGTM**) and Cultures (**FGTC**) ☐₁ Yes ☐₀ No
7. Semen Sample (**SEMEN**) ☐₁ Yes ☐₀ No
Note: Repeat only if semen culture positive at screening visit.
8. Uroflow and PVR (**URO**) - **Note: PVR Only** ☐₁ Yes ☐₀ No
9. Collect Voiding Log (**VOID**) ☐₁ Yes ☐₀ No
10. Treatment Stop (**TSTOP**) ☐₁ Yes ☐₀ No
11. Distribute *two* copies of **CPSI**, **SYM**, and **SF12** and *one* copy of **RMED** ☐₁ Yes ☐₀ No

If **No** for any of the above, please comment: _____

Review Completed forms (initial and date): _____

First Entry (initial and date): _____

Verification (initial and date): _____

5.5.22 Visit 5 Checklist [VISIT5]

Binder: Participant's Study Binder

The Visit #5 Checklist [VISIT5] form lists all the forms and tests to be completed for Visit #5 phone contact. This form *must* be completed for every participant, and filed in the participant's study binder.

Any forms marked **No** must have an explanation provided in the comment section.

The review, first entry, and verification section *must* be initialed and dated.

**C
P
C
R
N**

**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

VISIT 5 CHECKLIST - WEEK 9 PHONE CONTACT

- | | | | |
|----|--|---|--|
| 1. | Follow-Up Contacts (FUP) | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 2. | Adverse Events and Serious Adverse Events (AE) | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 3. | Instruct participant to complete and mail the NIH-CPSI, the SF-12 and the Follow-Up Symptoms | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 4. | Schedule next visit | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |
| 5. | Receive the NIH-CPSI, the SF-12, and the Follow-Up Symptoms in the mail | <input type="checkbox"/> ₁ Yes | <input type="checkbox"/> ₀ No |

If **No** for any of the above, please comment: _____

Review Completed forms (initial and date): _____

First Entry (initial and date): _____

Verification (initial and date): _____

5.5.23 Visit 6 Checklist [VISIT6]

Binder: Participant's Study Binder

The Visit #6 Checklist [VISIT6] form lists all the forms and tests to be completed for Visit #6 phone contact. This form *must* be completed for every participant, and filed in the participant's study binder.

Any forms marked **No** must have an explanation provided in the comment section.

The review, first entry, and verification section *must* be initialed and dated.

**C
P
C
R
N**

**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: _____ / _____ / _____
RC ID: _____

VISIT 6 CHECKLIST - WEEK 12 PHONE CONTACT

1. Follow-up Contacts (**FUP**) ☐ ₁ Yes ☐ ₀ No
2. Adverse Events and Serious Adverse Events (**AE**) ☐ ₁ Yes ☐ ₀ No
3. Semen Sample (**SEMEN**) ☐ ₁ Yes ☐ ₀ No
Note: Repeat only if semen culture positive at screening visit
4. Study Stop (**SSTOP**) ☐ ₁ Yes ☐ ₀ No
5. Instruct participant to complete and mail the NIH-CPSI, the SF-12 the Follow-up Symptoms, and the Medication Diary. ☐ ₁ Yes ☐ ₀ No
6. Complete Participant Status Log (**STATUS**) ☐ ₁ Yes ☐ ₀ No
7. Receive the NIH-CPSI, the SF-12, the Follow-up Symptoms and the Medication Diary in the mail. ☐ ₁ Yes ☐ ₀ No

If **No** for any of the above, please comment: _____

Review Completed forms (initial and date): _____

First Entry (initial and date): _____

Verification (initial and date): _____

5.5.24 Visit 98 Checklist [VISIT98]

Binder: Participant's Study Binder

The Visit #98 Checklist [VISIT98] form lists all the forms and tests to be completed for the PRN Visit #98, the early stop treatment contact. This form *must* be completed for any participant who discontinues study medications, for any reason, prior to Visit 4+, and filed in the participant's study binder.

Any forms marked **No** must have an explanation provided in the comment section.

The review, first entry, and verification section *must* be initialed and dated.

**C
P
C
R
N** **Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/_____
RC ID: _____

VISIT 98 CHECKLIST - EARLY STOP TREATMENT

- | | | | |
|----|---|---|--|
| 1. | NIH-CPSI (CPSI) | <input type="checkbox"/> _L Yes | <input type="checkbox"/> _G No |
| 2. | SF-12 (SF12) | <input type="checkbox"/> _L Yes | <input type="checkbox"/> _G No |
| 3. | Follow-Up Symptoms (SYM) | <input type="checkbox"/> _L Yes | <input type="checkbox"/> _G No |
| 4. | Treatment Stop (TSTOP) | <input type="checkbox"/> _L Yes | <input type="checkbox"/> _G No |
| 5. | Complete Study Medication Tracking Log (TRACK) | <input type="checkbox"/> _L Yes | <input type="checkbox"/> _G No |

If **No** for any of the above, please comment: _____

Review Completed forms (initial and date): _____

First Entry (initial and date): _____

Verification (initial and date): _____

5.5.25 Visit 99 Checklist [VISIT99]

Binder: Participant's Study Binder

The Visit #99 Checklist [VISIT99] form lists all the forms and tests to be completed for the PRN Visit #99, the rescue treatment event contact. This form *must* be completed for any participant, at the first incidence of using a rescue medication or treatment for symptoms of prostatitis or pelvic pain, after completing the six-week study medication portion of the trial. **Note:** this set of forms is not to be used to record any medications or treatments the participant may have been using during the six-week study medication portion of the trial. This form should be filed in the participant's study binder.

Any forms marked **No** must have an explanation provided in the comment section.

The review, first entry, and verification section *must* be initialed and dated.

**C
P
C
R
N**

**Randomized
Clinical
Trial #1**

Participant ID: _____
Participant Initials: _____
Clinical Center: _____
Visit Number: _____
Visit Date: ____/____/____
RC ID: _____

VISIT 99 CHECKLIST - RESCUE TREATMENT EVENT

- | | | | |
|----|--|---|--|
| 1. | NIH-CPSI (CPSI) | <input type="checkbox"/> _I Yes | <input type="checkbox"/> _O No |
| 2. | SF-12 (SF12) | <input type="checkbox"/> _I Yes | <input type="checkbox"/> _O No |
| 3. | Follow-Up Symptoms (SYM) | <input type="checkbox"/> _I Yes | <input type="checkbox"/> _O No |
| 4. | Rescue Treatment Event (RMED) | <input type="checkbox"/> _I Yes | <input type="checkbox"/> _O No |

If **No** for any of the above, please comment: _____

Review Completed forms (initial and date): _____

First Entry (initial and date): _____

Verification (initial and date): _____

5.6 Directions for CRF Transfer

The CPCRN RCT#1 represents the first clinical intervention trial to be conducted by the CPCRN. Reporting to the DCC is an important part of ensuring the proper conduct throughout the trial. This is accomplished in two ways:

5.6.1 *Sending Copies of Completed CRFs to the DCC*

While data entry and verification is being performed at the clinical center, the DCC will review the first two (2) sets of completed forms to determine the level of completion of the forms themselves as well as the accuracy of the data entry and verification. Also an audit will be done for randomly selected participants. DCC will notify the RC of the participant IDs to be copied and sent. The following will be sent to the DCC:

- All screening and follow-up CRFs for the first two (2) participants
- All screening and follow-up CRFs for randomly selected participants

NOTE: Any CRFs and lab reports sent to the DCC must have all participant identifiers obliterated other than Participant ID and Participant Initials. However, all **source** documents kept on-site **must** maintain the participant's identity. Therefore, the original source document should be copied with the participant's name still visible. Then the name should be obscured **only on the copy**, which then will be forwarded to the DCC.

5.6.2 *Participant Logs*

The Participant Status Tracking Log [**STATUS**] form **must** be faxed to the DCC on the first Monday of every month. The DCC will send an E-mail reminder.

6 Clinical Centers' and/or DCC Responsibilities

6.1 Clinical Centers' Responsibilities

Each clinical site is responsible for staffing one RC to coordinate all activities (at the site level) required to achieve the goals of the study. The RC plays an integral part in keeping the study on course, and therefore every effort should be made to retain these individuals throughout the course of the study. If a RC leaves the study, however, the on-site investigator is responsible for hiring a replacement immediately to ensure overlap among the relevant individuals. The departing RC is responsible for training the replacement person or RC on issues concerning the study specific to the clinical site.

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

- Emphasizing the advantage of having a dedicated RC available to answer calls.
- Making a dedicated phone line with voice mail available to study participants.
- It is expected that each site will manage the study with integrity, professionalism, and confidentiality and will adhere to all applicable federal regulations and Good Clinical Practice Guidelines. The RC is expected to provide the most complete and accurate data possible.

The responsibilities of each Clinical Site RC include:

- Recruiting, screening, enrolling, and following participants throughout the course of the clinical trial.
- Confirming eligibility of each participant based on the study criteria identified in the protocol.
- Double data entry of CRFs with batch verification will be performed at the clinical sites.
- Faxing Participant Status Log [**STATUS**] form to the DCC on the first Monday of every month.
- Adhering to study protocol and the MOP in the implementation of procedures and the acquisition of data.
- Responding to queries regarding study information from the DCC in a **timely** fashion.

- In-servicing staff at clinical site to the study protocol.
- Enlisting aid of staff at clinical sites to assist with identification of potential participants.
- Maintaining approval from regulatory affairs board for study site.
- Completing and submitting annual/final reports to regulatory affairs board for study site.
- Serving as liaison with study site pharmacists and co-investigators.
- Submitting information regarding adverse events according to Federal and study site policy.

It is the responsibility of each clinical site to provide the appropriate IRB with all pertinent material, including a copy of the informed consent. Approval of the protocol and the Informed Consent Form must be obtained and forwarded to the DCC's Project Manager prior to screening or enrolling any participants. Each clinical site also maintains the responsibility of initiating protocol re-approval, notification of protocol and/or consent form changes, notification of adverse events, and termination of the study according to the appropriate IRB requirements.

The PI/RC must maintain documentation of appropriate licensure or accreditation for all clinical laboratory facilities used for study samples analysis.

6.2 DCC Responsibilities

The DCC, located at the University of Pennsylvania Medical Center, will provide data management/computing and biostatistical leadership for design/conduct of the trial. Responsibilities include:

- Overall leadership regarding study design and conduct of the trial.
- Preparation and distribution of the MOP, based on collaboration with the project team.
- Collaboration with study investigators in the development, testing, and use of all CRFs and study procedures.
- Provision of an efficient DMS for data entry into the central database at the DCC, and implementation of 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 site monitoring.
- Preparation of specified reports.
- Collaboration with study investigators in the analysis and publication of study results.

6.3 Maintenance and Disposition of Study Documents, Data and Materials

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

6.3.1 *Internal Distribution of Study Documents*

The DCC is responsible for maintaining a record of all documents, reports, and meeting minutes pertaining to the study. During the conduct of this protocol, the DCC will be responsible for the distribution of the MOP and CRFs to the clinical sites. At the end of the study, these documents will be internally archived at the DCC. Minutes of all appropriate committee meetings will be maintained in the files at the DCC.

6.3.2 *External Distribution of Study Documents*

The CPCRN Research Group will be responsible for the distribution of study documents and manuscripts requested by individuals not associated with this study.

6.3.3 *Data Collection – CRFs*

At the close of the study, all CRFs on file at the DCC, without personal identifiers, will be archived and stored at the DCC.

6.3.4 *Data Queries*

There will be occasions when information on the CRFs will require clarification. When this occurs, the DCC will send a query requesting action on the part of the RC to clarify the data. This is a critical step in protecting the safety of study participants; adhering to GCP's/regulations and capturing clean, accurate data. Corrections to data entered into the database can only be performed once the DCC receives the clarification in writing.

6.3.5 *Record Retention*

The DCC must maintain all study records for a time period in accordance to their internal Standard of Procedures (SOP) and applicable FDA regulations. The sites should retain all source documents, informed consent form, and CRFs (in accordance to

applicable FDA regulations) and until written notification is received from the DCC or sponsor.

6.3.6 Data Tapes and Analysis of Results

The DCC will prepare a computer tape of the study data, results, and analysis at the conclusion of the study. This tape will be accompanied by appropriate documentation. One copy will be forwarded to CPCRN Research Group. 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 the CPCRN Research Group. The DCC will provide documentation of all formulas and statistical analysis used in the study or referred to in the study documents.

6.4 Standard Monitoring and Auditing Activities

6.4.1 Protocol Monitoring

Study conduct and protocol adherence will be monitored by the DCC via the generation of standard reports describing study accrual, eligibility confirmation, visit schedule deviation, missing data, query rate, and other reports associated with quality control measures. Reports will be generated quarterly by the DCC throughout the course of the study. Site monitors will incorporate the information contained within to address issues at each site.

A review of data recorded on the CRF versus that contained on the actual source document (patient chart, lab reports, etc.). During Year 1, the DCC will require a copy of all source documents for the first two (2) subjects enrolled per site. When it has been determined that data are accurately being transferred from source documents to CRF, sites will no longer be required to send copies of source documents to the DCC for verification.

6.4.2 Data Audits

Throughout the course of the study, the DCC may periodically perform internal data audits in an effort to ensure data quality across all clinical sites.

6.4.3 Database Auditing

A review of the data entered into the database versus that recorded on the Case Report Forms (CRFs). During Year 1, internal audits may be conducted on a percentage of participants.

6.4.4 Site Monitoring

Two (2) monitoring visits per site will take place over the course of the study. The first will occur after 4 – 5 patients have been enrolled. The second will occur approximately

six (6) months later. Visits will be scheduled in advance with the center investigator and staff. Site visits may occur earlier or more often, depending on the results of data review and clinical events. A specific monitoring plan will be described. The primary areas of interest are: GCP compliance, case report forms and source document verification, informed consent process, study agent storage and accountability, adverse event reporting, protocol compliance and documentation. A minimum of 100% data review for 10% of subjects will occur. These services will be performed by an external clinical monitoring organization.

7 Data Management System User Guide

7.1 Overview

Description

This chapter provides specific instructions on the use of the software application used to enter data into the CPCRn – Protocol 3 Data Management System (DMS).

System Support Plan

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.

7.2 CPCRn Main Menu

Purpose: To allow access to CPCRn DMS system CC applications.

Users: Clinical center personnel:

- Data Management/Data Entry Personnel
- Research Coordinator

User Actions:

Open the “CPCRn – 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.

Press the “CPCRn RCT#1” Button to open the “Protocol 3 (CPCRn RCT#1): 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)
3. Enter Database (CPCRn RCT#1)
4. Press “Connect” button
5. The **CPCRn—Protocol 3 (CPCRn RCT#1)** Menu appears
6. Dialog box displays user name and role

7. Press OK button

7.3 CPCRN—Protocol 3 (CPCRN RCT#1) 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 to be eligible for the study.
- c. Performs Participant Randomization and issues the Randomization Number.
- d. Requires that all Screening and Eligibility CRFs be entered and verified.
- e. Requires Participant ID, Participant Initials and Clinical Center.

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 CRFs.

- b. Requires a complete visit packet of CRFs for a specific participant and visit.
- c. Allow entry and verification of Study Stop Point [**SSTOP**], 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.

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 and or Code Name of drug.

7. Reports Menu: Opens the Reports Menu Application

8. Cancel: Exits the CPCR N -- Protocol 3 (CPCR N RCT#1) Clinical Center Menu

7.4 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.

7.5 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 (can not perform randomization)
- Research Coordinator

User Actions:

1. Enter participant ID

- a. The participant initials will be cross checked 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
- b. Choose Screening Entry Type:
 - 1) *Entry*: To perform first entry of the CRFs.
 - 2) *Verification*: To perform the second entry verification of the CRFs.
 - 3) *RAND*: To Randomize the Participant.
 - 4) *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] and Concomitant Medication [CMED] 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 specimen and void log fields.
- 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).

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 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 date 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 is 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.

7.6 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 a Participant ID registered with the randomization site is entered.
2. Enter Participant Initials
 - a. The participant initials will be cross checked 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.

7.7 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 a Participant ID registered with the Clinical Center is entered.
2. Enter participant initials
 - a. The participant initials will be cross checked 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.
 - b. 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.
6. After entering the mandatory fields, choose:
 - a. CRF Type:
 - 1) All visit forms: To enter a visit packet of CRFs.
Study Stop Point [**SSTOP**], 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 Appendix A.
 - 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**], Four-Glass Treatment Cultures [**FGTC**], Semen Sample [**SEMEN**], and Voiding Log [**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.

- c. 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 specimen, Concomitant Medication [**CMED**], Adverse Events/Serious Adverse Events [**AE**], and Void Log [**VOID**] fields.
- 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).

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 field in Four-Glass Test Cultures [**FGTC**] and Semen Sample [**SEMEN**], or the fields in the Concomitant Medication [**CMED**], Adverse Events/Serious Adverse Events [**AE**], or Void Log [**VOID**]; 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.

7.8 **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. Randomized Participant: 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 person who registered the participant into the DMS,
 - e. *Randomization Number*: The randomization number assigned to the participant upon successfully randomizing the participant, 4 or 5 digits.
 - 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).

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.

7.9 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. Changed Sort Criteria, if necessary. The list is sorted by Generic Name, by default.
4. After entering the drug name, press enter (enter key on the keyboard), the list of matching medication names along with the medication code and the cross-reference medication name appears in the “Drug Names and Codes” block.
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.

7.10 Reports and CRF's

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.

7.11 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

The zip code on the Demographics [**DEMO**] form is the only alpha-numeric field.

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**] and Concomitant Medications [**CMED**] 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.

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.

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 text field that will be entered is the event description 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. All other comments and descriptions will not be entered.

Adverse Events/Serious Adverse Events [AE] & Concomitant Medications [CMED] Description Fields

These fields will not be entered. The DMS will provide a description based on the Adverse Events/Serious Adverse Events [AE] or Concomitant Medications [CMED] event or drug code.

7.12 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.

7.13 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.

7.13.1 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 networking hardware.

7.13.2 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.

7.13.3 Procedures For Obtaining Help Desk Support

Study personnel can contact the CRCU Software Systems Help Desk by telephone or e-mail.

7.13.3.1 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
- Project Name
- Name/Location of Clinical Center

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
- Project Name
- Clinical Center
- Brief description of the problem that initiated the call.

7.13.3.2 E-mail Support

The CRCU Software Systems Help Desk can be e-mailed at:
sshelpdesk@cceb.upenn.edu

When sending e-mail, the following information must be provided:

- Name
- Project Name
- Clinical Center
- Phone number
- Nature of the technical problem

7.13.4 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, problems may occur that require additional interaction between the caller, help desk, and Data Management System designers. 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.

7.14 Help Desk Availability

The CRCU Software Systems Help Desk is available during normal business hours (8:00am – 5:00pm EST).

References

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2. Stamey T. *Pathogenesis and treatment of urinary tract infections*. Baltimore: Williams and Wilkins; 1980.
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4. Nickel JC, Sorensen R. Transurethral microwave thermotherapy for nonbacterial prostatitis: a randomized double-blind sham controlled study using new prostatitis specific assessment questionnaires. *Journal of Urology* 1996; **155**:1950-1954.
5. Anonymous. Executive Summary. *Chronic Prostatitis Workshop*. Bethesda, MD: NIDDK; 1995.
6. Egan KJ, Kreiger JL. Chronic abacterial prostatitis - a urological chronic pain syndrome? *Pain* 1997; **69**:213-218.
7. Litwin MS, McNaughton-Collins M, Fowler FJ, Jr., Nickel JC, Calhoun EA, Pontari MA et al. The National Institute of Health Chronic Prostatitis Symptom Index: Development and Validation of a New Outcome Measure. *Journal of Urology* 1999; **162**(2):369-375.

Acronyms/Abbreviations

AIP – Asymptomatic Inflammatory Prostatitis
AE – Adverse Events and Serious Adverse Events Form
AUTH – Authorization to Unmask
BCG – Bacille Calmette-Guerin
CC – Clinical Center
CCORRESP – Clinic Correspondence Log
CMED – Concomitant Medications
CONTACT – Participant Contact Information Form
CP – Chronic Prostatitis
CPC – Chronic Prostatitis Cohort
CPCRN – Chronic Prostatitis Collaborative Research Network
CPPS – Chronic Pelvic Pain Syndrome
CPSI – NIH-Chronic Prostatitis Symptom Index Form
CRCs – Clinical Research Centers
CRFs – Case Report Forms
CTC – Common Toxicity Criteria
CVs – Curriculum Vitae
DCC – Data Coordinating Center
DEMO – Demographics Form
DIARY – Medication Diary Form
DISP – Dispensing Log Form
DMS – Data Management System
ELIG – Eligibility Checklist Form
EMED – Exclusionary Medications
EPS – Expressed Prostatic Secretions
EXAM – Physical Exam Form
FGTC – Four-Glass Test Cultures
FGTM – Four-Glass Test Microscopy
FUP – Follow-up Contacts Form
HOWTO – How To Complete Your Voiding Log Form
IRB – Internal Review Board
LAB – Lab Tracking Log Form
LOG – Participant ID Assignment Log Form
MED – Medical History Form
MONITOR – Monitoring Log Form
MOP – Manual of Procedures
NCI – National Cancer Institute
NIDDK – National Institute of Diabetes Digestive and Kidney
NIH – National Institute of Health
OTC – Over-the-counter drugs
PCORRESP – Participant Correspondence Log Form
.pdf – Portable Document Format
PI – Principal Investigator
PROGRESS – Progress Notes Form

RAND – Randomization Form
RC – Research Coordinator
RCT #1 – Randomized Clinical Trial #1
RMED – Rescue Treatment Event Form
SAE – Serious Adverse Event
SEMEN – Semen Sample Form
SCHEDULE – Forms Administration Schedule
SF12 – SF-12 Form
SIGN – Authorized Signature Log Form
SSTOP – Study Stop Form
STATUS – Participant Status Log Form
SYM – Follow-up Symptoms Form
TRACK – Study Medication Tracking Log Form
TRANS – Participant Transfer Form
TSTOP – Treatment Stop Form
TUIBN – Transurethral Incision of the Bladder Neck
TUIP – Transurethral Incision of the Prostate
TUMT – Transurethral Microwave Thermotherapy
TUNA – Transurethral Needle Ablation (prostatic)
TURP – Transurethral Resection of the prostate; transurethral prostatectomy
UCAL – Uropathogens Worksheet Form
UNMASK – Unmasking Record Form
UPenn IDS – The University of Pennsylvania Investigational Drug Service
URO – Uroflow Form
VB-3 – Voided Bladder Urine-3
VISIT1 – Visit 1 Checklist Form
VISIT2 – Visit 2 Checklist Form
VISIT3 – Visit 3 Checklist Form
VISIT4 – Visit 4 Checklist Form
VISIT5 – Visit 5 Checklist Form
VISIT6 – Visit 6 Checklist Form
Visit98 – Early Stop Treatment Contact Checklist Form
Visit99 – Rescue Treatment Event Contact Checklist Form
VOID – Voiding Log Form

Manual of Procedure

Agreement Page

CPCRN RCT #1

CPCRN Randomized Clinical Trial #1

I will provide copies of the MOP, any subsequent MOP amendments and access to all information furnished by the sponsor to study personnel under my supervision. My signature constitutes my understanding and provides the necessary assurance that this study will be conducted according to all stipulations of the MOP, including all statements regarding confidentiality.

I agree to conduct this clinical trial according to the MOP described herein, except when mutually agreed to in writing. I also agree to conduct this study in compliance with all applicable federal, state and local regulations, as well as with the requirements of the appropriate Institutional Review Board and any other institutional requirements.

Signature (Principal Investigator)

Date

Name (Please Print)

Institution

Appendix A

Participant Recruitment Brochure

The CPRN is comprised of the following ten clinical research centers and a Data Coordinating Center (DCC) which coordinates all activities related to the study.



PARTICIPATING CLINICAL CENTERS AND PRINCIPAL INVESTIGATORS

Brigham and Women's Hospital
Boston, MA
Michael P. O'Leary, MD, MPH

Cleveland Clinic Florida
FL, Lauderdale, FL
Daniel Shoskes, MD

MLK Drew Medical Center
Los Angeles, CA
Nand S. Datta, MD

Northwestern University
Chicago, IL
Anthony J. Schaeffer, MD

Queen's University
Kingston, Ontario
J. Curtis Nickel, MD

Temple University
Philadelphia, PA
Michel A. Pontari, MD

University of Arizona
Tucson, AZ
Craig Comiter, MD
University of California – Los Angeles
Los Angeles, CA
Mark S. Litwin, MD, MPH

University of Maryland
Baltimore, MD
Richard B. Alexander, MD

University of Mississippi
Jackson, MS
Jackson E. Fowler, MD

University of Pennsylvania (DCC)
Philadelphia, PA
J. Richard Landis, PhD



For more information, please contact
the medical center at the bottom of the page
or Lee Randall, Project Manager,
University of Pennsylvania
(215) 573-6318 Phone
(215) 573-6262 Fax
lranda1@cceb.upenn.edu

TO MAKE AN APPOINTMENT, PLEASE
CONTACT:

CHRONIC PROSTATITIS COLLABORATIVE RESEARCH NETWORK (CPCRn)

RANDOMIZED CLINICAL TRIAL #1



INFORMATION FOR PATIENTS



Chronic Prostatitis (CP) is a disabling condition affecting an untold number of men of all ages and ethnic origins. CP is a disease of chronic pelvic discomfort and/or pain for which there is no standardized method of diagnosis and treatment. Under the direction of the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) and the National Institutes of Health (NIH), the Chronic Prostatitis Collaborative Research Network (CPCRn) has been established to study all aspects of this puzzling disease.



Men who have experienced pelvic discomfort and/or pain for at least three months and meet certain eligibility requirements, may be eligible to enroll in the first randomized clinical trial. Patients will be asked to comply with the following trial requirements:

- ◆ Symptom Questions
- ◆ Medical History
- ◆ Physical Exam
- ◆ Urine Specimen
- ◆ Semen Specimen
- ◆ Expressed Prostatic Secretions Specimen
- ◆ Uroflow Study
- ◆ Urethral Swab
- ◆ Voiding Log

Each procedure and questionnaire contributes a wealth of information to the trial database, which tracks information about *all* patients enrolled in the trial.

Confidentiality is guaranteed through the use of unique identification numbers for all patient information.

Once a patient is enrolled into the trial, he will be randomized into one of four treatment groups. This means you have a 75% chance of receiving a study drug. Patients will take the study drug or its matching placebo for 6 weeks and participate in a follow up period for an additional 6 weeks, for a total of 12 weeks. This study includes 3 doctor visits and 3 telephone contacts.

These established research steps will enable the CPRN to study the natural history of this disease while testing diagnostic tools and potential therapies, with the ultimate goal to develop effective treatment for patients.

Appendix B

Informed Consent Form

Consent Form

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

SUGGESTED PARTICIPANT CONSENT FORM

A MULTICENTER, RANDOMIZED CLINICAL TRIAL (RCT) TO EVALUATE THE EFFICACY OF ORAL CIPRO®, ORAL FLOMAX® AND THE COMBINATION OF ORAL CIPRO® & ORAL FLOMAX® FOR THE TREATMENT OF CHRONIC PROSTATITIS

Chronic Prostatitis Clinical Research Network (CPCRN) CPCRN RCT#1 PROTOCOL

You are being asked to participate in a research study because you have been diagnosed with Chronic Prostatitis and have been informed that you may be eligible for the investigational study known as: "A Multicenter, Randomized Clinical Trial to Evaluate the Efficacy of Oral CIPRO®, Oral FLOMAX® and the Combination of Oral CIPRO® and Oral FLOMAX® for the Treatment of Chronic Prostatitis."

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

What is the purpose of the study?

The purpose of this study is to investigate the efficacy of Ciprofloxacin (trade name: CIPRO®), a clinically available drug and oral tamsulosin hydrochloride (trade name: Flomax®), to treat the symptoms of Chronic Prostatitis (CP). This study will attempt to determine if any of these treatments are effective in providing relief for CP: oral ciprofloxacin (CIPRO®), oral tamsulosin hydrochloride (FLOMAX®), or the combination of these two drugs.

An evaluation will be made to determine if you are eligible for this study. If so, and you agree to participate, you will be randomly assigned to one of four treatment groups. The combination of the medications you will receive in the study will be randomized, that is by chance, like a flip of a coin. Neither your physician nor you will know to which treatment group you will be assigned. Group One will receive two oral placebos (like sugar pills). Group Two will receive oral CIPRO® plus an oral placebo. Group Three will receive oral FLOMAX® plus an oral placebo. Group Four will receive oral CIPRO® plus oral FLOMAX®. However, information regarding which treatment you are receiving will be made available to your physician in case of an emergency.

What is Ciprofloxacin (CIPRO®)?

Ciprofloxacin has been approved by the United States Food and Drug Administration (FDA) for the treatment of infections in conditions such as: acute sinusitis (nasal sinus infection), lower respiratory tract infections (lower chest infection), urinary tract infections (bladder infection), chronic bacterial prostatitis (long term infection of the prostate gland), bone and joint infections, skin and intra-abdominal infections (infection within the part of the body between the chest and pelvis), infectious diarrhea, and typhoid fever. CIPRO® (and similar drugs) are often used to treat chronic prostatitis and you may have all ready been treated with this drug.

What is Tamsulosin Hydrochloride (FLOMAX®)?

Tamsulosin Hydrochloride (FLOMAX®) is an FDA approved drug for the treatment of the signs and symptoms of benign (non cancerous) prostatic hyperplasia (excessive, rapid reproduction of normal cells). FLOMAX® is a newer alpha-adrenergic agent (a substance that blocks transmission of stimuli) and is has been suggested that such drugs may be useful in the treatment of Chronic Prostatitis.

Who is being invited to participate in this study?

You will be invited to participate in this study if:

- You are a male;
- You must have had symptoms of discomfort or pain in the pelvic region for at least a three (3) month period within the last six (6) months;
- You have at least a moderate score on the National Institutes of Health (NIH)–Chronic Prostatitis Symptom Index (CPSI) with overall score ≥ 15 out of a potential of 0 - 43 points.

Approximately 184 participants with clinically diagnosed CP will be involved in this study. If you choose to participate, your involvement in the study will last at least 12 weeks.

What will I be asked to do if I participate in this study?

If you choose to participate in this study, and after you have signed and dated the consent form, the clinical research coordinator will evaluate your eligibility for the study. The following will then be performed:

1. Complete a thorough health history and physical examination.

The costs of these tests will be covered as part of the study. Your health history and physical examination will include 1) an abdominal examination, external genital exam, rectal exam, prostate exam, and perineal exam (area around the scrotum and anus), 2) urinalysis and a urine culture (examining a urine sample under a microscope to detect the presence of blood, infection and other processes, 3) an EPS specimen (expressed prostatic secretion) which involves a rectal exam. These tests will be repeated once at week six (6) during the twelve (12) week trial. You will also complete questionnaires to assess your pain/discomfort, Urinary Symptoms and a Quality of Life Index.

2. Take the study medication.

You need to take one or two tablets from each bottle of study medication once or twice a day. You will receive specific instructions regarding how to take the study medication by the research staff. You will take study medications for six (6) weeks.

3. Participate in study follow up.

You will be required to participate in 2 telephone contacts at week nine (9) and week twelve (12).

What benefits will I receive from the study?

You may receive no direct benefit from participating in this study. The purpose of this study is to determine the effectiveness of CIPRO®, FLOMAX® and the combination of CIPRO® and FLOMAX® to improve the symptoms of CP. Even though you may receive CIPRO® or FLOMAX®, or both, or a placebo, there is no assurance that you will receive any benefit from participating in this study. It is possible that your symptoms may even worsen while participating in this study. At the present time, no representation can be made that your participation will be of certain benefit.

What are the risks of participating in the study?

In general, oral administration of CIPRO® has been safe and well tolerated. CIPRO® may cause you to experience: nausea, vomiting, abdominal pain/discomfort, rash, agitation (nervousness), confusion, delirium, seizures or convulsions, dysphasia (difficulty speaking), constipation, dyspepsia (heartburn), flatulence (gas), hypersensitivity to sunlight, hepatic necrosis (damage to the liver), jaundice (yellowing of the skin), pancreatitis (infection of the pancreas), colitis (inflammation of the colon), anemia (low blood count), prolongation of prothrombin time (lengthening of the time it takes for your blood to clot), elevation of certain elements in your blood (i.e. cholesterol, blood glucose, potassium), muscular pain,

tendinitis/tendon rupture, worsening of the symptoms associated with hyperthyroidism (Graves Disease), allergic reaction, and taste loss.

For oral FLOMAX®, the side effects may include: headache, infection, dizziness, back and chest pain, skin rash, pruritis (itching), urticaria (development of raised itching skin areas), or angioedema (giant hives), lowering of blood pressure, dizziness, fainting, lightheadedness, diarrhea, nausea, insomnia (difficulty sleeping), drowsiness, decreased libido and/or abnormal ejaculation, sinusitis (nasal infection), upper respiratory infection (infection in your upper airway), and visual disturbances.

Risks associated with the tests include risk of drawing blood (fainting, bruising, numbness and pain at the site of the blood draw).

What else do I need to know?

Alternatives:

The alternative is not to participate in the study. Should you choose not to participate, you will receive the usual standard of medical care for your chronic prostatitis.

Voluntary Participation

Your participation in this study is voluntary. You are free to withdraw from the study at any time. If you decline to participate or choose to withdraw, you will still receive the same health care you would have otherwise received.

Confidentiality

You understand that every attempt will be made by the investigator to maintain all information collected in this study strictly confidential, except as required by law. You further understand that authorized representatives of the Sponsor, the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), National Institute of Health (NIH), (insert your institution's name), as well as the Food and Drug Administration (FDA), will have access to and may copy, both your medical records and records from your participation in this study. This access is necessary to insure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this research, you will not be identified by name.

Financial Costs

You will not have to pay to be in this study.

Compensation

You will receive no money for enrolling in this study. CIPRO® and/or FLOMAX®, the study medications, will be provided free of charge during your participation.

Medical Treatment or Compensation for Injury

You understand that in the event of any physical injury resulting from the research procedures, medical treatment will be provided without cost to you, but financial compensation is not otherwise available from the (insert your Institution's name).

New Information

If new information becomes available during the study that may impact on your willingness to continue to participate in the study, we will share that information with you.

Contact Persons

If at any time you have questions, concerns or comments about this study or a research-related injury, you should contact:

Telephone:
Principal Investigator:

Institutional Review Boards/Subject Rights

(Insert your Institution's name) has a committee called the Institutional Review Board (IRB). It is their responsibility to make sure that the research being conducted is safe and that people in the study are informed about risks and benefits of the research project. If you have questions regarding your rights as a research participant, or if problems arise which you do not feel you can discuss with Dr. _____, please contact your doctor's IRB by calling **(Insert your IRB's name and phone number)**.

PARTICIPANT'S STATEMENT:

I have read the above information about CIPRO® and FLOMAX® Study. I have been given an opportunity to ask questions about it and to discuss it with **Investigator's name or Authorized Personnel**. All of my questions/concerns have been answered to my satisfaction. I understand that I need to contact the **(insert your Institution's name and telephone number)**, if I move or change my telephone number. My signature below indicates my voluntary participation in this research program and that no procedures associated with this study have been performed on me prior to my signing this consent.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that I may refuse to participate or withdrawal from the study at any time without consequence to my present or future care at the **(insert your Institution's name)**.

DOCUMENTATION OF CONSENT

The original and one copy of this consent form will be kept in a research folder and a second copy of this Consent Form will be given to me to keep.

Consent of Subject:

I _____ certify that I have explained to the subject named below the nature and purpose of the study, potential benefits, and possible risks associated with participation in the study. I have answered any questions that have been raised and have witnessed the signature of this subject. I have explained the information contained in this document to the subject on the date stated on this consent form.

_____ Name of Person Obtaining Consent (print)	_____ Signature	_____ Date
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I have read and received a copy of this consent form. I agree voluntarily to participate in this research study.

_____ Name of Subject (print)	_____ Signature of Subject	_____ Date
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_____ Legally Authorized Representative Signature (If Patient is Unable to Sign)	_____ Relationship to Patient	_____ Date
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_____ Name of Investigator (print)	_____ Signature of Investigator	_____ Date
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_____ Name of Impartial Witness (print) (Completed <u>Only</u> if patient or their legal representative is unable to read this consent form and an impartial witness is present for the entire discussion).	_____ Signature of Witness	_____ Date
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Appendix C

Common Toxicity Criteria (CTC)

Appendix D

Drug Product Insert

CIPRO®

Cipro Tablets (Bayer):

CIPRO® (ciprofloxacin hydrochloride) Tablets and CIPRO® (ciprofloxacin) Oral Suspension are synthetic broad spectrum antimicrobial agents for oral administration. Ciprofloxacin hydrochloride, USP, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance with a weight of 385.8. empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$.

Ciprofloxacin is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its molecular weight is 331.4. It is a faintly yellowish to light yellow crystalline substance.

Ciprofloxacin differs from other quinolones in that it has a fluorine atom at the 6-position, a piperazine moiety at the 7-position, and a cyclopropyl ring at the 1-position.

CIPRO® film-coated tablets are available in 100-mg, 250-mg, 500-mg and 750-mg (ciprofloxacin equivalent) strengths. The inactive ingredients are starch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, methylcellulose, titanium dioxide, polyethylene glycol and water.

Ciprofloxacin Oral Suspension is available in 5% (5 g ciprofloxacin in 100 mL) and 10% (10 g ciprofloxacin in 100 mL) strengths. Ciprofloxacin Oral Suspension is a white to slightly yellowish suspension with strawberry flavor which may contain yellow-orange droplets. It is composed of ciprofloxacin microcapsules and diluent which are mixed prior to dispensing (See instructions for USE/HANDLING). The components of the suspension have the following compositions:

Microcapsules--ciprofloxacin, polyvinylpyrrolidone, methacrylic acid copolymer, hydroxypropyl methylcellulose, magnesium stearate, and Polysorbate 20.

Diluent--medium-chain triglycerides, sucrose, lecithin, water, and strawberry flavor.

CLINICAL PHARMACOLOGY

Ciprofloxacin given as an oral tablet is rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism.

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500, or 750-mg are 0.1, 0.2, and 0.4 µg/mL, respectively. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Serum concentrations increase proportionately with doses up to 1000-mg.

A 500-mg oral dose given every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours. A 750-mg oral dose given every 12 hours has been shown to produce an AUC at steady-state equivalent to that produced by an intravenous infusion of 400 mg over 60 minutes every 8 hours. A 750-mg oral dose results in a C_{max} similar to that observed with a 400-mg I.V. dose. A 250-mg oral dose given every 12 hours produces an AUC equivalent to that produced by an infusion of 200 mg ciprofloxacin given every 12 hours.

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. After a 250-mg oral dose, urine concentrations of ciprofloxacin usually exceed 200 mg/mL during the first two hours and are approximately 30 mg/mL at 8 to 12 hours after dosing. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1 to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20 to 35% of an oral dose is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination. Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin.

With oral administration, a 500-mg dose, given as 10 mL of the 5% CIPRO® Suspension (containing 250-mg ciprofloxacin/5 mL) is bioequivalent to the 500-mg tablet. A 10 mL volume of the 5% CIPRO® Suspension (containing 250-mg ciprofloxacin/5mL) is bioequivalent to a 5 mL volume of the 10% CIPRO® Suspension (containing 500-mg ciprofloxacin/5mL).

When CIPRO® Tablet is given concomitantly with food, there is a delay in the absorption of the drug, resulting in peak concentrations that occur closer to 2 hours after dosing rather than 1 hour whereas there is no delay observed when CIPRO® Suspension is given with food. The overall absorption of CIPRO® Tablet or CIPRO® Suspension, however, is not substantially affected. The pharmacokinetics of

ciprofloxacin given as the suspension are also not affected by food. Concurrent administration of antacids containing magnesium hydroxide or aluminum hydroxide may reduce the bioavailability of ciprofloxacin by as much as 90%. (See **PRECAUTIONS.**)

The serum concentrations of ciprofloxacin and metronidazole were not altered when these two drugs were given concomitantly.

Concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. (See **PRECAUTIONS.**)

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Dosage adjustments may be required. (See **DOSAGE AND ADMINISTRATION.**)

In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated.

The binding of ciprofloxacin to serum proteins is 20 to 40% which is not likely to be high enough to cause significant protein binding interactions with other drugs.

After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humors of the eye.

Microbiology Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase which is needed for the synthesis of bacterial DNA. Ciprofloxacin does not cross-react with other antimicrobial agents such as beta-lactams or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. *In vitro* studies have shown that additive activity often results when ciprofloxacin is combined with other antimicrobial agents such as beta-lactams, aminoglycosides, clindamycin, or metronidazole. Synergy has been reported particularly with the combination of ciprofloxacin and beta-lactam; antagonism is observed only rarely.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for CIPRO® (ciprofloxacin hydrochloride) Tablets and CIPRO® (ciprofloxacin) 5% and 10% Oral Suspension.

Aerobic gram-positive microorganisms

Enterococcus faecalis

(Many strains are only moderately susceptible.)

Staphylococcus aureus (methicillin susceptible)

Staphylococcus epidermidis

Staphylococcus saprophyticus

Streptococcus pneumoniae

Streptococcus pyogenes

Aerobic gram-negative microorganisms

Campylobacter jejuni

Citrobacter diversus

Citrobacter freundii

Enterobacter cloaca

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Aerobic gram-negative microorganisms (Cont.)

Moraxella catarrhalis

Morganella morganii

Neisseria gonorrhoeae

Proteus mirabilis

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Pseudomonas aeruginosa

Salmonella typhi

Serratia marcescens

Shigella boydii

Shigella dysenteriae

Shigella flexneri

Shigella sonnei

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for CIPRO® I.V. (ciprofloxacin for intravenous infusion).

Aerobic gram-positive microorganisms*Enterococcus faecalis**Many strains are only moderately susceptible.)**Staphylococcus aureus (methicillin susceptible)**Staphylococcus epidermidis**Staphylococcus saprophyticus**Streptococcus pneumoniae**Streptococcus pyogenes***Aerobic gram-negative microorganisms***Citrobacter diversus**Citrobacter freundii Enterobacter cloacae Escherichia coli**Haemophilus influenzae**Haemophilus parainfluenzae**Klebsiella pneumoniae**Morganella morganii**Proteus mirabilis**Proteus vulgaris**Providencia rettgeri**Providencia stuartii**Pseudomonas aeruginosa**Serratia marcescens*

The following *in vitro* data are available, **but their clinical significance is unknown.**

Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 µg/mL or less against most (>=90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms*Staphylococcus haemolyticus**Staphylococcus hominis***Aerobic gram-negative microorganisms***Acinetobacter lwoffii**Aeromonas hydrophila**Legionella pneumophila**Pasteurella multocida***Aerobic gram-negative microorganisms (cont.)***Salmonella enteritidis**Vibrio cholerae**Vibrio parahaemolyticus**Vibrio vulnificus**Yersinia enterocolitica**Edwardsiella tarda**Enterobacter aerogenes**Klebsiella oxytoca*

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2. Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation).

Susceptibility Tests

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method ¹ (broth or agar) or < equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the following criteria:

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure ² requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures.

INDICATIONS AND USAGE

CIPRO® is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Acute Sinusitis caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Moraxella catarrhalis*.

Lower Respiratory Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Streptococcus pneumoniae*. Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, or *Enterococcus faecalis*.

Acute Uncomplicated Cystitis in females caused by *Escherichia coli* or *Staphylococcus saprophyticus*. (See **DOSAGE AND ADMINISTRATION**.)

Chronic Bacterial Prostatitis caused by *Escherichia coli* or *Proteus mirabilis*.
Complicated Intra-Abdominal Infections (used in combination with metronidazole) caused by *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, or *Bacteroides fragilis*. (See **DOSAGE AND ADMINISTRATION**.)

Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (methicillin susceptible), *Staphylococcus epidermidis*, or *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, or *Pseudomonas aeruginosa*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella boydii* *, *Shigella dysenteriae*, *Shigella flexneri* or *Shigella sonnei* * when antibacterial therapy is indicated.

Typhoid Fever (Enteric Fever) caused by *Salmonella typhi*.

NOTE: The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has not been demonstrated.

Uncomplicated cervical and urethral gonorrhea due to *Neisseria gonorrhoeae*.

*Although treatment of infections due to this organism in this organ system demonstrated a clinically significant outcome, efficacy was studied in fewer than 10 patients.

If < anaerobic organisms are suspected of contributing to the infection, appropriate therapy should be administered.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with CIPRO® may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

CIPRO® (ciprofloxacin hydrochloride) is contraindicated in persons with a history of hypersensitivity to ciprofloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use Pregnancy, and Nursing Mothers subsections.) The oral administration of ciprofloxacin caused lameness in immature dogs.

Histopathological examination of the weight bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone- class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY**.)

Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (e.g. severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g. certain drug therapy, renal dysfunction). (See **PRECAUTIONS: General, Information for Patients, Drug Interactions** and **ADVERSE REACTIONS**.)

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND THEOPHYLLINE. These reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. Although similar serious adverse effects have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been rarely reported in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon.

Ciprofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high dose for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with ciprofloxacin should have a follow-up serologic test for syphilis after three months.

PRECAUTIONS

General: Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline. (See **ANIMAL PHARMACOLOGY**). Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving ciprofloxacin. Patients should be well hydrated to prevent the formation of highly concentrated urine.

Quinolones, including ciprofloxacin, may also cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia. (See **WARNINGS, Information for Patients, and Drug Interactions.**)

Alteration of the dosage regimen is necessary for patients with impairment of renal function.

(See **DOSAGE AND ADMINISTRATION.**)

Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction has been observed in patients who are exposed to direct sunlight while receiving some members of the quinolone class of drugs. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Information for Patients:

Patients should be advised:

- that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should be advised to drink fluids liberally and not take antacids containing magnesium, aluminum, or calcium, products containing iron or multivitamins containing zinc. Ciprofloxacin should not be taken concurrently with milk or yogurt alone, since absorption of ciprofloxacin may be significantly reduced. Dietary calcium as part of a meal, however, does not significantly affect ciprofloxacin absorption.
- that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.
- to avoid excessive sunlight or artificial ultraviolet light while receiving ciprofloxacin and to discontinue therapy if phototoxicity occurs.
- to discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain inflammation, or rupture of a tendon.
- that ciprofloxacin may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.
- that ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking quinolones.
- that convulsions have been reported in patients taking quinolones, including ciprofloxacin, and to notify their physician before taking the drug if there is a history of this condition.

Drug Interactions: As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. (See **WARNINGS**.) If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Some quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life.

Concurrent administration of ciprofloxacin with antacids containing magnesium, aluminum, or calcium; with sucralfate or divalent and trivalent cations such as iron may substantially interfere with the absorption of ciprofloxacin, resulting in serum and urine levels considerably lower than desired. To a lesser extent this effect is demonstrated with zinc-containing multivitamins. (See **DOSAGE AND ADMINISTRATION** for concurrent administration of these agents with ciprofloxacin.)

Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin.

The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has, on rare occasions, resulted in severe hypoglycemia.

Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated of the patient condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Carcinogenesis Mutagenesis, Impairment of Fertility: Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

Salmonella/Microsome Test (Negative)

E. coli DNA Repair Assay (Negative)

Mouse Lymphoma Cell Forward Mutation Assay (Positive)

Chinese Hamster V₇₉ Cell HGPRT Test (Negative)

Syrian Hamster Embryo Cell Transformation Assay (Negative)

Saccharomyces cerevisiae Point Mutation Assay (Negative)

Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)

Rat Hepatocyte DNA Repair Assay (Positive)

Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay

Micronucleus Test (Mice)

Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in mice and rats have been completed. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose upon mg/m²), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones.³

In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (0.8 times the highest recommended human dose of 1200 mg based upon body surface area) revealed no evidence of impairment.

Pregnancy: Teratogenic Effects. Pregnancy Category C: Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Ciprofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (See **WARNINGS**.)

Nursing Mothers: Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients and adolescents less than 18 years of age have not been established. Ciprofloxacin causes arthropathy in juvenile animals. (See **WARNINGS**.)

Short-term safety data from a single trial in pediatric cystic fibrosis patients are available. In a randomized, double-blind clinical trial for the treatment of acute pulmonary exacerbations in cystic fibrosis patients (ages 5-17 years), 67 patients received ciprofloxacin I.V. 10 mg/kg/dose q8h for one week followed by ciprofloxacin tablets 20 mg/kg/dose q12h to complete 10-21 days treatment and 62 patients received the combination of ceftazidime I.V. 50 mg/kg/dose q8h and tobramycin I.V. 3 mg/kg/dose q8h for a total of 10-21 days. Patients less than 5 years of age were not studied. Safety monitoring in the study included periodic range of motion examinations and gait assessments by treatment-blinded examiners. Patients were followed for an average of 23 days after completing treatment (range 0-93 days). This study was not designed to determine long term effects and the safety of repeated exposure to ciprofloxacin.

In the study, injection site reactions were more common in the ciprofloxacin group (24%) than in the comparison group (8%). Other adverse events were similar in nature and frequency between treatment arms. Musculoskeletal adverse events were reported in 22% of the patients in the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was reported in 12% of the subjects in the ciprofloxacin group and 16% in the comparison group. Arthralgia was reported in 10% of the patients in the ciprofloxacin group and 11% in the comparison group. One of sixty-seven patients developed arthritis of the knee nine days after a ten day course of treatment with ciprofloxacin. Clinical symptoms resolved, but an MRI showed knee effusion without other abnormalities eight months after treatment. However, the relationship of this event to the patient's course of ciprofloxacin can not be definitively determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease process.

ADVERSE REACTIONS

During clinical investigation with the tablet, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of patients treated, possibly related in 9.2% (total of 16.5% thought to be possibly or probably related to drug therapy), and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of patients treated, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%).

The most frequently reported events, drug related or not, were nausea (5.2%), diarrhea (2.3%), vomiting (2.0%), abdominal pain/discomfort (1.7%), headache (1.2%), restlessness (1.1%), and rash (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin patients are listed below.

CARDIOVASCULAR palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

CENTRAL NERVOUS SYSTEM: dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesias (See above.) (See **PRECAUTIONS.**)

GASTROINTESTINAL: painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding (See above.) Cholestatic jaundice has been reported.

MUSCULOSKELETAL arthralgia or back pain, joint stiffness, achiness, neck or chest pain, flare up of gout.

RENAL UROGENITAL: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

RESPIRATORY: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism.

SKIN HYPERSENSITIVITY: pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum (See above.)

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported. (See **WARNINGS.**)

SPECIAL SENSES: blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste.

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances nausea, vomiting, tremor, irritability, or palpitation were judged by investigators to be related to elevated serum levels of theophylline possibly as a result of drug interaction with ciprofloxacin.

In domestic clinical trials involving 214 patients receiving a single 250-mg oral dose, approximately 5% of patients reported adverse experiences without reference to drug relationship. The most common adverse experiences were vaginitis (2%), headache (1%), and vaginal pruritus (1%). Additional reactions, occurring in 0.3%-1% of patients, were abdominal discomfort, lymphadenopathy, foot pain, dizziness, and breast pain. Less than 20% of these patients had laboratory values obtained, and these results were generally consistent with the pattern noted for multi-dose therapy.

In randomized, double-blind controlled clinical trials comparing ciprofloxacin tablets (500 mg BID) to cefuroxime axetil 250 mg - 500 mg BID) and to clarithromycin (500 mg BID) in patients with respiratory tract infections, ciprofloxacin demonstrated a CNS adverse event profile comparable to the control drugs.

Post-Marketing Adverse Events: Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ciprofloxacin, are:

BODY AS A WHOLE: change in serum phenytoin.

CARDIOVASCULAR postural hypotension, vasculitis.

CENTRAL NERVOUS SYSTEM: agitation, confusion, delirium, dysphasia, myoclonus, nystagmus, toxic psychosis.

GASTROINTESTINAL: constipation, dyspepsia, flatulence, hepatic necrosis, jaundice, pancreatitis, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.)

HEMIC LYMPHATIC: agranulocytosis, hemolytic anemia, methemoglobinemia, prolongation of prothrombin time.

METABOLIC/NUTRITIONAL: elevation of serum triglycerides, cholesterol, blood glucose, serum potassium.

MUSCULOSKELETAL: myalgia, possible exacerbation of myasthenia gravis, tendinitis tendon rupture.

RENAL/UROGENITAL: albuminuria, candiduria, renal calculi, vaginal candidiasis.

SKIN/HYPERSENSITIVITY: anaphylactic reactions, erythema multiforme/Stevens Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis.

SPECIAL SENSES: anosmia, taste loss (See **PRECAUTIONS**.)

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship are listed below:

Hepatic--Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Hematologic--Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal--Elevations of serum creatinine (1.1%), BUN (0.9%), CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, leukocytosis.

OVERDOSAGE

In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

In mice, rats, rabbits and dogs, significant toxicity including tonic/clonic convulsions was observed at intravenous doses of ciprofloxacin between 125 and 300 mg/kg.

Single doses of ciprofloxacin were relatively non-toxic via the oral route of administration in mice, rats, and dogs. No deaths occurred within a 14-day post treatment observation period at the highest oral doses tested; up to 5000 mg/kg in either rodent species, or up to 2500 mg/kg in the dog. Clinical signs observed included hypoactivity and cyanosis in both rodent species and severe vomiting in dogs. In rabbits, significant mortality was seen at doses of ciprofloxacin >2500 mg/kg. Mortality was delayed in these animals, occurring 10-14 days after dosing.

DOSAGE AND ADMINISTRATION

The recommended adult dosage for acute sinusitis is 500-mg every 12 hours.

Lower respiratory tract infections may be treated with 500-mg every 12 hours. For more severe or complicated infections, a dosage of 750-mg may be given every 12 hours.

Severe/complicated urinary tract infections or urinary tract infections caused by organisms not highly susceptible to ciprofloxacin may be treated with 500-mg every 12 hours. For other mild/moderate urinary infections, the usual adult dosage is 250-mg every 12 hours.

In acute uncomplicated cystitis in females, the usual dosage is 100-mg every 12 hours. For acute uncomplicated cystitis in females, 3 days of treatment is recommended while 7 to 14 days is suggested for other mild/moderate, severe or complicated urinary tract infections.

The recommended adult dosage for chronic bacterial prostatitis is 500-mg every 12 hours.

The recommended adult dosage for oral sequential therapy of complicated intra-abdominal infections is 500-mg every 12 hours. (To provide appropriate anaerobic activity, metronidazole should be given according to product labeling.) (See CIPRO® I.V. package insert.)

Skin and skin structure infections and bone and joint infections may be treated with 500-mg every 12 hours. For more severe or complicated infections, a dosage of 750-mg may be given every 12 hours.

The recommended adult dosage for infectious diarrhea or typhoid fever is 500-mg every 12 hours. For the treatment of uncomplicated urethral and cervical gonococcal infections, a single 250-mg dose is recommended.

Complicated Intra-Abdominal Infections: Sequential therapy [parenteral to oral - 400-mg CIPRO® I.V. q 12 h (plus I.V. metronidazole) -> 500-mg CIPRO® Tablets q 12 h (plus oral metronidazole)] can be instituted at the discretion of the physician.

The determination of dosage for any particular patients must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defense mechanisms, and the status of renal function and hepatic function.

The duration of treatment depends upon the severity of infection. Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days; however, for severe and complicated infections more prolonged therapy may be required. Bone and joint infections may require treatment for 4 to 6 weeks or longer. Chronic Bacterial Prostatitis should be treated for 28 days. Infectious diarrhea may be treated for 5-7 days. Typhoid fever should be treated for 10 days.

Concurrent Use With Antacids or Multivalent Cations: Concurrent administration of ciprofloxacin with sucralfate or divalent or trivalent cations such as iron or antacids containing magnesium, aluminum, or calcium may substantially interfere with the absorption of ciprofloxacin, resulting in serum and urine levels considerably lower than desired. Therefore, concurrent administration of these agents with ciprofloxacin should be avoided. However, usual dietary intake of calcium has not been shown to alter the bioavailability of ciprofloxacin. Single dose bioavailability studies have shown that antacids may be administered either 2 hours after or 6 hours before ciprofloxacin dosing without a significant decrease in bioavailability. Histamine H₂-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

Impaired Renal Function: Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternate pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment.

Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction.

In patients with severe infections and severe renal impairment, a unit dose of 750-mg may be administered at the intervals noted above; however, patients should be carefully monitored and the serum ciprofloxacin concentration should be measured periodically. Peak concentrations (1-2 hours after dosing) should generally range from 2 to 4 µg/mL.

For patients with changing renal function or for patients with renal impairment and hepatic insufficiency, measurement of serum concentrations of ciprofloxacin will provide additional guidance for adjusting dosage.

HOW SUPPLIED

CIPRO® (ciprofloxacin hydrochloride) Tablets are available as round, slightly yellowish film-coated tablets containing 100-mg or 250-mg ciprofloxacin. The 100-mg tablet is coded with the word "CIPRO" on one side and "100" on the reverse side. The 250-mg tablet is coded with the word "CIPRO" on one side and "250" on the reverse side. CIPRO® is also available as capsule shaped, slightly yellowish film-coated tablets containing 500-mg or 750-mg ciprofloxacin. The 500-mg tablet is coded with the word "CIPRO" on one side and "500" on the reverse side. The 750-mg tablet is coded with the word "CIPRO" on one side and "750" on the reverse side. CIPRO® 250-mg, 500-mg, and 750-mg are available in bottles of 50, 100, and Unit Dose packages of 100. The 100-mg strength, is available only as CIPRO® Cystitis pack containing 6 tablets for use only in female patients with acute uncomplicated cystitis.

ANIMAL PHARMACOLOGY

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See **WARNINGS**.) Damage of weight bearing joints was observed in juvenile dogs and rats. In young beagles, 100 mg/kg ciprofloxacin, given daily for 4 weeks, caused degenerative articular changes of the knee joint. At 30 mg/kg, the effect on the joint was minimal. In a subsequent study in beagles, removal of weight bearing from the joint reduced the lesions but did not totally prevent them.

Crystalluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacin under alkaline conditions, which predominate in the urine of test animals; in man, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy has been noted after single oral doses as low as 5 mg/kg. After 6 months of intravenous dosing at 10 mg/kg/day, no nephropathological changes were noted; however, nephropathy was observed after dosing at 20 mg/kg/day for the same duration.

In dogs, ciprofloxacin at 3 and 10 mg/kg by rapid IV injection (15 sec.) produces pronounced hypotensive effects. These effects are considered to be related to

histamine release, since they are partially antagonized by pyrilamine, an antihistamine. In rhesus monkeys, rapid IV injection also produces hypotension but the effect in this species is inconsistent and less pronounced.

In mice, concomitant administration of nonsteroidal anti-inflammatory drugs such as phenylbutazone and indomethacin with quinolones has been reported to enhance the CNS stimulatory effect of quinolones.

Ocular toxicity seen with some related drugs has not been observed in ciprofloxacin-treated animals.

CLINICAL STUDIES

Acute Sinusitis Studies

Ciprofloxacin tablets (500-mg BID) were evaluated for the treatment of acute sinusitis in two randomized, double-blind, controlled clinical trials conducted in the United States. Study 1 compared ciprofloxacin with cefuroxime axetil (250-mg BID) and enrolled 501 patients (400 of which were valid for the primary efficacy analysis). Study 2 compared ciprofloxacin with clarithromycin (500-mg BID) and enrolled 560 patients (418 of whom were valid for the primary efficacy analysis). The primary test of cure endpoint was a follow-up visit performed approximately 30 days after the completion of treatment with study medication.

In ciprofloxacin-treated patients enrolled in controlled and uncontrolled acute sinusitis studies, all of which included antral puncture, bacteriological eradication/presumed eradication was documented at the 30 day follow-up visit in 44 of 50 (88%) *H. influenzae*, 17 of 21 (80.9%) *M. catarrhalis*, and 42 of 51 (82.3%) *S. pneumoniae*. Patients infected with *S. pneumoniae* strains whose baseline susceptibilities were intermediate or resistant to ciprofloxacin had a lower success rate than patients infected with susceptible strains.

Uncomplicated Cystitis Studies

Efficacy: Two U.S. double-blind, controlled clinical studies of acute uncomplicated cystitis in women compared ciprofloxacin 100-mg BID for 3 days to ciprofloxacin 250-mg BID for 7 days or control drug.

FLOMAX®

Flomax Capsules (Boehringer Ingelheim):

DESCRIPTION

Tamsulosin hydrochloride is an antagonist of α_{1A} adrenoceptors in the prostate.

Tamsulosin HCl is (-)-(*R*)-5-[2-[[2-(0-ethoxyphenoxy) ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride. Tamsulosin HCl occurs as white crystals that melt with decomposition at approximately 230°C. It is sparingly soluble in water and in methanol, slightly soluble in glacial acetic acid and in ethanol, and practically insoluble in ether.

The empirical formula of tamsulosin HCl is $C_{20}H_{28}N_2O_5S \cdot HCl$. The molecular weight of tamsulosin HCl is 444.98.

Each FLOMAX capsule for oral administration contains tamsulosin HCl 0.4 mg, and the following inactive ingredients methacrylic acid copolymer, microcrystalline cellulose, triacetin, polysorbate 80, sodium laurylsulfate, calcium stearate, talc, FD&C blue No. 2, titanium dioxide, ferric oxide, gelatin, and trace amounts of shellac, industrial methylated 74OP, soya lecithin, 1-ethoxyethanol, dimethylpolysiloxane, and black iron oxide E172.

CLINICAL PHARMACOLOGY

The symptoms associated with hyperplasia (BPH) are related to bladder outlet obstruction, which is comprised of two underlying components: static and dynamic. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to constriction of the bladder outlet. Smooth muscle tone is mediated by the sympathetic nervous stimulation of α_1 adrenoceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and bladder neck. Blockade of these adrenoceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement urine flow rate and a reduction in symptoms of BPH.

Tamsulosin, an α_1 adrenoceptor blocking agent, exhibits selectivity for α_1 receptors in the human prostate. At least three discrete α_1 adrenoceptor subtypes have been identified: α_{1A} , α_{1B} and α_{1D} ; their distribution differs between human organs and tissue. Approximately 70% of the α_1 - receptors in human prostate are of the α_{1A} subtype.

FLOMAX capsules are not intended for use as an antihypertensive drug.

Pharmacokinetics: The pharmacokinetics of tamsulosin HCl have been evaluated in adult healthy volunteers and patients with BPH after single and/or multiple administration with doses ranging from 0.1 mg to 1 mg.

Absorption: Absorption of tamsulosin HCl from FLOMAX capsules 0.4 mg is essentially complete (>90%) following oral administration under fasting conditions. Tamsulosin HCl exhibits linear kinetics following single and multiple dosing, with achievement of steady-state concentrations by the fifth day of once-a-day dosing.

Effect of Food: The time to maximum concentration (T_{max}) is reached by four to five hours under fasting conditions and by six to seven hours when FLOMAX capsules are administered with food. Taking FLOMAX capsules under fasted conditions results in a 30% increase in bioavailability (AUC) and 40% to 70% increase in peak concentrations (C_{max}) compared to fed conditions.

Distribution: The mean steady-state apparent volume of distribution of tamsulosin HCl after intravenous administration to ten healthy male adults was 16L, which is suggestive of distribution into extracellular fluids in the body. Additionally, whole body autoradiographic studies in mice and rats and tissue distribution in rats and dogs indicate that tamsulosin HCl is widely distributed to most tissues including kidney, prostate, liver, gall bladder, heart, aorta, and brown fat, and minimally distributed to the brain, spinal cord, and testes.

Tamsulosin HCl is extensively bound to human plasma proteins (94% to 99%), primarily alpha-1 acid glycoprotein (AAG), with linear binding over a wide concentration range (20 to 600 ng/mL). The results of two-way *in vitro* studies indicate that the binding of tamsulosin HCl to human plasma proteins is not affected by amitriptyline, diclofenac, glyburide, simvastatin plus simvastatin-hydroxy acid metabolite, warfarin, diazepam, propranolol, trichlormethiazide, or chlormadinone. Likewise, tamsulosin HCl had no effect on the extent of binding of these drugs.

Metabolism: There is no enantiometric bioconversion from tamsulosin HCl [R(-) isomer] to the S(+) isomer in humans. Tamsulosin HCl is extensively metabolized by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. Additionally, the cytochrome P450 enzymes that primarily catalyze the Phase I metabolism of tamsulosin HCl have not been conclusively identified. Therefore, possible interactions with other cytochrome P450 metabolized compounds cannot be discerned with current information. The metabolites of tamsulosin HCl undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

Incubations with human liver microsomes showed no evidence of clinically significant metabolic interactions between tamsulosin HCl and amitriptyline, albuterol (beta agonist), glyburide (glibenclamide) and finasteride (5alpha-reductase inhibitor treatment

of BPH). However, results of the *in vitro* testing of the tamsulosin HCl interaction with diclofenac and warfarin were equivocal.

Excretion: On administration of the radiolabeled dose of tamsulosin HCl to four healthy volunteers, 97% of the administered radioactivity was recovered, with urine (76%) representing the primary route of excretion compared to feces (21%) over 168 hours.

Following intravenous or oral administration of an immediate-release formulation, the elimination half-life of tamsulosin HCl in plasma range from five to seven hours. Because of absorption rate-controlled pharmacokinetics with FLOMAX capsules, the apparent half-life of tamsulosin HCl is approximately 9 to 13 hours in healthy volunteers and 14 to 15 hours in the target population. Tamsulosin HCl undergoes clearance in humans, with a relatively low systemic clearance (2.88 L[hairspace]/h).

Special Populations: Geriatrics (Age): Cross-study comparison of FLOMAX capsules overall exposure (AUC) and half-life indicate that the pharmacokinetic disposition of tamsulosin HCl may be slightly prolonged in geriatric males compared to young, healthy male volunteers. Intrinsic clearance is independent of tamsulosin HCl binding to AAG, but diminishes with age, resulting in a 40% overall higher exposure (AUC) in subjects of age 55 to 75 years compared to subjects of age 20 to 32 years.

Renal Dysfunction: The pharmacokinetics of tamsulosin HCl have been compared in 6 subjects with mild - moderate ($30 \leq \text{CLcr} < 70 \text{ mL/min/1.73m}^2$) or moderate - severe ($10 \leq \text{CLcr} < 30 \text{ mL/min/1.73m}^2$) renal impairment and 6 normal subjects ($\text{CLcr} < 90 \text{ mL/min/1.73m}^2$). While a change in the overall plasma concentration of tamsulosin HCl was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin HCl, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in FLOMAX capsules dosing. However, patients with endstage renal disease ($\text{CLcr} < 10 \text{ mL/min/1.73m}^2$) have not been studied.

Hepatic Dysfunction: The pharmacokinetics of tamsulosin HCl have been compared in 8 subjects with moderate hepatic dysfunction (Child-Pugh's classification: Grades A and B) and 8 normal subjects. While a change in the overall plasma concentration of tamsulosin HCl was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin HCl does not change significantly with only a modest (32%) change in intrinsic clearance of unbound tamsulosin HCl. Therefore, patients with moderate hepatic dysfunction do not require an adjustment in FLOMAX capsules dosage.

Drug-Drug Interactions: Nifedipine, Atenolol, Enalapril: In three studies in hypertensive subjects (age range 47-79 years) whose blood pressure was controlled with stable doses of Procardia XL®, atenolol, or enalapril for at least three months, FLOMAX capsules 0.4 mg for seven days followed by FLOMAX capsules 0.8 mg for another seven days (n=8 per study) resulted in no clinically significant effects on blood pressure and pulse rate compared to placebo (n=4 per study). Therefore, dosage adjustments

are not necessary when FLOMAX capsules are administered concomitantly with Procardia XL®, atenolol, or enalapril.

Warfarin: A definitive drug-drug interaction study between tamsulosin HCl and warfarin was not conducted. Results from limited *in vitro* and *in vivo* studies are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and FLOMAX capsules.

Digoxin and Theophylline: In two studies in healthy volunteers (n=10 per study; age range 19-39 years) receiving FLOMAX capsules 0.4 mg/day for two days, followed by FLOMAX capsules 0.8 mg/day for five to eight days, single intravenous doses of digoxin 0.5 mg or theophylline 5 mg/kg resulted in no change in the pharmacokinetics of digoxin or theophylline. Therefore, dosage adjustments are not necessary when a FLOMAX capsule is administered concomitantly with digoxin or theophylline.

Furosemide: The pharmacokinetic and pharmacodynamic interaction between FLOMAX capsules 0.8 mg/day (steady-state) and furosemide 20 mg intravenously (single dose) was evaluated in ten healthy volunteers (age range 21-40 years). FLOMAX capsules had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced an 11% to 12% reduction in tamsulosin HCl C_{max} and AUC, these changes are expected to be clinically insignificant and do not require adjustment of the FLOMAX capsules dosage.

Cimetidine: The effects of cimetidine at the highest recommended dose (400 mg every six hours for six days) on the pharmacokinetics of a single FLOMAX capsule 0.4 mg dose was investigated in ten healthy volunteers (age range 21-38 years). Treatment with cimetidine resulted in a significant decrease (26%) in the clearance of tamsulosin HCl which resulted in a moderate increase in tamsulosin HCl AUC (44%). Therefore, FLOMAX capsules should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

Clinical Studies: Four placebo-controlled clinical studies and one active-controlled clinical study enrolled a total of 2296 patients (1003 received FLOMAX capsules 0.4 mg once daily, 491 received FLOMAX capsules 0.8 mg once daily, and 802 were control patients) in the U.S. and Europe.

In the two U.S. placebo-controlled, double-blind, 13-week, multicenter studies [Study 1 (US92-03A) and Study 2 (US93-01)], 1486 men with the signs and symptoms of BPH were enrolled. In both studies, patients were randomized to either placebo, FLOMAX capsules 0.4 mg once daily, or FLOMAX capsules 0.8 mg once daily. Patients in FLOMAX capsules 0.8-mg once daily treatment groups received a dose of 0.4 mg once daily for one week before increasing to the 0.8-mg once daily dose. The primary efficacy assessments included 1) total American Urological Association (AUA) Symptom Score questionnaire, which evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms, where a decrease in score is consistent with improvement in symptoms; and

2) peak urine flow rate, where an increased peak urine flow rate value over baseline is consistent with decreased urinary obstruction.

Mean changes from baseline to week 13 in total AUA Score were significantly greater for groups treated with FLOMAX capsules 0.4 mg and 0.8 mg once daily compared to placebo in both U.S. studies. The changes from baseline to week 13 in flow rate were also significantly greater for the FLOMAX capsules 0.4-mg and 0.8-mg once daily groups compared to placebo in Study 1, and for the FLOMAX capsules 0.8-mg once daily group in Study 2. Overall there were no significant differences in improvement observed in total AUA Symptom Scores or peak urine flow rates between the 0.4-mg and the 0.8-mg dose groups with the exception that the 0.8-mg dose Study 1 had a significantly greater improvement in total AUA Symptom Score compared to the 0.4-mg dose.

Mean total AUA Symptom Scores for both FLOMAX capsules 0.4-mg and 0.8-mg once daily groups showed a rapid decrease starting at one week after dosing and remained decreased through 13 weeks in both studies.

In Study 1, 400 patients (53% of the originally randomized group) elected to continue in their originally assigned treatment groups in a double-blind, placebo controlled, 40 week extension trial (138 patients on 0.4 mg, 135 patients on 0.8 mg and 127 patients on placebo). Three hundred and twenty-three patients (43% of the originally randomized group) completed one year. Of these, 81% (97 patients) on 0.4 mg, 74% (75 patients) on 0.8 mg and 56% (57 patients) on placebo had a response $\geq 25\%$ above baseline in total AUA Symptom Score at one year.

INDICATIONS AND USAGE

FLOMAX® (tamsulosin HCl) capsules are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). FLOMAX capsules are not indicated for the treatment of hypertension.

CONTRAINDICATIONS

FLOMAX capsules are contraindicated in patients known to be hypersensitive to tamsulosin HCl or any component of FLOMAX capsules.

WARNINGS

The signs and symptoms of orthostasis (postural hypotension, dizziness and vertigo) were detected more frequently in FLOMAX capsule treated patients than in placebo recipients. As with other alpha-adrenergic blocking agents there is a potential risk of syncope (see ADVERSE REACTIONS).

Patients beginning treatment with FLOMAX capsules should be cautioned to avoid situations where injury could result should syncope occur.

PRECAUTIONS

General

- 1) *Carcinoma of the prostate:* Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently co-exist. Patients should be evaluated prior to the start of FLOMAX capsules therapy to rule out the presence carcinoma of the prostate.
- 2) *Drug-Drug Interactions:* The pharmacokinetic and pharmacodynamic interactions between FLOMAX capsules and other alpha-adrenergic blocking agents have not been determined. However, interactions may be expected and FLOMAX capsules should NOT be used in combination with other alpha- blocking agents.

The pharmacokinetic interaction between cimetidine and FLOMAX capsules was investigated. The results indicate significant changes in tamsulosin HCl clearance (26% decrease) and AUC (44% increase). Therefore, FLOMAX capsules should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

Results from limited *in vitro* and *in vivo* drug-drug interaction studies between tamsulosin HCl and warfarin are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and FLOMAX capsules.

(See also drug-drug interaction studies in CLINICAL PHARMACOLOGY Pharmacokinetics subsection.)

Information for Patients (see Patient Package Insert)

Patients should be told about the possible occurrence of symptoms related to hypotension such as dizziness when taking FLOMAX capsules, and they should be cautioned about driving, operating machinery or performing hazardous tasks.

Patients should be advised not to crush, chew or open the FLOMAX capsules.

Laboratory Tests

No laboratory test interactions with FLOMAX capsules are known. Treatment with FLOMAX capsules for up to 12 months had no significant effect on prostate-specific antigen (PSA).

Pregnancy Teratogenic Effects, Pregnancy Category B. Administration of tamsulosin HCl to pregnant female rats at dose levels up to 300 mg/kg/day (approximately 50 times the human therapeutic AUC exposure) revealed no evidence of harm to the fetus. Administration of tamsulosin HCl to pregnant rabbits at dose levels up to 50 mg/kg/day

produced no evidence of fetal harm. FLOMAX capsules are not indicated for use in women.

Nursing Mothers FLOMAX capsules are not indicated for use in women.

Pediatric Use FLOMAX capsules are not indicated for use in pediatric populations.

Carcinogenesis, Mutagenesis, and Impairment of Fertility Rats administered doses up to 43 mg/kg/day in males and 52 mg/kg/day in females had no increases in tumor incidence with the exception of a modest increase in the frequency of mammary gland fibroadenomas in female rats receiving doses ≥ 5.4 mg/kg ($P < 0.015$). The highest doses of tamsulosin HCl evaluated in the rat carcinogenicity study produced systemic exposures (AUC) in rats 3 times the exposures in men receiving the maximum therapeutic dose of 0.8 mg/day.

Mice were administered doses up to 127 mg/kg/day in males and 158 mg/kg/day in females. There were no significant tumor findings in male mice. Female mice treated for 2 years with the two highest doses of 45 and 158 mg/kg/day had statistically significant increases in the incidence of mammary gland fibroadenomas ($P < 0.0001$) and adenocarcinomas ($P < 0.0075$). The highest dose levels of tamsulosin HCl evaluated in the mice carcinogenicity study produced systemic exposures (AUC) in mice 8 times the exposures in men receiving the maximum therapeutic dose of 0.8 mg/day.

The increased incidences of mammary gland neoplasms in female rats and mice were considered secondary to tamsulosin HCl-induced hyperprolactinemia. It is not known if FLOMAX capsules elevate prolactin in humans. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is not known.

Tamsulosin HCl produced no evidence of mutagenic potential *in vitro* in the Ames reverse mutation test, mouse lymphoma thymidine kinase assay, unscheduled DNA repair synthesis assay, and chromosomal aberration assays in Chinese hamster ovary cells or human lymphocytes. There were no mutagenic effects in the *in vivo* sister chromatid exchange and mouse micronucleus assay.

Studies in rats revealed significantly reduced fertility in males dosed with single or multiple daily doses of 300 mg/kg/day of tamsulosin HCl (AUC exposure in rats about 50 times the human exposure with the maximum therapeutic dose). The mechanism of decreased fertility in male rats is considered to be an effect of the compound on the vaginal plug formation possibly due to changes of semen content or impairment of ejaculation. The effects on fertility were reversible showing improvement by 3 days after a single dose and 4 weeks after multiple dosing. Effects on fertility in males were completely reversed within nine weeks of discontinuation of multiple dosing. Multiple doses of 10 and 100 mg/kg/day tamsulosin HCl (1/5 and 16 times the anticipated

human AUC exposure) did not significantly alter fertility in male rats. Effects of tamsulosin HCl on sperm counts or sperm function have not been evaluated.

Studies in female rats revealed significant reductions in fertility after single or multiple dosing with 300 mg/kg/day of the R-isomer or racemic mixture of tamsulosin HCl, respectively. In female rats, the reductions in fertility after single doses were considered to be associated with impairments in fertilization. Multiple dosing with 10 or 100 mg/kg/day of the racemic mixture did not significantly alter fertility in female rats.

ADVERSE REACTIONS

The incidence of treatment-emergent adverse events has been ascertained from six short-term U.S. and European placebo-controlled clinical trials in which daily doses of 0.1 to 0.8 mg FLOMAX capsules were used. These studies evaluated safety in 1783 patients treated with FLOMAX capsules and 798 patients administered placebo.

Signs and Symptoms of Orthostasis In the two U.S. studies, symptomatic postural hypotension was reported by 0.2% of patients (1 of 502) in the 0.4-mg group, 0.4% of patients (2 of 492) in the 0.8-mg group, and by no patients in the placebo group. Syncope was reported by 0.2% of patients (1 of 502) in the 0.4-mg group, 0.4% of patients (2 of 492) in the 0.8-mg group and 0.6% of patients (3 of 493) in the placebo group. Dizziness was reported by 15% of patients (75 of 502) in the 0.4-mg group, 17% of patients (84 of 492) in the 0.8-mg group, and 10% of patients (50 of 493) in the placebo group. Vertigo was reported by 0.6% of patients (3 of 502) in the 0.4-mg group, 1% of patients (5 of 492) in the 0.8 mg group and by 0.6% of patients (3 of 493) in the placebo group.

Multiple testing for orthostatic hypotension was conducted in a number of studies. Such a test was considered positive if it met one or more of the following criteria: (1) a decrease in systolic blood pressure of ≥ 20 mmHg upon standing from supine position during the orthostatic tests; (2) a decrease in diastolic pressure ≥ 10 mmHg upon standing, with the standing diastolic blood pressure < 65 mmHg during the test; (3) increase rate of ≥ 20 bpm upon standing with a standing pulse rate ≥ 100 bpm during test; and (4) the presence of clinical symptoms (faintness, lightheadedness/lightheaded, dizziness, spinning sensation, vertigo, or postural hypotension) upon standing during the orthostatic test.

Following the first dose of double-blind medication in Study 1, a positive orthostatic test result at 4 hours post-dose was observed in 7% of patients (37 of 498) who received FLOMAX capsules 0.4 mg once daily and in 3% of the patients (8 of 253) who received placebo. At 8 hours post-dose, a positive orthostatic test result was observed for 6% of the patients (31 of 498) who received FLOMAX capsules 0.4 mg once daily and 4% (9 of 250) who received placebo. (Note: patients in the 0.8-mg group received 0.4 mg once daily for the first week of Study 1.)

In Studies 1 and 2, at least one positive orthostatic test result was observed during the course of these studies for 81 of the 502 patients (16%) in the FLOMAX capsules 0.4-mg once daily group, 92 of the 491 patients (19%) in the FLOMAX capsules 0.8-mg once daily group and 54 of the 493 patients (11%) in the placebo group.

Because orthostasis was detected more frequently in FLOMAX capsule-treated patients than in placebo recipients, there is a potential risk of syncope (WARNINGS).

Abnormal Ejaculation Abnormal ejaculation failure, disorder, retrograde ejaculation and ejaculation decrease. Withdrawal from these clinical studies of FLOMAX capsules because of abnormal ejaculation was also dose-dependent with 8 of 492 patients (1.6%) in the 0.8-mg group, and no patients in the 0.4-mg placebo groups discontinuing treatment due to abnormal ejaculation.

Post-Marketing Experience Allergic-type reactions such as skin rash angioedema tongue, lips and face and urticaria have been reported positive rechallenge in some cases.

OVERDOSAGE

Should overdose of FLOMAX capsules lead to hypotension (See WARNINGS and ADVERSE REACTIONS), support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, then administration of intravenous fluids should be considered. If necessary, vasopressors should then be used and renal function should be monitored and supported as needed. Laboratory data indicate that tamsulosin HCl is 94% to 99% protein bound; therefore, dialysis is unlikely to be of benefit.

One patient reported an overdose of thirty 0.4-mg FLOMAX capsules. Following the ingestion of the capsules, the patient reported a severe headache.

DOSAGE AND ADMINISTRATION: FLOMAX capsules 0.4 mg once daily is recommended as the dose for the treatment of the signs and symptoms of BPH. It should be administered approximately one-half hour following the same meal each day.

For those patients who fail to respond to the 0.4-mg dose after two to four weeks of dosing, the dose of FLOMAX capsules can be increased to 0.8 mg once daily. If FLOMAX capsules administration is discontinued or interrupted for several days at either the 0.4-mg or 0.8-mg dose, therapy should be started again with the 0.4-mg once daily dose.

HOW SUPPLIED: FLOMAX capsules 0.4 mg are supplied in density polyethylene bottles containing 100 or 1000 hard gelatin capsules with green opaque cap and orange opaque body. The capsules are imprinted on one side with "Flomax 0.4 mg" and on the other side with "BI 58."

Appendix E Visit Schedule

C P C R N Randomized Clinical Trial #1

FORMS ADMINISTRATION SCHEDULE

	Screening		+3 weeks	+6 weeks	+9 weeks	+12 weeks	Early Stop Treatment	Rescue Event
Form	Visit 1 (clinic)	Visit 2 (clinic)	Visit 3 (phone)	Visit 4 (clinic)	Visit 5 (phone)	Visit 6 (phone)	Visit 9B (PRN)	Visit 99 (PRN)
Eligibility Checklist (ELIG)	X							
NIH-CPSI (CPSI)	X	X	X	X	X	X	X	X
Randomization (RAND)		X						
SF-12 (SF12), Follow-Up Symptoms (SYM)		X	X	X	X	X	X	X
Demographics (DEMO)		X						
Dispensing Log (DISP)		X						
Concomitant Medication (CMED)		X		X				
Follow-Up Contacts (FUP)			X	X	X	X		
Adverse Events/Serious Adverse Events (AE)			X	X	X	X		
Medical History (MED)	X							
Physical Exam (EXAM)	X			X				
Four Glass Test Microscopy (FGTM)	X			X				
Four Glass Test Cultures (FGTC)	X			X				
Semen Sample (SEMEN)		X		X				
Uroflow and PVR (URO)		X		X*				
Voiding Log (VOID)		X		X				
Treatment Stop (TSTOP)				X			X	
Study Stop (SSTOP)						X		
Rescue Treatment Event (RMED)								X
Unmasking** (UNMASK)								
Patient Contact Information	X							
Visit Checklist	X	X	X	X	X	X	X	X
Study Medication Tracking Log		X		X			X	
Participant Status Log	X	X				X		
Participant ID Assignment Log	X							
* PVR Only. ** This form is completed only when clinically needed.								

Appendix F

Laboratory Procedures

Four Glass Test - Procedure

Participant Test Schedule: (Screening Visit #1): 4 glass urine microscopy and culture

(Visit #4 - Week 6): 4 glass urine microscopy and culture

1. Instruct participant to retract foreskin (if uncircumcised).
2. Wipe head of penis with one alcohol pad.
3. Collect the first 10 ml sample (**VB1**) directly into sterile container. (Range 5 - 30 ml)
Centrifuge, examine and culture as described below.*
4. Collect midstream sample (**VB2**).
Dip VB2 for pH, glucose and protein. Record results
Centrifuge, examine and culture as described below.*
5. **EPS** - Prostatic massage
 - a.) Collect EPS on a sterile surface. (Example: lid of urine cup)
 - b.) Estimate volume of EPS in μL . (1 drop \sim 50 μL)
 - c.) Examine 5 μL at 400X power.
Count WBC's, RBC's, hyphae.
 - d.) Place 10 μL on sheep blood agar (5%) of a urocult paddle and incubate at 37°C for 5 days. Record results at five days.
 - e.) If it grows, replate colonies on MacConkey agar for identification.
 - f.) Store any remaining volume of EPS in 1.0 - 1.5 ml cryovials.
 - g.) Snap freeze in liquid Nitrogen for later storage at -70°C.
6. Collect first 10 ml sample post massage (**VB3**) within 30 minutes. (Range 5 - 30 ml)
Centrifuge, examine and culture as described below.*

*VB1, VB2 and VB3 SPECIMENS

- a) Centrifuge 2-3 mls of urine for five minutes.
- b) Examine at 400X power.
- c) Count WBC's, RBC's, hyphae (average of three fields rounded to nearest whole number.)
- d) Place 100 μL of specimen on sheep blood agar (5%) plate and 100 μL of specimen on MacConkey agar plate.
- e) Culture at 37°C for 5 days. Record VB2 results at 48 hours and five days. All other specimens will be recorded at 5 days only.

***Chlamydia trachomatis PCR**

- a.) Participant must not have urinated in the previous two (2) hours.
- b.) Collect 10 to 50 mL of first catch urine into a clean, empty plastic cup without preservatives.
- c.) Cap the specimen cup and label appropriately.

Uroflow and Post Void Residual Procedure

Participant Test Schedule: (Screening Visit #2)
(Visit #4 – Week 6- **PVR ONLY**)

1. Instruct participant to have a full bladder for this test. A minimum volume of 150 cc's constitutes a valid test. This can be assessed by ultrasound of the bladder.
2. Record three values -
Total Volume (ml)
Peak Flow (ml/second)
Mean Flow (ml/second)
3. Post-uroflow, an abdominal ultrasound will be performed to measure post-void residual, which will be reported in cc's. Regular ultrasound machines with curvilinear or linear arrays or ultrasound units specifically designed to measure bladder volume may be used. Because of the variety of types of ultrasounds, which will be available to the researchers, it is critical that each center determines and documents the accuracy and variability of their particular ultrasound's determination of post-void residual.

Semen Sample Procedure

Participant Test Schedule: (Screening Visit #2)
(Post Clinic Visit #4*)

1. Instruct participant to remain abstinent for three days.
2. Collect specimen in a sterile urine cup.
3. Measure volume in mls.
4. Plate 100 μ L on sheep blood agar (5%) plate and 100 μ L on MacConkey agar. Culture at 37°C for 5 days. Record results at 48 hours and 5 days.
5. Allow sample to stand at room temperature for thirty minutes.
6. Centrifuge for five minutes.
7. Aliquot seminal plasma into 1.0 - 1.5 ml cryovials.

* Only for participants with localizing uropathogens at baseline visit #2 will provide semen sample 2-3 days after clinic visit #4.

Specimen Labeling and Storage

Specimens will be stored at each clinical center as described in the specific procedures above. Every specimen should be labeled with the following information: CPC Study, date of procedure, patient initials, and patient ID. If a participant generates > 600 ml of seminal plasma, the volume >than 600 ml can be used at each site for center specific research projects. EPS will be used at the discretion of the PI for center specific research projects. Access to all other specimens will be controlled by a sub-group of the PP&AS Committee, entitled “The Committee on Access to CPC Study Data and Patient Specimens”.

Appendix G

DMS, Helpdesk, and Training Guides

Appendix H

MedWatch 3500 Form