

Chronic Prostatitis Collaborative Research Network-2 (CPCRN-2)

Randomized Clinical Trial #1

A Randomized Multicenter Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of 10mg Alfuzosin in the Treatment of Chronic Prostatitis / Chronic Pelvic Pain Syndrome (CP/CPPS) in Recently-Diagnosed and/or Newly-Symptomatic Alpha-blocker Naïve Patients

**MANUAL OF PROCEDURES
(MOP)**

**Chronic Prostatitis Collaborative Research Network- 2
Data Coordinating Center
University of Pennsylvania
Philadelphia, PA**

**February 1, 2005
Version 1.0**

INTRODUCTION

The prostatitis classification system proposed by the National Institute of Diabetes, Digestive and Kidney (NIDDK) Diseases has become the reference standard for research studies in Prostatitis.¹ This classification proposes the absence of demonstrable bacterial infection, as determined by conventional microbiological techniques, in the diagnosis of Category 3 prostatitis: *Chronic abacterial prostatitis/chronic pelvic pain syndrome (CP/CPPS)*. Abnormalities in the expressed prostatic secretions (EPS) are the primary objective features of Category 3 prostatitis and chronic pain is the primary subjective symptom. Subtypes of this category include:

- 3A *Inflammatory chronic pelvic pain syndrome*, where white cells are found in the semen, EPS, or voided bladder urine-3 (VB-3).
- 3B *Non-inflammatory chronic pelvic pain syndrome*, where white cells are NOT found in the semen, EPS, and VB-3.

The majority of patients with chronic prostatitis are Category 3² stressing the need for more research and larger clinical studies for this class of prostatitis. It was with this goal in mind that the NIDDK funded the Chronic Prostatitis Collaborative Research Network, effective October 1, 1997. The objectives of this original network, comprised of seven (7) Clinical Research Centers (CRCs) and the Data Coordinating Center (DCC) at the University of Pennsylvania were to address primary research questions encompassing the diagnosis, etiology, natural history and prognosis, and the development of treatment strategies focused on CP/CPPS.

A number of accomplishments have been achieved by the CPCRn including: 1) the development of a longitudinal Chronic Prostatitis Cohort (CPC) Study, to which patients have been accrued and followed, 2) the development and validation of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI), a symptom severity index for CP/CPPS that has subsequently been translated into Spanish and German and is now being used as a primary endpoint for clinical trials in CP, and 3) the completion of the network's first NIH-funded multi-center RCT. A manuscript describing the results of this RCT, evaluating placebo, tamsulosin hydrochloride alone, ciprofloxacin alone, and the combination of tamsulosin hydrochloride and ciprofloxacin has recently been published in *Annals of Internal Medicine*.³ Further funding provided by the NIDDK to continue pursuing the network's objectives for the next five years has resulted in the establishment of CPCRn-2, comprised of 11 sites (the majority of which participated in the first CPCRn) and the Data Coordinating Center at the University of Pennsylvania.

This Manual of Procedures (MOP) documents the first randomized clinical trial (RCT#1) to be conducted by the CPCRn-2 and aims to evaluate the efficacy and safety of the alpha adrenergic blocker Alfuzosin (Uroxatral®) in the treatment of newly-diagnosed Chronic Prostatitis / Chronic Pelvic Pain Syndrome (CP/CPPS) patients. Alfuzosin is a once daily (10mg dosage), FDA approved medication, marketed by Sanofi-Synthelabo for an indication in benign prostatic hyperplasia (BPH) and under development for acute urinary retention (AUR), a relatively common complication of BPH.⁴ The effectiveness of alfuzosin in improving lower urinary tract

symptoms in patients with BPH has been documented in a number of placebo-controlled studies.⁴ A number of small studies have also suggested that alfuzosin ameliorates chronic prostatitis symptoms through a similar alpha-blockade mechanism. This study will enable further testing of this hypothesis in men with relatively new onset of CP/CPPS, referred to as “recently-diagnosed” and/or “newly symptomatic”. It has also been hypothesized that this population may be more likely to respond to alpha blocker treatment.

The potential benefit derived from this study would be to identify a course of treatment that would provide symptom improvement for a particular population of CP/CPPS patients or a subset of this population. Even a subtle improvement may be helpful, and is particularly important in a population of men with more recent onset of symptoms and have been less pre-treated.

Table of Contents

1	STUDY DESIGN, OBJECTIVES, AND ENDPOINTS	1
1.1	STUDY DESIGN AND OBJECTIVES	1
1.2	STUDY TIME LINE AND ENDPOINTS	1
1.3	GENERAL PROTOCOL POLICY	2
1.3.1	<i>Changing the Protocol</i>	2
1.3.2	<i>Initiating a Protocol Change</i>	2
2	PARTICIPANT ENROLLMENT.....	3
2.1	PARTICIPANT POPULATION AND RECRUITMENT	3
2.1.1	<i>Participant Population</i>	3
2.1.2	<i>Participant Recruitment</i>	3
2.2	PRE-SCREENING.....	4
2.3	INFORMED CONSENT	5
2.3.1	<i>Administration of Informed Consent</i>	6
2.3.2	<i>Confidentiality</i>	7
2.4	ASSIGNMENT OF PARTICIPANT ID	7
2.5	STUDY ELIGIBILITY CRITERIA.....	9
2.5.1	<i>Inclusion Criteria</i>	9
2.5.2	<i>Exclusion Criteria</i>	10
2.5.3	<i>Deferral Criteria</i>	10
2.6	SCREENING FAILURES	12
2.7	RANDOMIZATION PROCEDURE	12
2.7.1	<i>Back-up Manual Randomization</i>	13
2.8	PARTICIPANT WITHDRAWAL AND WITHDRAWAL CONSENT	13
2.9	PARTICIPANT TRANSFERS	14
2.9.1	<i>Transfer of a Participant during the Screening Phase</i>	15
2.9.2	<i>Transfer of a Participant during the Treatment/Follow-up Phase</i>	15
2.10	STUDY AND PARTICIPANT DOCUMENTS	15
3	VISIT SCHEDULING AND ADMINISTRATION.....	18
3.1	SCREENING/BASELINE PHASES	18
3.1.1	<i>Screening Visit #1</i>	18
3.1.2	<i>Screening Visit #2</i>	19
3.1.3	<i>Reporting of Pre-Existing Conditions and Adverse Events</i>	20
3.2	TREATMENT/FOLLOW-UP PHASE	23
3.2.1	<i>Participant Follow-Up Contact Schedule</i>	23
3.2.2	<i>Missed Study Contacts</i>	24
3.2.3	<i>Visit # 3 - Week Six (6)</i>	24
3.2.4	<i>Visit # 4 - Week Twelve (12)</i>	25
4	PARTICIPANT SAFETY	27
4.1	RISKS AND BENEFITS	27
4.1.1	<i>Risks</i>	27
4.1.2	<i>Benefits</i>	27

4.2	DEFINITION OF AN ADVERSE EVENT [AE]	27
4.2.1	<i>Recording and Reporting Adverse Events (AEs)</i>	27
4.2.2	<i>Definition of a Serious Adverse Event (SAE)</i>	28
4.2.3	<i>Collecting Adverse Event Information</i>	28
4.2.4	<i>Background of the CTCAE</i>	29
4.2.5	<i>Using the CTCAE</i>	30
4.2.6	<i>Recording and Reporting Serious Adverse Events (SAEs)</i>	31
4.2.7	<i>IND Safety Reports (21CFR 312.32)</i>	31
4.3	UNMASKING	34
4.3.1	<i>Unmasking for Serious Adverse Event (SAE)</i>	34
4.3.2	<i>Storage of Unmasking Envelopes</i>	35
4.3.3	<i>Return of Unmasking Envelopes</i>	35
4.3.4	<i>Unmasking in the absence of SAE</i>	35
5	DATA AND ADMINISTRATIVE FORMS PROCEDURES	36
5.1	PERSONNEL IDENTIFICATION (ID) NUMBERS	36
5.2	ACQUISITION OF FORMS FROM THE DCC	36
5.3	GENERAL INSTRUCTIONS FOR THE COMPLETION OF CRFs	36
5.3.1	<i>Time Frame for Completion and Data Entry of CRFs</i>	37
5.3.2	<i>Forms Completion</i>	37
5.3.3	<i>Participant Completed Forms</i>	37
5.3.4	<i>Participant Interview Completed Forms</i>	38
5.3.5	<i>Header Information on CRF:</i>	38
5.4	SPECIFIC INSTRUCTIONS FOR COMPLETING DATA ENTRY CRFs	38
5.4.1	<i>Adverse Events and Serious Adverse Events [AE]</i>	39
5.4.2	<i>NIH-Chronic Prostatitis Symptom Index [CPSI]</i>	42
5.4.3	<i>Demographics [DEMO]</i>	43
5.4.4	<i>Dispensing Log [DISP]</i>	43
5.4.5	<i>Drug Compliance [DCOMP]</i>	44
5.4.6	<i>Eligibility Checklist [ELIG]</i>	44
5.4.7	<i>EPS and Urine Testing [EUT]</i>	45
5.4.8	<i>Health Status Questionnaire ® [SF12]</i>	46
5.4.9	<i>Hospital Anxiety and Depression Scale© [HADS]</i>	46
5.4.10	<i>The International Index of Erectile Functions® [IIEF]</i>	46
5.4.11	<i>The Male Sexual Health Questionnaire [MSHQ]</i>	47
5.4.12	<i>The McGill Pain Questionnaire® (MPQ) [MCGILL]</i>	47
5.4.13	<i>Medical History [MEDHX]</i>	47
5.4.14	<i>Participant Expectations Questionnaire</i>	47
5.4.15	<i>Physical Exam [EXAM]</i>	48
5.4.16	<i>Pre-Screening Summary [PRESCR]</i>	48
5.4.17	<i>Randomization [RAND]</i>	49
5.4.18	<i>Study Stop Point [SSTOP]</i>	49
5.4.19	<i>Symptoms Assessment [SYM]</i>	50
5.4.20	<i>Treatment Stop Point [TSTOP]</i>	50
5.4.21	<i>Unmasking Record [UNMASK]</i>	51
5.5	SPECIFIC INSTRUCTIONS FOR COMPLETING ADMINISTRATIVE CRFs	52

5.5.1	<i>Clinical Center Staff “Signature and Delegation of Responsibilities” Log [STAFFLOG]</i>	53
5.5.2	<i>Clinic Correspondence Log [CCORRESP]</i>	53
5.5.3	<i>Concomitant Medications [CMED]</i>	53
5.5.4	<i>Participant Contact Information [PTCONT]</i>	54
5.5.5	<i>Participant Correspondence Log [PCORRESP]</i>	54
5.5.6	<i>Participant ID Assignment Log [PTLOG]</i>	54
5.5.7	<i>Participant Transfer [TRANS]</i>	54
5.5.8	<i>Progress Notes [PROGRESS]</i>	55
5.5.9	<i>Visit #1 Checklist [VISIT1]</i>	55
5.5.10	<i>Visit #2 Checklist [VISIT2]</i>	55
5.5.11	<i>Visit #3 Checklist [VISIT3]</i>	55
5.5.12	<i>Visit #4 Checklist [VISIT4]</i>	56
5.6	DIRECTIONS FOR CRF TRANSFER	56
5.6.1	<i>Database Audit by the DCC</i>	56
5.7	DATA QUALITY MANAGEMENT PROCEDURES	57
5.7.1	<i>Queries</i>	57
5.7.2	<i>Types of queries generated by manual monitoring</i>	58
5.7.3	<i>Making Corrections Based on Queries</i>	59
5.7.4	<i>Query Response to the DCC</i>	59
6	CLINICAL CENTERS’ AND DATA COORDINATING CENTER (DCC) RESPONSIBILITIES	60
6.1	CLINICAL CENTERS’ RESPONSIBILITIES	60
6.2	DCC RESPONSIBILITIES	61
6.3	MAINTENANCE AND DISPOSITION OF STUDY DOCUMENTS, DATA AND MATERIALS.....	62
6.4	CLINICAL SITE MONITORING	63
7	DATA MANAGEMENT SYSTEM USER GUIDE.....	64
7.1	OVERVIEW	64
7.2	CPCR2 MAIN MENU.....	64
7.3	CPCR2—PROTOCOL 1 (CP01) CLINICAL CENTER MENU	65
7.4	REGISTER PARTICIPANT	66
7.5	ELIGIBILITY AND RANDOMIZATION	67
7.6	CRF ENTRY	70
7.7	CRFs AND REFERENCES	73
7.8	PRE-SCREENING SUMMARY.....	73
7.9	ENTRY STATUS	74
7.10	MEDICATION REFERENCE	76
7.11	REPORTS	76
7.12	DATA FIELD SPECIFICATIONS	77
7.13	MESSAGES	78
7.14	CRCU SOFTWARE SYSTEMS HELP DESK.....	79
7.14.1	<i>Sponsored Project Help Desk (SPHD)</i>	79
7.14.2	<i>Assignment of DMS Accounts</i>	80
7.14.3	<i>Procedures for Obtaining Help Desk Support</i>	80

8 REFERENCES.....	82
ACRONYMS/ABBREVIATIONS	83
MANUAL OF PROCEDURE AGREEMENT PAGE	86
APPENDIX A: PARTICIPANT RECRUITMENT BROCHURE	87
APPENDIX B: INFORMED CONSENT FORM.....	89
APPENDIX C: DRUG PRODUCT INSERT	95
APPENDIX D: VISIT SCHEDULE.....	108
APPENDIX E: CTCAE v3.0.....	108
APPENDIX F: MEDICATION MANUAL.....	109

1 STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

1.1 Study Design and Objectives

This CPCRN-2 randomized clinical trial (RCT #1) will utilize a double-blinded, 2 arm design to evaluate the efficacy and safety of the alpha-blocker alfuzosin in newly-diagnosed CP/CPPS patients, as compared to placebo.

The primary objectives of this trial are:

1. To compare 12 weeks of treatment with alfuzosin versus placebo in newly-diagnosed, alpha-blocker naïve CP/CPPS participants with respect to the primary endpoint in the NIH-CPSI.
2. To evaluate the safety and tolerability of 12 weeks of alfuzosin in newly-diagnosed, alpha-blocker naïve CP/CPPS participants.

The secondary objectives of this trial are:

1. To characterize newly-diagnosed, alpha-blocker naïve CP/CPPS participants with respect to symptom severity.
2. To assess the incidence of depression and anxiety, and its relationship to symptom severity and response to treatment, in newly-diagnosed, alpha-blocker naïve CP/CPPS participants.
3. To assess domains of male sexual function and its relationship to symptom severity and response to treatment, in newly-diagnosed, alpha-blocker naïve CP/CPPS participants.
4. To assess the impact of patient expectations on symptom severity and response to treatment, in newly-diagnosed, alpha-blocker naïve CP/CPPS participants.

1.2 Study Time Line and Endpoints

Approximately 270 eligible patients will be randomized and followed for a period of twelve (12) weeks after randomization. All participants who meet eligibility criteria at baseline screening (a two-to-four week period that will require two clinic visits- Visit #1 and 2) will be randomized to either alfuzosin or placebo (a 1:1 randomization) at Visit #2. The participant will be required to take the provided study medication every day for six weeks and return for the first primary endpoint evaluation (Visit #3) thereafter. No more than one week may lapse between completion of study medication and Visit #3. At Visit #3, the participant will be provided with study medication for the remaining six weeks of the trial. In total, it is anticipated that participant involvement in this study will not exceed 17 weeks, from the first screening visit to the final clinic visit.

The primary endpoint to be used for efficacy evaluation is the response rate, defined as a 4-point decrease from baseline to 12 weeks in the NIH-CPSI Total Score (scale of 0 - 43).⁵ The primary endpoint will be evaluated at the Visit #4/ Week 12 following randomization. Baseline is defined as the NIH-CPSI Total Score assessed at the Visit #2 screening visit and will be used for all analyses. The NIH-CPSI Total Score assessed at Visit #1 will be only be used to determine participant eligibility.

1.3 General Protocol Policy

1.3.1 Changing the Protocol

The objectives of the CPCRN-2 RCT #1 are most likely to be achieved if the protocol does not require alteration. Any changes in the protocol will result in some degree of heterogeneity of the data, which complicates the analyses and may compromise the scientific integrity of the study. However, occasions may arise in which protocol changes are necessary. Therefore, changes in the protocol will be considered only if they are required to ensure participant safety or will significantly enhance the scientific validity of the study.

1.3.2 Initiating a Protocol Change

Any member of the CPCRN-2 may request a change to any portion of the study protocol. The member wishing to change the protocol should present the proposed change(s) in writing to either the Chair of the Steering Committee or the Principal Investigator of the Data Coordinating Center (DCC), who will then contact the others. The DCC Principal Investigator and the Chair of the Steering Committee will then jointly decide on the appropriate mechanism (letter, conference call, meeting) to handle the proposal depending on the implications of the proposed change. Proposed changes with only a minor impact on the current course of the CPCRN-2 RCT #1 can be properly handled through a letter to each member of the Steering Committee. Proposed changes with a greater impact on the course of the CPCRN-2 RCT #1 will be presented to the Steering Committee via conference call or formal meeting to allow all members to benefit from the scientific debate generated in these discussions. Proposed changes can be implemented only after the Steering Committee reaches a majority vote and the NIDDK Project Officer approves the proposed changes. Once a proposed change has been approved, the DCC will coordinate all activities required to implement the change via the issuance of a protocol amendment document and revised protocol.

2 PARTICIPANT ENROLLMENT

2.1 Participant Population and Recruitment

2.1.1 Participant Population

This study will attempt to recruit “newly diagnosed” and “alpha-blocker treatment naïve” CP/CPPS patients. The study population will be drawn from patients presenting with symptoms of discomfort or pain in the pelvic region for at least a six-week interval at the time of presentation. Additionally, the participant’s symptoms must be present for two years or less, with the severity bothersome enough to have prompted a physician visit. Given that the participants will be “newly diagnosed”, the total overall score on the NIH-CPSI has been dropped to ≥ 12 for inclusion.

2.1.2 Participant Recruitment

The successful recruitment and retention of these “newly diagnosed” and “alpha-blocker treatment naïve” CP/CPPS patients is the most important factor for the success of this trial. Each clinical center has recruitment goals of approximately 25 participants, at a rate of one participant per month. It is expected that approximately two years or 25 months, will be needed for patient recruitment. Recruitment data will be monitored by the DCC in order to continually assess recruitment rates at each site. Each clinical center will be responsible for determining how best to recruit participants from its local population. Some recruitment methods are described below:

- Investigator’s Own Clinical Practice

Many potential participants can and will be identified simply by considering the current participant population at the investigator’s 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 and Home Page*

Prior to the start of this trial, the National Institutes of Health (NIH) will arrange a press release to introduce the study to the media and public. Thereafter, the trial 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*

The DCC will prepare a brochure (see Appendix A; Participant Recruitment Brochure) that can be distributed to potential participants. In the brochure, the trial will be described and the participant study requirements 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 further study and enrollment information. Also, these brochures may be used at health fairs and other educational and promotional events to advertise the trial. These brochures will need to be approved by your local IRB prior to use.

- *Participant Recruitment Video*

In addition, a participant recruitment video, which also describes the study and participation requirements, will be developed. Copies will be provided to each of the clinical sites if requested, and a script will be provided for local IRB approval prior to use. However, your local IRB 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 visit schedule. This should be done to ensure not only the participant’s eligibility, but also his willingness and ability to meet the demands/responsibilities of the study.

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 **exclusion** and **deferral** criteria may be reviewed in order to reduce the number of potential participants scheduled for Visit #1. **The RC should NOT give the potential participant information about study-specific inclusion criteria.**

- If pre-screening determines that the potential participant is eligible and willing, the RC should schedule a time to review and complete the informed consent (see Appendix B; Informed Consent) and schedule Visit #1.
- The potential participant should receive a copy of the informed consent, either in person, by mail or by fax.
- The RC should allow the potential participant time to consider the study obligations and discuss the study with his/her family members before signing the consent form.
- The informed consent form must be signed in the presence of the PI or the RC, **prior to** Visit #1 procedures.
- The RC will instruct the potential participant to bring all his medications (prescription and over-the-counter) to Visit #1.
- When scheduling Visit #1, the participant should be informed that he should remain abstinent (without an ejaculation) for two (2) days prior to the scheduled visit because EPS and urine samples will be collected.

2.3 Informed Consent

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

- The participant must be informed that participation in the study is **voluntary** and that refusal to participate will involve no penalty or loss of benefits.
- The participant must be informed that the study involves **research**.
- The participant must be informed of any **alternative procedures**.
- The participant must be informed of any reasonable foreseeable **risks**.
- The participant must be informed of any **benefits** from the research.
- An outline of safeguards to protect participant **confidentiality** must be included, as well as an indication of which parties are allowed to review the record and of the participant's right to withdraw without penalty. This should be balanced with a discussion of the effect withdrawals have on the study, and the responsibility a participant has, within limits, to continue in the study if 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.

- The participant must be provided with a HIPAA authorization to sign, either as a part of the informed consent or as a stand-alone document to be presented at the time of consent, which details all potential risks of disclosure and individuals and organizations who may have access to participant research data.

An informed consent must be obtained from the participant before any 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 the participant or their legal representative cannot read the written material, then an impartial witness should be present for the entire consent process. After the participant has had a chance to ask questions and has signed the consent form, the witness would then sign and date the consent, to affirm the process (See Appendix B; Consent Form).

NOTE: For non-English speaking participants, the individual clinical center must provide a professionally translated, IRB approved version of the consent form and all supporting materials. In addition, a clinical research staff member who is fluent in the participant's native language or a professional interpreter will be utilized to explain the study and answer the participant's questions.

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

If the participant wishes to take the Informed Consent Form home before reaching a decision, then 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 throughout the Screening and the Treatment/Follow-up phases of this trial. 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, and the person "obtaining consent". 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 the trial **before** the participant has signed the informed consent form.

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

2.4 Assignment of Participant ID

A Participant Log [**PTLOG**] has been developed for each Clinical Center. It includes columns for unique Participant ID number, for participants' names, initials, and randomization (drug packet) number. After the participant has signed the informed consent document, the participant is logged in the PTLOG and assigned a Participant ID number. Each participant should be assigned the next available Participant ID number.

All communication with the DCC regarding individual participants must be through the Participant ID number and your clinical center code. Once a Participant ID number has been assigned, it should never, for any reason, be reassigned. The [**PTLOG**] form should be stored in a secure, locked filing cabinet. A backup copy of this log should be made at the end of every other week and the copy stored in a separate, secure location.

The 5-digit Participant ID number is composed as follows:

- The first digit of the number is the protocol number.
- The last 4 digits indicate the sequential ordering of participants.

Clinical centers are numbered as followed:

- 01 = Cleveland Clinic- Florida
- 02= Harvard Medical Center Boston, MA
- 03= Northwestern University
- 04 = Temple University Hospital, Philadelphia, PA
- 05 = UCLA Medical Center, Los Angeles, CA
- 06= University of Mississippi
- 07= University of Washington, Harborview
- 08= Queen's University
- 09= Stanford University
- 10= University of Maryland
- 11= University of Washington, Seattle
- 18= University of Sciences Malaysia
- 19= Drew University

Participant ID Assignment Log Example

Clinical Center Code	Participant ID	Participant Initials	Participant Name
02	10001	JD	John Doe
02	10002	RS	Robert Smith
02	10003	MDC	Michael D. Cohen
02	10004	DW	Doug Weiss

2.5 Study Eligibility Criteria

- 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-2 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-2 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.

2.5.1 Inclusion Criteria

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

1. Participant has signed and dated the appropriate Informed Consent document.
2. Participant is male.
3. Participant is ≥ 18 years of age.
4. Participant has an overall score on the NIH-CPSI of ≥ 12 out of a potential of 0–43 points at both screening visits.
5. Participant has had symptoms of discomfort or pain in the pelvic region for at least a six-week interval at the time of presentation.
6. Symptoms bothersome enough to prompt a physician visit have been present for two years or less.

2.5.2 Exclusion Criteria

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

1. Participant has evidence of facultative Gram negative or enterococcus with a value of ≥ 1000 CFU/ml in mid-stream urine (VB2).
2. Participant has previously received alfuzosin (Uroxatral®), tamsulosin hydrochloride (Flomax®), doxazosin mesylate (Cardura®), terazosin HCL (Hytrin®), or other alpha-adrenergic receptor blockers for symptoms of CP/CPPS or within the past two years for any other reason.
3. Participant has a history of prostate, penile, testicular, bladder, or urethral cancer or has undergone pelvic radiation, systemic chemotherapy, or intravesical chemotherapy.
4. Participant has a history of moderate or severe hepatic impairment, severe renal insufficiency, severe or unstable cardiovascular (i.e. prolonged QT), respiratory, hematological, endocrinological, neurological or other somatic disorders.
5. Participant has unilateral orchialgia without pelvic symptoms, active urethral stricture, or neurological disease or disorder affecting the bladder.
6. Participant has uninvestigated, significant hematuria.
7. Participant has undergone TURP, TUIP, TUIBN, TUMT, TUNA, balloon dilation of the prostate, open prostatectomy or any other prostate surgery or treatment such as cryotherapy or thermal therapy.
8. Participant has a neurological impairment or psychiatric disorder preventing his understanding of consent and his ability to comply with the protocol.
9. Participant is currently taking exclusionary medications such as potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, or ritonavir) or erythromycin.

2.5.3 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 the RCT.

Deferral Checklist	Re-entry Criteria (Participant deferred until...)
1. Participant has had a urinary tract infection, with a urine culture value of >100,000 CFU/ml, within the past three (3) months, <i>then</i>	Condition absent for three (3) months.
2. If the participant has had clinical evidence of urethritis, i.e. 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, <i>then</i>	Condition absent for three (3) months.
3. If the participant has had a prostate biopsy in the past three (3) months, <i>then</i>	3 months from date of procedure.
4. If the participant has experienced symptoms of acute or chronic epididymitis within the past three (3) months, <i>then</i>	Condition absent for 3 months.
5. If the participant has been diagnosed with or treated for symptomatic genital herpes in the past twelve (12) months, <i>then</i>	12 months from date diagnosed, and until they have been symptom free for a 12-month period (asymptomatic for 12 months).
6. If the participant has been taking excluded medications such as Cialis®, Levitra®, and Viagra® in the past one (1) week, <i>then</i>	Medication free for one (1) week.
7. If the participant has been taking prescription drugs with 5-alpha reductase activity (i.e. dutasterade or finasteride) in the past twelve (12) months, <i>then</i>	Medication free for twelve (12) months.

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 prescription drugs with 5-alpha reductase activity, but his medical record clearly

indicates that he was on this class of medication approximately two (2) months ago, then the medical record should be considered correct. The participant is deferred until he has been off the medication for twelve (12) months.

If a participant was previously deferred, he must begin the screening process again, beginning at Visit #1. This includes assigning a new participant ID, completing all new CRF's and procedures normally scheduled at Visit #1. To determine the re-screening date for a participant who has been deferred for more than one criterion, the RC will select one date that allows sufficient time for all deferral criteria to have been resolved.

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

Review the study with the participant,

Determine whether the condition is absent or has subsided, and

Ascertain if the participant is still interested in beginning the screening process again.

2.6 Screening Failures

A participant who does not complete the Screening procedures for whatever reason will be considered a screening failure and will **not** be randomized to the trial. 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 Source Documentation Binder and should not be sent to the DCC.

NOTE: Participants must be able to provide a VB2 sample AND either an EPS or VB3 sample to be included in the study. If the participant is not able to provide these samples, then he will be considered a screening failure and will **not** be randomized.

2.7 Randomization Procedure

The inclusion and exclusion criteria will be reviewed and checked against the Eligibility Checklist [**ELIG**], the NIH-CPSI scores from both Screening Visit #1 and 2, and lab results for the 48 hour VB2 culture. Only those participants, who have completed the entire screening phase and meet eligibility at both visits, will be randomized to the trial. The Randomization [**RAND**] form will be completed, and the research coordinator will perform computer randomization.

NOTE: The participant needs to have an individual baseline NIH-CPSI score of ≥ 12 at both visits; an average score of baseline NIH-CPSI score of ≥ 12 calculated from both visits does not warrant eligibility. Only the NIH-CPSI score obtained during visit 2 will be used as the baseline score for determining primary endpoint efficacy.

The DMS is designed to prevent ineligible participants from being randomized. If the eligibility data for a participant proves a participant is **ineligible**, the DMS will **not** allow data entry. If the data entered are consistent with the requirements for randomization into the study, the computer application will assign a five-digit randomization number which will be recorded on the Randomization form [**RAND**]. The five-digit randomization number also directly corresponds to a study medication kit that will be dispensed to the participant. *The RC will notify the clinical center pharmacist of the randomization number.*

NOTE: The University of Sciences Malaysia will not be permitted to randomize more than approximately 50% of the University of Washington-Harborview's target of 25 participants (cap of 12 participants so that a balanced randomization results in 6 participants per arm).

2.7.1 Back-up Manual 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 215-306-0555, 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 and Visit #2– NIH/CPSI [**CPSI**], Eligibility Checklist [**ELIG**], and Randomization [**RAND**], and whether this data have been entered and verified.

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

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.

2.8 Participant Withdrawal and Withdrawal Consent

Participants are free to withdraw (or be withdrawn) from the study at any time. There are many reasons a participant may want to do so. They include:

- Adverse Event/Serious Adverse Event (AE/SAE)
- Significant concurrent illness
- Protocol noncompliance
- Investigator's discretion

- Withdrawn informed consent
- Relocation
- Use of unacceptable concomitant medications
- Dissatisfaction with treatment
- Loss of interest in the study
- Lost to follow-up

Reason(s) for withdrawal will be documented on case report forms and recorded at the DCC. For those participants who withdraw (or are withdrawn) due to AE/SAE, the Adverse Event/Serious Adverse Events [AE] and **MedWatch 3500A** forms must be completed and faxed to the DCC.

The RC will instruct the participant to contact the site prior to stopping study drug. 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. If this document is mailed to the participant, it must be sent certified mail. The certified mail receipt should be kept with the participant's records. The letter should contain the following information:

I voluntarily withdraw my consent to participate in this study.

- I no longer wish to be contacted by the clinic regarding this study.
- I understand that my records will be kept confidential.
- I can continue to receive my 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. Every effort should be made to encourage participants to continue with study visits even if they stop treatment early.

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 DCC Project Manager is informed of the participant's withdrawal, so that the data archival process at the DCC can be initiated.

2.9 Participant Transfers

It is possible for a study participant to transfer to another CPCR-2 RCT #1-participating clinical center during the course of the study. However, it is preferred, from a scientific, as well as operational point of view that a participant completes the study at the same clinical center in which 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 Participant Study Binder throughout the entire study. If a participant indicates his desire to transfer to another clinical center during the treatment/follow-up phase of the trial, 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 records to the receiving clinical center.
- The receiving RC must create a new file for the participant's records, and for all future follow-up contacts.
- Before any 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 RCs to ensure the completeness and accuracy of the participant's 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 CPCRN-2 RCT #1 Study Group, Sanofi-Aventis, 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:

Clinic Regulatory Binder (1 per clinical center)

This binder 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 [**STAFFLOG**]
- Study Medication Tracking/Inventory Log [**TRACK**]
- Study Medication Shipment Receipts
- Monitoring 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)

This binder 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.

Source Documentation Binder (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.

Participant Study Binder (1 per clinical center)

This binder contains Participant ID Assignment Log, a copy of all participant signed informed consents and all financial documents related 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 VISIT SCHEDULING AND ADMINISTRATION

3.1 Screening/Baseline Phases

Screening consists of, at a minimum, two (2) screening/baseline visits: Visit #1 and Visit #2. 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.

- If at any time during the screening process the patient is found to be ineligible, they must be informed of this fact as soon as possible.
- If the participant seems eligible at Visit #1, Visit #2 must be scheduled no less than seven (7) days and no more than four (4) weeks apart.
- Participants must meet eligibility criteria at both Visits 1 and 2 before undergoing the rest of the procedures for the screening phase and for randomization into the study.
- Participants who initially are deferred from entry in the study based on deferral criteria may be reconsidered for inclusion at a later date, **if the condition(s) resolves** according to the specified time frame. A participant previously **excluded** based on the exclusion criteria **cannot** be re-screened.

3.1.1 Screening Visit #1

Forms to be completed at this visit include:

- Informed Consent
- NIH-CPSI [**CPSI**]
- Eligibility Checklist [**ELIG**]
- Medical History [**MEDHX**]
- Demographics [**DEMO**]
- EPS and Urine Testing [**EUT**]
- Physical Exam [**EXAM**]
- Urine Screening [**URINE**]
- Symptom Assessment [**SYM**]
- Concomitant Medication [**CMED**]
- Participant Contact Information [**PTCONT**]
- Participant ID Assignment Log [**PTLOG**]
- Visit Checklist [**VISIT1**]

Laboratory Procedures to be completed at this visit include a physical exam, urinalysis, urine and EPS testing by microscopy and culture. The RC should have reminded the participant that he needs to remain abstinent (without an ejaculation) for two (2) days prior to the sample collection

for urine cultures. 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. The RC must inform the participant that in order to be eligible for the trial a VB2 sample **AND** a VB3 or EPS sample **must** be obtained. If cannot be obtained, the participant will be considered a screening failure and cannot be included in the study.

The RC will review all over-the-counter and prescribed medications that the participant is currently taking and will complete the Concomitant Medications [**CMED**] form, which is an administrative form and is not entered into the database.

The RC will review the visit checklist [**VISIT1**] form to ensure that all required forms and procedures were completed and schedule Screening Visit #2.

3.1.2 Screening Visit #2

Forms to be completed at this visit include:

- NIH-CPSI [**CPSI**]
- Eligibility Checklist [**ELIG**]
- Adverse Events/Serious Adverse Events [**AE**] – Pre-existing medical conditions (see note below)
- Randomization [**RAND**]
- Dispensing Log [**DISP**]
- Study Medication Tracking Log [**TRACK**]
- Concomitant Medications [**CMED**]
- Participant Expectations Questionnaire [**EXP**]
- Symptom Assessment Form [**SYM**]
- MOS SF-12 Health Status Questionnaire [**SF-12**]
- McGill Pain Questionnaire [**MCGILL**]
- Hospital Anxiety and Depression Scale [**HADS**]
- International Index of Erectile Function [**IIEF**]
- Male Sexual Health Questionnaire [**MSHQ**]
- Visit Checklist [**VISIT2**]

The research staff will review the VB2 culture lab results from Screening Visit #1 to determine participant eligibility and record this on the [**ELIG**] form. The participant's score on the [**CPSI**] will also be recorded on the [**ELIG**] form.

The RC will update the CMED form, if there are any changes in the participant's medication use.

The RC will randomize those eligible participants and dispense study medication, completing both the dispensing log [**DISP**] form and Study Medication Tracking Log [**TRACK**] form. The participant will be given one bottle of study medication and the RC will provide the participant with specific instructions on how to take the study medication (A Medication Manual will be provided by the University of Pennsylvania's Investigational Drug Service (IDS)).

The RC will instruct the patient to begin taking the study medication on the day they receive it. In this way, the date of Visit#2 will be the "Date of First Dose". The patient will also be instructed to take study medication at the same time each day, immediately after a meal.

The RC will do a pill count to confirm that there are 50 tablets in each bottle. It is also important that the RC check that the label on the bottle and the participant's 5-digit randomization number on the [**RAND**] form are the same and that the bottle is dispensed to the participant whose Participant ID is on the [**DISP**] form.

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

At this randomization visit, Visit #2, the RC will also begin recording all current pre-existing conditions reported by the patient. This information will be recorded on the Adverse Event [**AE**] form and the column for "pre-existing conditions" completed for these events. More detailed instructions on how to define and elicit pre-existing conditions and adverse events follow. Please also refer to *Section 4-Participant Safety* for additional information on the recording and reporting of adverse events. Instructions on how to fill out the [**AE**] form can be found in *Section 5.4.1*.

3.1.3 Reporting of Pre-Existing Conditions and Adverse Events

The following outlines pre-existing condition information and adverse events information collected at the randomization visit. The purpose of recording adverse event information related to pre-existing medical conditions is to provide ongoing monitoring of any changes in pre-existing conditions, and to allow comparison of adverse event information related to pre-existing medical conditions with adverse events that may occur once study drug has begun.

Definitions:

a. Pre-Existing Condition- A pre-existing condition is any chronic or acute sign, symptom, illness, or condition that the participant has at the time of entering the clinical trial.

b. Adverse Event (AE) - An adverse event is any unfavorable or unintended sign, symptom, or disease occurring in a clinical trial participant at any stage of the study. Adverse events may include the following:

- All suspected adverse medication (or device) reactions, drug interaction, drug overdose, failure of expected action or significant worsening of the disease under study.
- Worsening of a pre-existing condition, or apparent unrelated illness.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event.
- An event that may compromise the rights, safety, or welfare of research subjects.

Any event that could be characterized by the definitions above is an AE, **whether or not considered related to the study or investigational product.**

Non-serious adverse events are all adverse events that do not meet the criteria for "serious."

c. Serious Adverse Event (SAE) – A Serious adverse event is defined to include any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity; or
- A congenital anomaly/birth defect in the subject's offspring
- Important medical events that, based on appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent a serious adverse event.

Eliciting and Monitoring Pre-Existing Conditions and Adverse Events:

Consistent with clinical research adverse event reporting guidelines, the reporting of adverse events will be accomplished by collecting information on adverse experiences during the screening process and at all treatment and follow-up visits. All adverse events (serious and non-serious; treatment-emergent and baseline-emergent) must be recorded on the Adverse Event Report Form.

A baseline-emergent adverse event is defined as any event that occurs or worsens during the staged screening process (after informed consent) including the randomization visit.

A treatment-emergent adverse event is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.

Questions for Eliciting Pre-Existing Conditions and Adverse Events:

In order to avoid bias in eliciting *Pre-existing Conditions*, participants will be asked the following question at screening:

"Do you currently have any pre-existing symptoms, injuries, illness or condition?"

In order to avoid bias in eliciting *Adverse Events (AEs)*, participants will be asked the following questions at treatment and follow-up visits:

"Since your last visit, have you had any new symptoms, injuries, illness, or side effects?"

AND

"Since your last visit, have you had any worsening of pre-existing conditions?"

Monitoring for Pre-Existing Conditions and Adverse Events:

Pre-existing condition information will be derived from participant interview and medical condition as assessed at baseline (See Participant Assessment below). A record (kept on comment form or worksheet) of all current pre-existing conditions will be initiated by the Study Coordinator for each participant randomized into the clinical trial. This record will be referenced by the Study Coordinator when monitoring for adverse events at every contact visit thereafter during the course of the trial.

At randomization, an adverse event symptom reported by the participant as related to a pre-existing condition will be entered on the Adverse Event form and coded and graded appropriately. A "yes" will be entered in the Pre-Existing box of the Adverse Event form, indicating that this symptom is related to a pre-existing condition. Pre-existing conditions that worsen during the study are to be reported as Adverse Events.

Participant Assessment:

The Investigator and Study Coordinator should assess each participant for adverse events (AE) throughout study participation. This includes conducting a thorough investigation on any suspected AE that may come from a variety of sources:

- Spontaneous reports by participant
- Observations by key study personnel
- Reports to study staff by the participant's family or medical care providers
- Possible AE documented in medical records, progress notes, etc.
- Death of participant

In addition to receiving reports of potential AE, the Investigator and Study Coordinator should develop and implement a plan to consistently and routinely monitor for AE through proactive measures such as:

- Interview participants
- Review lab reports
- Review participant's medical records for additional information
- Review participant's diaries
- Communicate with participant's medical providers

3.2 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 the trial. The participant will be required to return for two additional clinic visits, at week six (6) and at week twelve (12) post-randomization and treatment start.

3.2.1 Participant Follow-Up Contact Schedule

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 by referencing 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 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.

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.

3.2.2 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.

3.2.3 Visit # 3 - Week Six (6)

Forms to be completed at this visit include:

- NIH-CPSI [**CPSI**]
- Adverse Events/Serious Adverse Events [**AE**]
- Concomitant Medications [**CMED**]
- Visit Checklist [**VISIT3**]
- Study Medication Tracking Log [**TRACK**]
- Drug Compliance [**DCOMP**]
- Dispensing Log [**DISP**]
- Symptom Assessment Form [**SYM**]- including GRA
- MOS SF-12 Health Status Questionnaire [**SF-12**]
- McGill Pain Questionnaire [**MCGILL**]
- Hospital Anxiety and Depression Scale [**HADS**]
- International Index of Erectile Function [**IIEF**]
- Male Sexual Health Questionnaire [**MSHQ**]

At this visit, the RC will review with the participant any new adverse events which have occurred since Visit #2. The RC will also follow up with any pre-existing conditions until they have been resolved. Any change in pre-existing conditions while on study drug will also need to be recorded. All information will be recorded on the Adverse Event [**AE**] **CRF**. More detailed instructions on how to fill out this form can be found in Sections 4.2 and 5.4.1 of the MOP.

The RC will update the [**CMED**] form, if there are any changes in the participant's medication use.

The RC will instruct the participant to fill out the GRA question on the [**SYM**] form.

The RC will assess study medication compliance by collecting the first study medication bottle back from the participant, doing a pill count and recording the count on both the Drug Compliance [**DCOMP**] form and the Study Medication Tracking Log [**TRACK**]. If there appears to be an issue with adherence to study medication, the RC should explain to the participant the importance of taking the medication as directed and discuss ways in which to help the participant remember to take study medication.

The RC will provide the participant with a second bottle of study medication for the next 6 weeks, again confirming that there are 50 tablets in the bottle, and complete the Dispensing Log [**DISP**] form, as well.

The RC will review the Visit #3 checklist [**VISIT3**] form to ensure that all required forms and procedures were completed and schedule Visit #4 according to the participant's follow-up contact schedule.

3.2.4 Visit # 4 - Week Twelve (12)

Forms to be completed at this visit include:

- NIH-CPSI [**CPSI**]
- Adverse Events/Serious Adverse Events [**AE**]
- Concomitant Medications [**CMED**]
- Study Medication Tracking Log [**TRACK**]
- Drug Compliance [**DCOMP**]
- Symptom Assessment Form [**SYM**]- including GRA
- MOS SF-12 Health Status Questionnaire [**SF-12**]
- McGill Pain Questionnaire [**MCGILL**]
- Hospital Anxiety and Depression Scale [**HADS**]
- International Index of Erectile Function [**IIEF**]
- Male Sexual Health Questionnaire [**MSHQ**]
- Study Stop Point [**SSTOP**]
- Treatment Stop Point [**TSTOP**]

At this visit, the RC will review with the participant any new adverse events which have occurred since Visit #2. The RC will also follow up with any pre-existing conditions until they have been resolved. Any change in pre-existing conditions while on study drug will also need to

be recorded. All information will be recorded on the Adverse Event [**AE**] **CRF**. More detailed instructions on how to fill out this form can be found in Sections 4.2 and 5.4.1 of the MOP.

The RC will update the [**CMED**] form, if there are any changes in the participant's medication use.

The RC will instruct the participant to fill out the GRA question on the [**SYM**] form.

The participant will return the study medication bottle to the RC, who will do a pill count in order to assess study medication compliance. This will be recorded on both the Drug Compliance [**DCOMP**] form and the Study Medication Tracking Log [**TRACK**].

The RC will fill out both the Study Stop Point [**SSTOP**] and Treatment Stop Point [**TSTOP**] forms for study close-out.

4 PARTICIPANT SAFETY

4.1 Risks and Benefits

4.1.1 Risks

Before giving consent to participate in this study, the Research Coordinator must inform the participant of all potential risks related to participation in this study. Specifically, risks related to receiving alfuzosin, as outlined in the protocol, informed consent, and drug package insert.

4.1.2 Benefits

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

- Participation can help investigators gain further knowledge about the use of alfuzosin in the treatment of CP/CPPS
- Participants will maintain direct contact with Clinical Centers and Research Coordinators.
- Participants may have access to new clinical trials/therapies.

Adverse Event

Study participants must be evaluated at each clinic visit 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.

4.2 Definition of an Adverse Event [AE]

As defined previously, 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).

4.2.1 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.

4.2.2 Definition of a Serious Adverse Event (SAE)

As defined previously, 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 in-patient hospitalization or prolongation of existing hospitalization;
- 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); OR
- Is a congenital anomaly/birth defect in the subject's offspring

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 syncope (loss of consciousness), 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.

4.2.3 Collecting Adverse Event Information

At each contact with a participant, clinical staff must ask if any adverse events have occurred and capture the appropriate information for reporting events. The information recorded should be based on the signs or symptoms detected during the physical examination and clinical evaluation of the participant. In addition to the information obtained from those sources, adverse events may be elicited from the participant as described in the section entitled “Eliciting and Monitoring Pre-Existing Conditions and Adverse Events.” Complete reporting information includes the following:

- Specific condition or event and direction or change

- Abnormal laboratory value
- Whether a pre-existing condition has worsened (e.g. in severity and/or frequency)
- Dates of onset
- Grade (from mild to fatal)
- Attribution to study drug (from unrelated to definite)
- Outcome

While completion of the [AE] form is discussed in *Chapter 5: Data and Administrative Forms Procedure*, this section will describe the use of the coding tool for identifying adverse events, namely the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (see Appendix E; Common Toxicity Criteria Adverse Events).

4.2.4 Background of the CTCAE

The Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) created the Common Terminology Criteria as a way to categorize adverse events for reporting to funding agencies, for more efficient statistical analysis, and for use in publications.

The current CTCAE, version 3.0, provides definitions for AE terms and a grading (severity) scale for each AE. The CTCAE v3.0 and its associated grading criteria are very specific, providing an AE term and grade that precisely describes the event.

For the latest version of the CTCAE, each AE term is mapped to a specific code from the Medical Dictionary for Regulatory Activities (MedDRA) v6.0 (8-digit codes).

Structure of the CTCAE

There are four organizational levels to the CTCAE, each with unique features to assist with their use:

Category

The primary organization is pathophysiological (e.g., ALLERGY/IMMUNOLOGY) and anatomical (e.g., DERMATOLOGY/SKIN CATEGORIES) to facilitate location of related AEs.

Adverse Event (AE)/Supra-ordinate term

Multiple clinical terms are used to convey ‘Adverse Event’ including side effect, acute or late effect, complication, toxicity, morbidity, etc. – all essentially pointing to a change possibly caused by treatment.

For certain AEs, there are more specific terms under the “Select AE” column. These terms further specify AEs and provide more power for summarizing terms across clinical trials.

Grades

For each AE, grades are assigned and defined using a scale from 1 to 5. Specific criteria for each grade are included for each AE.

- 1 = Mild Adverse Event
- 2 = Moderate Adverse Event
- 3 = Severe and undesirable Adverse Event
- 4 = Life-threatening or disabling adverse event
- 5 = Death related to Adverse Event

Attribution

Attribution is the determination of whether an AE is related to a medical treatment or procedure. To report on attribution, clinicians must evaluate each AE the patient experiences to determine what might have caused the event or what interventions or conditions might have been associated with the event.

For certain adverse event listings, there are comments included that provide additional considerations when choosing the event. These comment types are as follows:

Remark

A remark clarifies an adverse event.

Also Consider

This comment references other adverse events that may be recorded if clinically significant.

Navigation Note

Navigation notes provides guidance for locating specific adverse event terms that are listed under the same or a separate category.

4.2.5 Using the CTCAE

The first step in identifying the exact AE term is to identify the event using the CTCAE v3.0 (see Appendix E). Each category is listed on the first page under the table of contents. Determine the most appropriate category for an AE and turn to that section of the CTCAE.

Example: Assume that a participant reports a headache upon waking in the morning during the trial. After discussing the event with the participant, you determine that the event is neurological, probably caused by tension. Turning to the NEUROLOGY CATEGORY (page 83), you follow down the list of events alphabetically. Where “Headache” should appear is a comment:

NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as *Pain – Select* in the PAIN CATEGORY.

Turning to the PAIN CATEGORY, you find that the AE/Supra-ordinate term is listed as “Pain” with many terms under the “Select AE” column. Here you locate the precise term, “Head/headache.” This term may be recorded on the AE case report form under, “Specify Event.” The MedDRA code for the event, 10019211, may be recorded on the AE case report form in the “MedDRA code” column.

The grade (severity) of the event must also be determined using the CTCAE v3.0. Beside each AE term is a list of grades from 1-5 along with descriptions. Once the appropriate grade is identified, this information may be recorded on the AE form.

4.2.6 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 3500A** form. In addition, the clinical site must promptly report all SAEs to their **IRB via written/dated notification** in accordance to their specific IRB reporting requirements. **Copies of all such correspondence must be maintained in the site’s main study binder.** All SAEs must be followed with appropriate medical management until resolved.

Within one (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 Sanofi-Aventis and the FDA.

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

4.2.7 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**, (i.e., not consistent with the current Investigator Brochure and/or product labeling).

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

The DCC will disseminate these IND safety reports to the investigational sites and the Sponsor will notify Sanofi-Aventis.

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 CPCRN-2 Study Binder.

Procedure for Reporting Adverse Events

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

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:

Serious Adverse Event Reporting and **Routine Adverse Event Reporting**

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

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

- *death*
- *life-threatening*
- *results in or prolongs hospitalization*
- *results in persistent or significant disability or incapacity*
- *congenital anomaly/birth defect in the subject's offspring*

If “YES”

Serious Adverse Event Reporting

Clinical site:

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

Data Coordinating Center:

- Notifies NIH/NIDDK and DSMB within 24 hrs of knowledge of event
- Prepares IND safety report
- Distributes safety report to all clinical sites as soon as possible but no later than 15 days from initial discovery

If “NO”

Routine Adverse Event Reporting

Clinical site:

- Report to site investigator
- Record on case report form
- Notifies site IRB according to reporting requirements

Data Coordinating Center:

- Prepares cumulative reports
- Distributes @ quarterly Steering Committee
- Distributes quarterly to NIH/NIDDK, DSMB
- Prepares annual IND report
- Send a copy of the annual IND report to Sanofi-Aventis

NIH/NIDDK

- Notifies FDA
- Notifies Sanofi-Aventis corporate pharmacovigilance (CPV)
Fax Number: (33) 01 69 79 70 70
- IND safety report should be transmitted to FDA and Sanofi-Aventis at the same time.
- Keep Sanofi-Aventis CPV informed of any significant safety issues, events, or results, and DSMB recommendations in evaluating the expectedness according to the current Investigator's Brochure.

NIH/NIDDK

- Submits annual IND report to FDA

4.3 Unmasking

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

4.3.1 Unmasking for Serious Adverse Event (SAE)

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

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

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 *Clinic Regulatory Binder*.

4.3.2 Storage of Unmasking Envelopes

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

4.3.3 Return of Unmasking Envelopes

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

4.3.4 Unmasking in the absence of SAE

There may be rare occasions in which the Principal Investigator will request unmasking for a particular participant at their site, in the absence of a SAE. In this case, a written request would be made to the Protocol Chairs, **Drs. Anthony Schaeffer OR Richard Alexander**, who in collaboration with the CPCRN-2 Executive Committee will decide whether to authorize the request.

5 DATA AND ADMINISTRATIVE FORMS PROCEDURES

5.1 Personnel Identification (ID) Numbers

Each Clinical Center staff involved in data collection, entry, or review will be assigned a 4-digit ID number. This number is entered in the Master Heading, located in the top right-hand corner of each CRF page. Principal Investigators at each site are also assigned a 4-digit ID number.

5.2 Acquisition of Forms from the DCC

The CRFs are provided to the Clinical Centers in electronic format as Adobe .pdf (portable document format) files. The Clinical Center is responsible for printing all data and administrative forms. To streamline the printing process, the forms necessary for each visit are grouped together, and are presented in the order they should be completed. 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. Please refer to the Data Entry Form and Administrative Form version logs to ensure that you are using the correct form versions.

5.3 General Instructions for the Completion of CRFs

The following guidelines are applicable to all CRFs being completed for CPCRN-2 RCT#1 (Protocol – CP01):

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

- Data Forms contain participant data that are 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 are 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. Missing CRF's in a visit packet can be printed from the Adobe .pdf files prior to the visit. As CRF amendments occur, the DCC will notify the clinical centers and make updated versions 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), as specified on the CRF. 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 RCs 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.

5.3.1 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. Please refer to the Adverse Event/Serious Adverse Event section for guidelines.

5.3.2 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.

5.3.3 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.

5.3.4 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.

5.3.5 Header Information on CRF:

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

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

Clinical Center: As described in the previous chapter, a 2-digit number identifies each Clinical Center. The numbers range from 01 – 11, and 18

Visit Number: Visit numbers have been identified in the protocol when specific events happen during the course of the study. Visit numbers range from 01-04

CRF Date: This is the date of the clinic visit.

RC ID: The RC ID identifies the Clinical Center staff entering the CRF into the database.

5.4 Specific Instructions for Completing Data Entry CRFs

This section provides specific instructions on how to complete each Data Entry CRF. **Please note the forms are listed alphabetically by Form Name.** 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
NIH – Chronic Prostatitis Symptom Index	CPSI
Demographics	DEMO
Dispensing Log	DISP
Drug Compliance	DCOMP
Eligibility Checklist	ELIG
EPS and Urine Testing	EUT
Health Status Questionnaire® (SF – 12)	SF12
Hospital Anxiety and Depression Scale©	HADS
International Index of Erectile Function®	IIEF
Male Sexual Health Questionnaire	MSHQ
McGill Pain Questionnaire® (MPQ)	MCGILL
Medical History	MEDHX
Participant Expectations Questionnaire	EXP
Physical Exam	EXAM
Pre-Screening Summary	PRESCR
Randomization	RAND
Study Stop Point	SSTOP
Symptoms Assessment	SYM
Treatment Stop Point	TSTOP
Unmasking Record	UNMASK

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 from the Baseline 2 visit through the 12 Week visit (*even if no study drug has been taken*) **MUST** be recorded whether or not the participant thinks it is significant (SEE Appendix E; Adverse Event Script).

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 Adverse Events (CTCAE) (see Appendix E; Common Toxicity Criteria Adverse Events).

When: Visits #2, #3, and #4. The RC completes a form each time a participant experiences an AE/SAE, either reported during a Clinic Visit, or if the participant contacts the study personnel to report an AE/SAE, between Clinic Visits. A new form is used at each contact/visit. Multiple AE/SAEs can be documented on the same form during a single Clinic Visit. If notice of an adverse event occurs

between visits, please use the visit number of the upcoming visit. For example, if you become aware of an adverse event between visits 3 and 4, you would record the visit as visit #4. A script will be provided to ensure standardization in eliciting baseline AE reporting among all the sites (see Appendix E).

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 or a closure of an event previously recorded, with the same grade, duration and frequency, as when originally recorded. Each newly reported event is recorded with the next, new, sequential number.

Event (MedDRA) Code: This is a 8-digit number identified by referring to the coded list of Common Toxicity Criteria Adverse Events (CTCAE)

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

If the event is a condition that began prior to study entry (baseline AE), also mark (X) in the box.

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

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

Frequency: Using the code provided in the coding key on the second page, 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 coding key on the second page.

Action taken Regarding Study Drug: The PI will determine whether an interruption or discontinuation of the study drug is necessary, using the coding key on the second page.

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 *Chapter 4: Participant Safety section 4.2.1* 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 *Chapter 4: 4.2.8*) and is marked with an asterisk, the event is serious. SAEs require a PI signature and date.

Specify Event (CTCAE criteria): This information is linked to the *Event Code*. Record the *Event Name*, as specified in the CTCAE 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 “ ”. Treatments, if prescribed by the physician, should also be described in this space. Attempts should be made by the RC to include all pertinent information, for monitoring and reporting purposes at the DCC.

All AE's and SAE's are signed and dated by the **PI**. 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.

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 3-digit AE# as was used when the event was first recorded, as well as the same Event Code, grade, duration and frequency. Mark (X) in date of onset field and date of resolution field. The outcome should be coded as 2 – Ongoing. The description should indicate this is an ongoing report of a previously recorded AE/SAE, along with any other information the RC believes is critical.

When resolving a previously recorded event, use the same 3-digit AE# as was used when the event was first recorded, as well as the same Event Code, grade, duration and frequency. Mark

(X) in date of onset field. The outcome should be coded as 1 – Resolved. 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/duration/frequency the event should be treated as a new event, and the original event should be “closed out” as resolved.

Serious Adverse Events Notification Procedure

For all Serious Adverse Events, the RC will notify the Clinical Center PI who will assess and confirm adverse event seriousness according to Outcomes Categories 3 through 7.

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

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 3500A** form.

MedWatch 3500A Form

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

A **MedWatch 3500A** 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 3500A** form.

5.4.2 NIH-Chronic Prostatitis Symptom Index [CPSI]

Purpose: To collect information regarding the participant’s assessment of their chronic prostatitis symptoms. Four domains are evaluated: pain/discomfort, urination, impact of symptoms, and quality of life. This is the primary endpoint evaluation for this study.

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

When: Visits #1, #2, #3, and #4

General Directions

Participant completes questions #1 through #9. The RC calculates overall score by taking the sum of the participants' responses from questions #1-#9 and recording the score at the bottom of page 2.

5.4.3 Demographics [DEMO]

Purpose: To collect demographic data on a participant, as well as family history of PBS/IC and CP/CPPS.

Who: Participant completed

When: Visit #1

General Directions

Qx #7 Annual family income is to be recorded in US dollars:
\$1 US is equivalent to 1.3 Canadian dollar; \$1 US is equivalent to 3.8 Malaysian Ringgit. But note that exchange rates vary on a given day. Currency calculators such as the one found at <http://www.x-rates.com/calculator.html#> can be used. Please note that the DCC is not responsible for the accuracy and maintenance of this website.

Qx #11: A partner can be someone of the same sex.

5.4.4 Dispensing Log [DISP]

Purpose: To record study medications dispensed to a participant

Who: RC completed

When: Visits #2 and #3

General Directions

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

The labels from the bottle of study medication should be removed from the bottle and affixed to the appropriate place on the form. The RC dispensing the medication should sign the label.

The RC should instruct the participant that he should begin study medication the day it is provided to him so that the CRF date on this form corresponds to Date of First Dose.

5.4.5 Drug Compliance [DCOMP]

Purpose: To collect information regarding study drug compliance and to compute a percentage representing compliance.

Who: RC completed

When: Visits #3 and #4

General Directions

Qx #1 Indicate which treatment period the medication was distributed, either Visit # 2 or Visit # 3.

Qx #2 Ask the participant about lost or damaged study drug each time this form is reviewed. In box A, document the amount of the drug dispensed. In box B, document the amount returned; and, in box C, the amount 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 by adding the number of days since drug was dispensed. Calculate the amount for Box F (which establishes percent compliance) by dividing the amount in box D by the amount in Box E and multiplying that result by 100. Document the date (mm/dd/yyyy) you determined the compliance in Box G and your initials in Box H.

Qx #3 If participant compliance (in box F) is less than 80%, the RC will remind the participant of the importance of taking study drug as prescribed and document the reasons for non-compliance.

5.4.6 Eligibility Checklist [ELIG]

Purpose: To determine and ensure the participant's eligibility for entry into the study. 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: Visits #1 and #2, prior to randomization

General Directions

This CRF contains inclusion, exclusion and deferral criteria as described in the protocol.

If the participant meets all the inclusion, exclusion and deferral criteria, then the data are entered and verified in the Data Management System (DMS) to randomize the participant. All information should be verified by reviewing the participant's medical records, if possible.

If any Deferral criteria are answered "YES", please enter the form and re-screen the participant after the participant's condition has been resolved or the deferral time has elapsed. Please note that if the participant is eligible after the washout, a new ELIG form is completed and a new participant ID number assigned

Qx #1, #2, and #3 are only completed at Visit #1 only.

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 #7: The ability to answer this exclusion criterion will require the results from the VB2 urine culture performed at Visit #1, but recorded at Visit #2.

Qx #23: This question must be answered at both Visits 1 and 2. This question must have a "yes" response for a successful randomization.

5.4.7 EPS and Urine Testing [EUT]

Purpose: To collect VB2 urine culture data for use as eligibility requirement and EPS and VB3 white blood cell count

Who: RC completed, based on lab reports

When: Visit #1

General Directions

The participant should be reminded to remain abstinent for 48 hours prior to the culture test.

The RC will complete this form based on availability of the clinic's lab report. The midstream urine specimen, VB2, will be cultured for 48 hours. 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.

Qx 4 If 'No growth' is indicated, the culture data does not need to be completed. 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.
- *Actual count:* enter the exact count as it is listed on the lab report.

NOTE: For VB2, if there is any culture count $\geq 1,000$ CFU/mL, the participant is ineligible for trial enrollment. This count must be recorded on the Eligibility Checklist (Question #7) in order to complete the randomization process.

Qx 7a If reported cell counts are less than 25, indicate actual count.

Qx 9a If reported cell counts are less than 25, indicate actual count.

Qx #7 and #9: This is a quantitative measurement obtained from the clinic's lab report.

5.4.8 Health Status Questionnaire® [SF12]

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

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

When: Visits #2, #3, and #4

5.4.9 Hospital Anxiety and Depression Scale© [HADS]

Purpose: To collect information assessing the participant's anxiety and depression symptoms/status.

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

When: Visits #2, #3, and #4

NOTE: The participant may find some of these questions sensitive in nature. The RC may need to address participant concerns and provide participant encouragement in the full completion of these questions

5.4.10 The International Index of Erectile Functions® [IIEF]

Purpose: To collect information regarding the participant's changes in domains of male sexual function, as related to their CP/CPSS

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

When: Visits #2, #3, and #4

NOTE: The participant may find some of these questions sensitive in nature. The RC may need to address participant concerns and provide participant encouragement in the full completion of these questions.

5.4.11 The Male Sexual Health Questionnaire [MSHQ]

Purpose: To collect information regarding the participant's change in ejaculatory function and ejaculatory bother, as related to their CP/CPPS

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

When: Visits #2, #3, and #4

NOTE: The participant may find some of these questions sensitive in nature. The RC may need to address participant concerns and provide participant encouragement in the full completion of these questions.

5.4.12 The McGill Pain Questionnaire® (MPQ) [MCGILL]

Purpose: To collect information regarding the participant's assessment of change in quality of pain

Who: RC completed, while interviewing the participant

When: Visits #2, #3, and #4

5.4.13 Medical History [MEDHX]

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

General Directions

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

Qx#2: This refers to when the participant's symptoms *first appeared*. This scenario is not necessarily the same as when the participant's symptoms were *first diagnosed* by a physician.

Please skip over the questions which are indicated as for "women only".

5.4.14 Participant Expectations Questionnaire

Purpose: To gauge the participant's expectations at the beginning of the study in order to assess whether this parameter affects symptoms

Who: Participant completed, and placed in a sealed envelope

When: Visit #2

General Directions

This form will not be administered until the patient has been randomized and provided with study drug, to assure the patient that their responses do not influence whether they will receive active drug or placebo. The RC will NOT review this form with the patient; rather, the patient will place the form in an envelope and seal it. This form will be data-entered at the same time as all the other forms for this visit. It is recommended that this form be data-entered by a second RC, however this may not be feasible for all sites.

5.4.15 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. Prior to data entry, the RC should review this form for completeness.

When: Visit #1

General Directions

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

Qxs #10 through #13 are for "women only" and are not to be completed for this study.

5.4.16 Pre-Screening Summary [PRESCR]

Purpose: To collect information regarding the prescreening process, documenting important information about the number of participants who entered each phase of the RCT. This data will be used to develop the (Consolidated Standards of Reporting Trials) CONSORT statement to improve reporting by using a checklist and flow diagram.

Who: RC completed

When: Once a month (This form should be entered by the 5th of every month.)

General Directions:

This form only requires 1st entry.

Qx #1: The month recorded indicates the requirement efforts for that particular month.

Qx #2: This is a required field, which will be used to develop the CONSORT statement. “Data sources” is defined as chart reviews or database reviews.

Qx #5: This is a required field, which will be used to develop the CONSORT statement. “Contacted” is defined as either someone from the clinical center initiates the contact or the participant initiates the contact.

Qx #6: This is a required field, which will be used to develop the CONSORT statement.

Qx #7: This is a required field, which will be used to develop the CONSORT statement.

5.4.17 Randomization [RAND]

Purpose: To ensure that a potential participant is eligible for CPCRN-2 RCT#1 (Protocol – CP01) and to document the randomization process.

Who: RC completed

When: Visit #2

General Directions

Qx #1 and #2: The participant must meet all inclusion, exclusion, and deferral criteria at both Visit #1 and Visit #2.

Qx #3: Record the 5-digit Randomization number supplied by the database system during web-based randomization or in some instances, manually assigned with the assistance of the DCC.

5.4.18 Study Stop Point [SSTOP]

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

Who: RC and PI completed

When: Visit #4, or at time of early study withdrawal

General Directions

The Study Stop Point [SSTOP] form is completed at the time of withdrawal, if a participant opts to withdraw from the study early. Otherwise, the form is completed at the end of Visit #4, the last study contact. If the participant withdraws in between visits, please use the visit number of the upcoming visit. For example, if the participant notifies you that he no longer wants to participate between visits 2 and 3, please use Visit #3 when completing the SSTOP form.

NOTE: This is listed as a “single” form in the database and can be entered and verified at Visit #4 or as needed .

Qx #1: Indicate if the participant has successfully completed the trial. If the answer is ‘No’, the reason for not successfully completing the trial must be indicated. Only one most applicable and appropriate reason must be checked. Reasons include, but are not limited to:

- Poor compliance in taking study medication (< 80%)
- Participant dissatisfied with treatment
- Missed clinic visits
- Participant has personal constraints
- Adverse Event/Serious Adverse Event
- Physician’s discretion

Qx #4 through #6: These questions should be completed with the participant. The purpose of these questions is to assess the participant’s perception of study drug effectiveness and study drug medication.

Qx #7: This question is completed by the RC.

Qx #9 and #10: The PI and the RC *must* sign and date the Study Stop Point [**SSTOP**] form.

5.4.19 Symptoms Assessment [SYM]

Purpose: To collect information regarding the participant’s assessment of symptom changes, specifically pain, urgency and frequency

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

When: Visits #1, #2, #3, and #4.

General Directions

Qx #1-3: These questions are to be filled out at all four visits.

Qx #4: This Global Response Assessment (GRA) question is ONLY completed at Visits #3 and #4.

5.4.20 Treatment Stop Point [TSTOP]

Purpose: To record the date and the primary reason for a participant's termination from the treatment phase of the study 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. If the participant stops treatment in between visits, please use the visit number of the upcoming visit. For example, if the participant notifies you that he no longer wants to take the study medication between visits 3 and 4, please use Visit #4 when completing the TSTOP form.

NOTE: This is listed as a “single” form in the database and can be entered and verified at Visit #4 or as needed.

General Directions

Qx #3: Unacceptable medications include 1) drugs that cause vasodilation or hypotension (i.e. antihypertensives, nitrates), 2) other alpha blockers such as tamsulosin hydrochloride (Flomax®), terazosin HCL (Hytrin®), and doxazosin mseylate (Cardura®), 3) potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir), and 4) erythromycin.

Qx #4: 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 #5: 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.

5.4.21 Urine Screening [URINE]

Purpose: To record the results of *pre-randomization* urine dipstick and culture.

Who: RC completed.

When: This CRF is completed at Visit 1.

General Directions:

This CRF is completed when the pre-randomization urine dipstick and culture results are completed for all participants.

If results are outside the Clinical Center’s normal reference ranges, the PI will determine whether the abnormality presents a medical risk to the participant.

If a clinically significant abnormality is noted, the PI will determine whether the participant must undergo further evaluation prior to enrollment into the study.

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

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

Questions #3-#5 are not required for this protocol.

5.4.22 Unmasking Record [UNMASK]

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

Who: RC completed in collaboration with the PI.

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

Completing the Form

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

This is listed as a "single" form in the database and can be entered and verified, as needed.

Also see Chapter 4: **Unmasking**.

For unmasking in the absence of a SAE, requests will be reviewed by either Dr. Tony Schaeffer or Dr. Richard Alexander. Requests must be made in writing, with a copy faxed to the DCC.

5.5 Specific Instructions for Completing Administrative CRFs

This section provides specific instructions on how to complete each Administrative CRF. Please note the forms are listed alphabetically by Form Name. 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 – Administrative Forms (in alphabetical order by Form Name)	
Form Name	Form Code
Clinical Center Staff “Signature and Delegation of Responsibilities” Log	STAFFLOG
Clinic Correspondence Log	CCORRESP
Concomitant Medications	CMED
Participant Contact Information	PTCONT
Participant Correspondence Log	PCORRESP
Participant ID Assignment Log	PTLOG
Participant Transfer	TRANS
Progress Notes	PROGRESS
Visit #1 Checklist	VISIT1
Visit #2 Checklist	VISIT2
Visit #3 Checklist	VISIT3
Visit #4 Checklist	VISIT4

5.5.1 Clinical Center Staff “Signature and Delegation of Responsibilities” Log [STAFFLOG]

Binder: Clinic Regulatory Binder

All personnel working on the CPCRN-2 RCT#1 (Protocol – CP01) must sign the Clinical Center Staff “Signature and Delegation of Responsibilities” Log [STAFFLOG].

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 are added or removed.

5.5.2 Clinic Correspondence Log [CCORRESP]

Binder: Source Documentation 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.

5.5.3 Concomitant Medications [CMED]

Binder: Source Documentation Binder

Concomitant medications need to be documented at each clinic visit to record all medications/supplements/vitamins currently taken by the participant, while in the study. This form will not be entered into the database.

5.5.4 Participant Contact Information [PTCONT]

Binder: Source Documentation Binder

The Participant Contact Information [PTCONT] 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.

5.5.5 Participant Correspondence Log [PCORRESP]

Binder: Source Documentation 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.

5.5.6 Participant ID Assignment Log [PTLOG]

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

The Participant ID Assignment Log [PTLOG] 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.

5.5.7 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 CPCR-2 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

5.5.8 Progress Notes [PROGRESS]

Binder: Source Documentation Binder

The Progress Notes [PROGRESS] form should be used to track the participant's clinic visits, 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.

5.5.9 Visit #1 Checklist [VISIT1]

Binder: Case Report Form Binder

The Visit #1 Checklist [VISIT1] form lists all the forms and tests to be completed for Visit #1, the first baseline (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.

5.5.10 Visit #2 Checklist [VISIT2]

Binder: Case Report Form Binder

The Visit #2 Checklist [VISIT2] lists all the forms and tests to be completed for Visit #2, the second baseline (randomization) 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.

5.5.11 Visit #3 Checklist [VISIT3]

Binder: Case Report Form Binder

The Visit #3 Checklist [VISIT3] form lists all the forms and tests to be completed for Visit #3, the 6 Week 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.

5.5.12 Visit #4 Checklist [VISIT4]

Binder: Case Report Form Binder

The Visit #4 Checklist [VISIT4] form lists all the forms and tests to be completed for Visit #4, the 12 Week 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.

5.6 Directions for CRF Transfer

This trial represents the first clinical intervention trial to be conducted by the CPCRN-2. Reporting to the DCC is an important part of ensuring the proper conduct throughout the trial.

5.6.1 Database Audit by the DCC

While data entry and verification is being performed at the clinical center, the DCC will conduct a manual review of 100% of the case report forms against the database fields to determine the level of form completion, as well as the accuracy of the data entry and verification. This audit will be conducted for the first two (2) patients enrolled in the study. The DCC will notify the Research Coordinator of the participant selected for audit, who will then be responsible for copying and sending the necessary documentation to perform the database audit.

- a) The information assessed is the presence or absence of forms, missing fields in the database or case report forms, and discrepancies between fields in the database and fields on the case report forms;
- b) The Clinical sites are expected to respond with the materials requested within 2 weeks of the initial request. Sites that demonstrate < 98 % accuracy will be counseled by CDM, with appropriate follow-up.
- c) All CRFs sent to the DCC will have all participant identifiers obliterated other than Participant ID and Participant Initials.
- d) All copies of the CRFs must be sent via traceable carrier to the DCC at the following address:

Attn: Clinical Data Management
University of Pennsylvania
Clinical Research Computing Unit
3535 Market Street, 5th Floor, Suite 560
Philadelphia, PA 19104-3309

In addition, the DCC will conduct an audit on one randomly selected participant (selected by the Biostatistician at the DCC) every six months throughout the length of the trial. The requirement is that this participant has completed the primary endpoint visit (Visit #2).

The following will be sent to the DCC:

- All baseline and follow-up CRFs for the first two (2) participants
- All baseline and follow-up CRFs for the one randomly selected participant every six months

NOTE: Any CRFs 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.

5.7 Data Quality Management Procedures

5.7.1 Queries

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

Types of queries generated by the database

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

Missing Fields

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

Skip Patterns

Skip patterns account for fields that should or should not be answered, depending on the response to the first question in the series. For example, for Question 5 on the *EPS and Urine Testing (EUT)* CRF, if an EPS sample was not done, you are instructed to go to Question 8 and leave Questions 6 and 7 blank. If an EPS was collected, you would complete Questions 6 and 7.

Logic Checks

These checks review the data to ensure the data is logical, e.g., men should respond “NA” to female-oriented questions, and women should respond “NA” to male oriented questions.

5.7.2 Types of queries generated by manual monitoring

Monitoring Checks

These checks monitor the data for completeness and accuracy. Data Management staff at the DCC will manually view the data and queries will be sent for data that looks incomplete or appears to conflict with the design of the study. The Research Coordinators will manage these queries in a similar manner as outlined above for the database-generated queries. If changes are necessary, a response with the corrected data can be sent via email. Types of monitoring queries include:

- **Safety issues** – Adverse events related coding issues.
- **Study Procedures** – Withdrawal, Data Entry and Verification Status.

Managing Queries

Receiving Queries from CDM

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

- CC ID
- Participant ID
- Participant Initials
- Visit Number
- CRF Name
- CRF Date
- RC ID
- Date Queried
- Description of the Problem
- The e-mail subject line of each query identifying an electronically generated query (Query – CCID/Participant ID/Visit Number/CRF name) or a monitoring query (Monitoring Query – CCID/Participant ID/Visit Number/CRF name).
- The subject line indicating the query as a second or third attempt at seeking response from the site (Second Query – CCID/Participant ID/Visit Number/CRF name).

5.7.3 Making Corrections Based on Queries

- The RCs will print all queries e-mailed by the DCC.
- The RCs will be responsible for identifying the correction to be made or providing an explanation. DCC Data Management staff will be available to assist the RCs in resolution of the queries, if needed.
- If a query results in a correction, the correction must be included on the query and documented on the original CRF (initialed and dated).
- If it is determined that a correction is not needed, an explanation (e.g. test not done, participant's height is correct), should be documented on the query.
- All queries should be initialed, dated and filed with the participant's case report form binder.
- Any questions related to the queries should be directed to the originator of the query at the DCC.

5.7.4 Query Response to the DCC

- Queries can be returned to the DCC via email *or* fax. A copy of the response e-mailed or faxed to the DCC is retained in the participant's case report form binder.
- The response to the query should be directed to the originator of the query at the DCC.
- A dedicated fax line [(215) 573-4790] is available at the DCC to accept query responses and data sent from the sites.
- Responses to safety-related queries are expected at the DCC in 3 working days. Responses to all other queries are expected at the DCC in 10 working days.

6 CLINICAL CENTERS' AND DATA COORDINATING CENTER (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 for achieving 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.
- 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 administrative, biostatistical, and data management/computing leadership for design/conduct of the clinical trial.

Responsibilities include:

- Overall leadership regarding study design and conduct of the clinical trial.
- Preparation and distribution of the study protocol and Manual of Procedures (MOP) based on collaboration with the Steering and Planning Committee and NIDDK Project Scientists.
- Collaboration with other study investigators in the development, testing, and use of all CRF's and study procedures.
- Provision of an efficient data management system (**DMS**) to enter data directly into the central database at the DCC, and to implement double data entry with verification.
- Development and application of quality assurance procedures including data tracking and validation, query processes, and maintenance of related documentation.
- Development of tracking and storage procedures for laboratory samples.
- Training of clinical site staff and coordination of the site monitoring.
- Coordination of Steering and Planning Committee and External Advisory Committee meetings.
- Preparation of detailed reports regarding participant recruitment and retention, data collection activities, and interim results to the Data Safety Monitoring Board (DSMB).
- 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 this trial.

Internal Distribution of Study Documents

The DCC is responsible for maintaining a record of all documents, reports and meeting minutes pertaining to this trial. During the conduct of this protocol, the DCC will be responsible for the distribution of the Protocol, Manual of Operations and Procedures, and study reports to the CPCRN-2 randomization sites. At the end of the study, these documents will be archived by the DCC and forwarded to the National Technical Information Service (NTIS). Minutes of all appropriate committee meetings will be maintained in the files at the DCC. At the conclusion of the study, these minutes will be archived and forwarded to the NIDDK.

External Distribution of Study Documents

The NIDDK will be responsible for the distribution of study documents and manuscripts requested by individuals not associated with CPCRN-2 RCT #1.

Case Report Forms (Data Collection Forms)

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

Data Tapes and Analysis of Results

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

Record Retention

The DCC must maintain all trial records in accordance with their internal standard operating procedures. Clinical sites must maintain all study related materials in accordance to applicable FDA regulations and until receiving written notification from the DCC or Study Sponsor.

6.4 Clinical Site Monitoring

The CPCRN-2 is a cooperative agreement study in which all investigators and the NIDDK have a shared responsibility for the overall quantity and quality of the data collection.

It will be the responsibility of the DCC to monitor the quantity and quality of data being collected throughout the course of the study. However, at the present time, there are no plans for site monitoring.

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 CPCR2 – Protocol 1 Data Management System (DMS).

7.2 CPCR2 Main Menu

Purpose: To allow access to CPCR2 DMS system CC applications and CRFs for each protocol.

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

User Actions:

Open the “CPCR2 – 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 “CP01” Button to open the “CPCR2 Protocol 1 (CP01): Clinical Center Menu”. The database logon dialog box will open.

Log on the database

Enter Username (Assigned by DCC helpdesk support)

Enter Password (Assigned by DCC helpdesk support)

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

Enter Database (CP01)

Press “Connect” button

The **CPCR2—Protocol 1 (CP01)** Menu appears

Dialog box displays user name and role

Press OK button

7.3 CPCRN2—Protocol 1 (CP01) Clinical Center Menu

Purpose: To allow access to CC DMS applications. These applications allow entry and verification of participant contact data into the DMS, along with review of the entered data and registered participant status.

Users: Clinical center personnel:

- Data Management/Data Entry Personnel
- Research Coordinator

User Actions: Choose a menu option:

1. Register Participant

- a. Register a Participant into the DMS
- b. Requires:
 - Protocol Registration Information:
 - Participant Identifier (PID)
 - Participant Initials

The protocol registration information is used to identify the participant data. It is recorded in the participant record. The PID is chosen and assigned by the clinical center research coordinator. The first digit of the number is the protocol number. The last four digits is a sequence number maintained and assigned by the research coordinator for each clinical center. The PID is unique for a center, but is not unique for the study. It must be referenced along with the clinical center number to identify the participant study data. The participant initials are used primarily as a second check when clinic personnel access or enter participant data into the DMS.

- Study Identifier (SID) Information:
 - Last four digits of the participant social security number
 - Participant birth date
 - Participant gender

The study identifier information is used to generate a study identifier (SID) for use cross protocols. This information is not stored in the database. It is discarded, after the SID is generated and recorded in the participant record.

Eligibility and Randomization

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

CRF Entry

- a. Allows entry and verification of visit packet CRFs.
- b. Requires a complete visit packet of CRFs for a specific participant and visit.

- c. Allow entry and verification of Study 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. Visit Date is also required for SSTOP, TSTOP, and UNMASK entry.

Entry Status

- a. Allows viewing of the participant status and CRF entry status and data.
- b. Choose Participant to view participant status.
- c. Choose Form to view CRF entry status and data.
- 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.

Medication Reference

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

Reports Menu: Opens the Reports Menu Application

Cancel: Exits the CPCRN2 – Protocol 1 (CPCRN2 CP01) 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 a 5 digit number.
- b. The first digit is the protocol number. The last four digits will represent the sequence of participant enrollment at the clinical center.
- 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.

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.

Enter the last four digits of the participant social security number (SSN)

- a. Must be four numeric digits.
- b. Error message is given if less than 4 digits or if non-numeric characters are entered.

Enter the Participant Birth Date

Enter the Participant Gender

All entered items must be confirmed by re-entry:

- a. If a re-entered field differs from the first entry, an error message is given and you are returned to the first entry screen.
- b. Each field has the same constraints as indicated above.
- c. After all items are entered and verified, repeat the process to register another participant into the DMS or return to the Clinical Center Menu by selecting the Cancel button.

Warning message given for duplicate SID.

- a. The four digits from the SSN, birth date, and gender are used to generate the SID. If a duplicate SID is generated, the system warns the RC.
 - Duplicate SID for the clinical center: This will occur when a participant is registered more than once at the center. A deferred participant would receive a new protocol identifier when they get registered into the DMS the second time, but the SID generated should be the same. This is expected for a deferred participant completing a second registration. The warning provides the RC with the indication that this issue exists and that the RC should review and accept the second registration (if it is a known issue and the cause of the issue is acceptable) or decline the registration until the problem is resolved.
 - Duplicate SID for the study. A warning is given if a duplicate SID is discovered at another clinical center. This should only occur if the same participant registered at different centers. Generally this should not occur. The RC should inform the DCC CDM and project manager and determine the cause of the duplicate SID prior to registering this participant.

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 (**cannot** perform randomization)
- Research Coordinator

User Actions:

1. Enter participant ID

- a. Participant ID has the same requirements as in the Registration Application.
- b. The participant ID will be checked against the participant records to verify that the participant does exist.
- c. If the Participant ID is not registered for the Clinical Center in the DMS, an error message will be generated and the user will not be allowed to proceed unless the Participant ID is registered.

Enter participant initials

- a. The participant initials will be crosschecked with the participant initials for the corresponding participant ID in the registration table.
- b. If initials do not match, then an error message will be generated and user will not be able to proceed until the correct initials are entered.

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.

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.

All four fields are mandatory.

After entering the mandatory fields, choose:

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

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.
- 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], Medical History [MEDHX], and Unmasking [UNMASK] forms. Review the special requirements under navigation. Specifications for these fields are described in the Data Field Specifications. If the entry does not meet the required range or specifications, then an error message is given in the message area at the lower left-hand corner of the application window.
- i. During First Entry for case report forms with multiple pages, the option to either proceed and move forward to next page of the form or move back to the preceding page is available. 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 exiting the entry process at any time. The data entered on any unsaved forms will be lost.

Navigation:

- a. Mouse navigation is limited to use with the buttons and for revisiting lab or event records.
- b. Navigation buttons are provided for First Entry.
- c. Entry is expected to proceed field by field using the tab key or enter key after entering the appropriate field data.
- d. Check box entry can be set with the spacebar or with the mouse if the cursor is on the check box (NOTE: generally there is a blinking cursor, but on check box fields this is not visible, so a message is presented in the bottom left part of the window and the box is highlighted in red).

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.

Eligibility and Screening Requirements:

- a. All entries are required on the Eligibility [**ELIG**] form. At the end of the Eligibility form you must acknowledge the eligibility status of the participant. If your indication as to the eligibility of the participant does not match the inclusion, exclusion, and deferral entry indication, you will not be allowed to save the Eligibility form entry until the discrepancy in the two indications is resolved.
- b. If the participant is not eligible, then the entry will be saved for review, but further entry (Visit #2 following an ineligible indication for Visit #1) and randomization will not allowed.

Randomization: After choosing Randomization [**RAND**]

- a. Entry is restricted to only allow data that leads to an eligible participant to be entered.
- b. The randomization number will be issued by the application in the controlled process described below:
 - 1) Instead of providing an entry field for the randomization number, a button (labeled “Randomize Participant”) is provided that causes the application to proceed to the randomization process.
 - 2) After the Randomization [**RAND**] form information has been entered, press the “Randomize Participant” button.
 - 3) The application enters the Participant ID, Participant Initials and the Randomization [**RAND**] form data into the DMS.
 - 4) The application issues the Randomization Number and records this event with the DMS.
 - 5) The user is requested to record the Randomization Number on the Randomization [**RAND**] form and confirm this by pressing the Continue button.
 - 6) The application requests that the user re-enter the number for verification purposes.
 - 7) If the number is **not** entered correctly, the application displays the correct Randomization Number and request that it be recorded on the Randomization [**RAND**] form.
 - 8) The verification process is repeated until the user enters the correct Randomization Number.
 - 9) After the Randomization Number has been properly verified, the application records the verification with the DMS and requests that the Continue button be pressed to complete the Randomization process.

7.6 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:

Enter the participant ID

- a. Participant ID has the same requirements as in the Registration Application.
- b. The participant ID will be checked against the registration table to verify that the participant does exist.
- c. If the Participant ID is not registered for the Clinical Center in the DMS, an error message will be generated and the user will not be allowed to proceed unless the Participant ID is registered.

Enter participant initials

- a. The participant initials will be crosschecked with the participant initials for the corresponding participant ID in the registration table.
- b. If initials do not match, then an error message will be generated and user will not be able to proceed until the correct initials are entered.

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.

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.

All four fields are mandatory. Visit Date is also required for SSTOP, TSTOP, and UNMASK.

After entering the mandatory fields, choose:

- a. CRF Type:
 - 1) All visit forms: To enter a visit packet of CRFs.
 - 2) Study Stop Point [**SSTOP**], Treatment Stop Point [**TSTOP**], or Unmasking Record [**UNMASK**] to enter one of the PRN 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 (not allowed for screening and eligibility).
- d. Cancel to exit the CRF Entry Application.

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 (CRFs).
- 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 a 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.
- f. For visit packet forms 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. For PRN forms the visit date is automatically filled in (the visit date is entered prior to opening the PRN form).

Enter the Research Coordinator ID in the upper right hand corner.

- a. Enter all data on the forms into the appropriate fields.
- b. The data fields fall into the following categories: alphabetic letter, alphanumeric, categorical, date, numeric, time, and free text. Specifications for these fields are described in the Data Field Specifications section.
- c. For case report forms with multiple pages, the option to either proceed and move forward to next page of the form or move backwards to the preceding page is available (for First Entry not for Verification).
- d. Upon completing data entry for each case report form a Commit button will allow the entries for that form to be saved and move onto the next form.
- e. The data cannot be changed after it has been saved.
- f. After the last form has been entered, the entry process can be repeated for the next participant.

You will have the option of exiting the entry process at any time. The data entered on any unsaved forms will be lost.

Special Requirements for Adverse Events/Serious Adverse Events [AE] and EPS and Urine Testing [EUT].

- 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 event or 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.

Navigation:

- a. Mouse navigation is limited to use with the buttons and for revisiting fields in Adverse Events/Serious Adverse Events [AE] and EPS and Urine Testing [EUT].
- b. Navigation buttons are provided for First Entry.
- c. Entry is expected to proceed field by field using the tab key or enter key after entering the appropriate field data.
- d. Check box entry can be set with the spacebar or with the mouse if the cursor is on the check box (NOTE: generally there is a blinking cursor, but on check box field this is not visible, so a message is presented in the bottom left part of the window and the box is highlighted in red).

Verification:

- a. All fields must be entered. Navigation (both key board and mouse) is limited.
- b. The data entered for each form field are compared to the data from the first entry.
- c. If it is different, a message is given (indicating first entry value, verification entry value, and other, you must choose which entry is correct). If other is chosen, you must enter the new value.
- d. You are not allowed to proceed to the next field without choosing the correct value.
- e. Revisiting entered fields is generally not allowed. The mouse can be used to revisit the record fields in EPS and Urine Testing [**EUT**] and Adverse Events and Serious Adverse Events [**AE**]; but the number of records cannot be changed.
- f. If it is required that a verified field be revisited, generally it will be necessary to exit the verification application and restart verification.

7.7 CRFs and References

Purpose:

- Provides access to CRFs
- Provides access to study documents.
- Provides access to CTCAE codes.

Users: ***Clinical center personnel***

- Research Coordinator

User Actions:

1. Choose “CRFs and References”:
 - A portal will list the study documents, CRFs, and CTCAE code lists.
 - The portal content is managed by DCC CDM.
 - The portal is designed specifically to allow rapid deployment of documents to the research coordinators at the clinical centers.
 - The documents will generally be in the form of files that can be saved to local workstations at the clinical centers. Some documents may be in PDF format and will be directly accessible using Adobe Acrobat.

7.8 Pre-screening Summary

Purpose:

- Allow entry of the monthly Pre-screening Summary [**PRESCR**] form.
- Allow review of the monthly Pre-screening Summary form.

Users:

- Clinical center personnel

- Research Coordinator

User Actions:

1. To Enter a Pre-screening Summary [**PRESCR**] form:

Enter Clinical Center (CC) 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 the assigned to the center, an error message is given.

Enter CRF Date

- a. This is the date on the PRESCR form.
- b. If the date is invalid, an error message will be given.
- c. The date must be after the study start date and prior to the date of entry. If not, an error message is given.

Enter Month

- a. This is a two digit number that indicates a previous month that occurs after study start. The Pre-screening Summary cannot be entered for the current month.
- b. If the month indicated is not a previous month that occurs after study start, an error message is given.

Enter Year

- a. This is a four digit number that indicates the year of the Pre-screening entry. It must be a year that occurs on or after study start and on or before the current year.
- b. If the year is outside the range indicated above, an error message is given.

Enter Research Coordinator Identifier (RC ID)

- a. This number must be the number assigned to a research coordinator at the clinical center.
- b. If the RC ID is not assigned to the clinical center, an error message is given.

All five fields (Clinical Center Number, CRF Date, Month, Year, and RC ID) are mandatory.

After entering the mandatory fields, choose:

- a. Proceed to enter the Pre-screening Summary [**PRESCR**] form, or
- b. Cancel to exit Pre-screening Summary.

2. Complete form entry and choose save. You are returned to the opening screen.

To Review a Pre-screening Summary [**PRESCR**] form:

1. Choose Review Entered Forms.
2. Choose the desired form from the list.
3. Press Exit when finished.

7.9 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. Participant Status: A list of registered participants is presented indicating the:
 - a. *Participant ID:* The participant identifier,
 - b. *Participant Initials:* The participant's initials,
 - c. *Date Registered:* The date the participant was registered into the DMS,
 - d. *Registered By:* The user name/ID of the DMS user that registered the participant into the DMS,
 - e. *Randomization Number:* The 5 digit randomization number assigned to the participant upon successfully randomizing the participant.
 - f. *Date Randomized:* The date that the randomization was completed,
 - g. *Randomized By:* The user name/ID of the person performing randomization,
 - h. *Date Issued:* The date that the randomization number was issued to the person performing randomization for the participant (should be the same as Date Randomized),
 - i. *Issued To:* The user name/ID of the person performing the randomization (should be the same as Randomized By),
 - j. *Date Verified:* The date that the randomization number was verified (should be the same as the Date Randomized)
 - k. *Verified By:* The user name/ID of the person verifying the randomization number (should be the same as Randomized By).
 - l. *Date Ineligible:* The date that Screening and Eligibility CRF data indicated that the participant was marked as an ineligible participant.
3. Form Status:
 - a. Form Entry Status is presented indicating:
 - Participant ID,
 - Visit Number,
 - Form,
 - Missing Status,
 - Visit Date,
 - Date Logged (into DMS),
 - Logged By (generally the first entry person),
 - Date Entered,
 - Entered By,
 - Date Verified, and

- Verified By.
- b. Entered data can be viewed by double clicking a form that has been entered.

7.10 Medication Reference

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

Users: Clinical Center Personnel

- Data Management/Data Entry Personnel
- Research Coordinator

User Actions:

1. The Medication Reference appears with the following options:
 - Brand Name
 - Generic Name
 - Drug Code
2. Enter Query Criteria:
 - Select Brand Name, Generic Name, or Drug Code then enter the drug name or code in the appropriate box.
 - If you are unsure of the spelling, just enter the first few letters.
3. Change Sort Criteria, if necessary. By default, the list is sorted by Generic Name.
4. After entering the drug name, press enter (or select the “Execute Query” button with the mouse), the list of matching medication names along with the medication code and the cross-reference medication name appears in the “Drug Names and Codes” block.
5. You can then review the list and choose the appropriate medication code.
6. Choose Cancel when finished, in order to return to the Clinical Center Menu.

7.11 Reports

Purpose: To allow the generation of monitoring reports.

Users: Clinical Center Personnel:

- Data Management/Data Entry Personnel
- Research Coordinator

User Actions:

1. The Report Menu appears with the following options:
 - a. Follow-up Schedule
 - b. Clinical Center Schedule
 - c. Outstanding Contacts
 - d. Incomplete Entry
 - e. Incomplete Verification
 - f. Cancel
2. Choose the desired report or choose Cancel to exit the application and return to the Clinical Center Menu.

7.12 Data Field Specifications

Alphabetic Letter Fields

The participant initials are the only alphabetic letter field in the Case Report Forms. Participant initials must be 2 to 3 uppercase letters. Errors will occur if you try to enter fewer than 2 or more than 3 letters, or any characters that is not a letter.

Alpha-numeric Fields

There are no alphanumeric fields.

Categorical Fields

A categorical field is a set of numeric choices as indicated in the Case Report Forms. The user must enter a number, and it must be contained within the range specified on the annotated case report forms. If user enters an out of range number, then the DMS will provide a status message as the lower left of the application window.

Check Box

Check boxes are used on the Adverse Events/Serious Adverse Events [**AE**], Concomitant Medications [**CMED**], and Unmasking [**UNMASK**] forms. A checked value will be recorded as a "1" in the DMS. An unchecked value will be recorded as a NULL with the DMS. The check boxes may be checked using the keyboard space bar or (if the cursor is on the check box) the mouse. When the cursor is on the check box, it may not be readily apparent, so a message will be displayed in the lower left of the application window and the check box will be highlighted in red.

Date Fields

The format for date fields: MM/DD/YYYY. The year always requires four digits. A slash (/) is not needed to separate the number, day, or year; however, a slash is allowed in entry when the date field is recorded.

Numeric Field

Numeric fields must contain numbers only, and an error should prevent the user from entering any value other than a number. The size of the field should correspond to the size indicated on the case report form. Floating-point numbers are formatted with decimal points and the required level of precision.

Time Field

The user may enter 3 or 4 digits for the time field. The hour may be represented by one or two-digits, and the minutes must be represented by two-digits. The colon “:” between the hour and the minutes does not have to be entered. All time fields are in the 24 hours format (00:00-23:59).

Free Text Fields

The **only free text field** that will be entered is the “Description of Event / Comments” on the Adverse Events/Serious Adverse Events [AE] form. During verification this text will be presented for review and edited, but **will not be verified** by the DMS verification process used to verify all other entry. Since there is no automatic verification process, use caution during the edit and review process to ensure that the text is not deleted or altered by mistake. The editor application (opened by selecting an edit button) allows a full view of the text and allows the edit process to be exited without saving changes.

DMS Entered Descriptive Fields: Adverse Events/Serious Adverse Events [AE] (AE Specify Event (CTCAE Criteria)) & Concomitant Medications [CMED] (CMED Drug Name)

These fields will not be entered. The DMS will provide the field value (for user review) based on the Adverse Events/Serious Adverse Events [AE] event code (for *Specify Event (CTCAE Criteria)*) or Concomitant Medications [CMED] drug code (for Drug Name).

7.13 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

Location: Messages pop up in dialog boxes.

1. 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.

2. 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.

7.14 CRCU Software Systems Help Desk

7.14.1 Sponsored Project Help Desk (SPHD)

The SPHD provides technical support to all study personnel using Data Management System (DMS) software developed and distributed by the [Application name, DMS, Web Portal, Hardware] SPHD. 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 software.

Technical Support

The Help Desk will provide technical support related to problems and issues that may arise when working with the application provided by the CRCU.

The Help Desk will not be responsible for providing technical support for hardware and/or software that was not provided by the CRCU (e.g. word processors, spreadsheets, modems, printers, and hardware) and has direct local institutional support.

7.14.2 Assignment of DMS Accounts

A DMS account consists of a username and password that uniquely identifies a user. DMS accounts are required for a user to gain access to the data entry area, and are the primary means for ensuring data security and confidentiality. Therefore, it is critically important that all DMS accounts are kept secure and confidential and are not shared with anyone.

NOTE: The username and password used to individually access your project Web site (<http://www.projectname.org/>) is **not** your DMS username and password. Access to the project Web site infers no access to the project DMS. You may reach the project DMS through a link from within the project Web site but will then be prompted for a specific DMS account username and password.

In addition to providing data security and confidentiality, DMS accounts provide a means to trace all database activities to individual user accounts.

To obtain DMS accounts, a Clinical Center or Site 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 Sponsored Project Help Desk of the new user request.

*****Important*****

When a DMS account has been created, the Sponsored Project Help Desk will contact the user with his/her account information.

When personnel leave the project, a representative from the Clinical Center or Site should contact the DCC Project Manager immediately. The Sponsored Project Help Desk will then take the necessary actions to deactivate that user's database account.

7.14.3 Procedures for Obtaining Help Desk Support

Study personnel can contact the Sponsored Project Help Desk by e-mail or telephone.

E-mail Support

- The Sponsored Project Help Desk can be e-mailed at: sshelpdesk@cceb.upenn.edu

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

- **Name (User Name)**
- **Study Name – (Project Name)**
- **Clinical Center Name / Location**
- **Phone number**
- **Detail description of the problem and level of urgency (low, medium, high)**

Telephone Support

- The Sponsored Project Help Desk can be contacted at **(215) 573-4623**.

When contacting the Help Desk, the caller **must** provide the following information:

- **Name (User Name)**
- **Study Name – (Project Name)**
- **Clinical Center or Site Name/Location**

If the Sponsored Project 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 (User Name)**
- **Study Name – (Project Name)**
- **Clinical Center Name / Location**
- **Phone number (where the user can be reached)**
- **Detail description of the problem and level of urgency (low, medium, high)**

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 when there is a new voicemail message. Whenever possible, the Sponsored Project Help Desk will attempt to resolve the issue during the initial call. Occasionally, a problem may occur that requires additional interaction between the caller, the Help Desk and the CRCU personnel. Client patience and cooperation is always appreciated during such periods. Our goal is to restore normal operations as quickly as possible.

Help Desk Availability

The Sponsored Project Help Desk is available during normal business hours (0800 – 1700 U.S. Eastern Standard Time).

8 REFERENCES

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3. Alexander, R. B., Propert, K. J., Schaeffer, A. J., Landis, J. R., Nickel, J. C., O'Leary, M. P., Pontari, M. A., McNaughton-Collins, M., Shoskes, D. A., Comiter, C. V., Datta, N. S., Fowler, J. E., Jr., Nadler, R. B., Zeitlin, S. I., Knauss, J. S, Kusek, J. W., Nyberg, L. M., Litwin, M. S., and The Chronic Prostatitis Collaborative Research Network (CPCRN). A randomized trial of ciprofloxacin and tamsulosin in men with chronic prostatitis/chronic pelvic pain syndrome. 200. Ref Type: Unpublished Work
4. Anonymous: Clinical Investigator's Brochure: Alvuzosin Hydrochloride Xatral - Alfuzosin hydrochloride. 91385 CHILLY-MAZARIN Cedex, France: Sanofi-Snythelabo Recherche, 2004
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ACRONYMS/ABBREVIATIONS

ACRONYMS / ABBREVIATIONS	
AE	Adverse Event
AE	Adverse Events/Serious Adverse Events Form
AE#	Adverse Event Number
AEs	Adverse events
AE/SAE	Adverse Event/Serious Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
AUR	Acute Urinary Retention
BPH	Benign Prostatic Hyperplasia
CC	Clinical Center
CCs	Clinical Centers
CC DMS	Clinical Center Data Management System
CCID	Clinic Center Identification Number
CCORRESP	Clinic Correspondence Log
CDM	Clinical Data Management
CFU/ml	Colony Forming Unit/milliliter
CMED	Concomitant Medications
CONSORT	Consolidated Standards of Reporting Trials
CP	Chronic Prostatitis
CP01	Chronic Prostatitis RCT #1
CPC	Chronic Prostatitis Cohort
CPCRN	Chronic Prostatitis Collaborative Research Network
CPCRN-2	the Second Chronic Prostatitis Collaborative Research Network
CPCRN-2 RCT #1	the first Randomized Control Trial for the Second Chronic Prostatitis Collaborative Research Network
CPPS	Chronic Pelvic Pain Syndrome
CPSI	NIH-Chronic Prostatitis Symptom Index Form
CRCs	Clinical Research Centers
CRCU	Clinical Research Computing Unit
CRF	Case Report Form
CRFs	Case Report Forms
CSTEP	Cancer Therapy Evaluation Program
CTCAE	Common Toxicity Criteria Adverse Event
CV	Curriculum Vitae
DCC	Data Coordinating Center
DCC CDM	Data Coordinating Center Clinical Data Management
DCOMP	Drug Compliance Form
DEMO	Demographics Form
DISP	Dispensing Log Form
DMS	Data Management System
DSMB	Data and Safety Monitoring Board
ELIG	Eligibility Checklist Form

ACRONYMS / ABBREVIATIONS	
EPS	Expressed Prostatic Secretions
EUT	EPS and Urine Testing Form
EXAM	Physical Exam Form
FEDEX	Federal Express
FDA	Food and Drug Administration
GRA	Global Response Assessment
HADS	Hospital Anxiety and Depression Scale
HIPPA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immuno-deficiency Virus
IC	Interstitial Cystitis
IDS	Investigational Drug Service
IEF	International Index of Erectile Function
IND	Investigational New Drug
IRB	Internal Review Board
MCGILL	McGill Pain Questionnaire Form
MedDRA	Medical Dictionary for Regulatory Activities
MEDHX	Medical History Form
MOP	Manual of Procedures
MOS	Medical Outcomes Study
MPQ	McGill Pain Questionnaire
MSHQ	Male Sexual Health Questionnaire
NA	Not Applicable
NCI	National Cancer Institute
NIDDK	National Institute of Diabetes Digestive and Kidney
NIH	National Institute of Health
NIH-CPSI	NIH-Chronic Prostatitis Symptom Index
NTIS	National Technical Information Service
NULL	No Value
PBS	Painful Bladder Syndrome
PCORRESP	Participant Correspondence Log
PENN's IDS	University of Pennsylvania Investigational Drug Service
PI	Principal Investigator
PID	Participant Identifier
PRESCR	Pre-Screening Log
PRN	As Needed
PROGRESS	Progress Notes
PTCONT	Patient Contact Information
PTLOG	Participant ID Assignment Log
Qx	Question
Qxs	Questions
RAND	Randomization Form
RC	Research Coordinator
RCs	Research Coordinators
RCID	Research Coordinator Identification Number

ACRONYMS / ABBREVIATIONS	
RCT	Randomized Clinical Trial
RCT #1	Randomized Clinical Trial #1
SAE	Serious Adverse Event
SAEs	Serious Adverse Events
SID	Study Identifier
SF-12	SF-12 Form
SPHD	Sponsored Project Help Desk
SSTOP	Study Stop Form
STAFFLOG	Signature and Delegation of Responsibilities Log
STDs	Sexually Transmitted Diseases
SYM	Symptom Assessment 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
URINE	Urine Screening Form
UNK	Unknown
UNMASK	Unmasking Record Form
UPenn	University of Pennsylvania
Penn IDS	University of Pennsylvania Investigational Drug Service
VB-2	Voided Bladder Urine-2
VB-3	Voided Bladder Urine-3
VISIT1	Visit 1 Checklist
VISIT2	Visit 2 Checklist
VISIT3	Visit 3 Checklist
VISIT4	Visit 4 Checklist

MANUAL OF PROCEDURE

AGREEMENT PAGE

CPCRN-2 RCT #1

CPCRN-2 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 MANY FACES OF
CHRONIC PROSTATITIS**

The following centers are participating
in this important research:

Cleveland Clinic
Texas Tech

Harvard Medical School
Massachusetts General Hospital
Brigham and Women's Hospital
Brown, Massachusetts

Netherlands University Hospital Groningen
of Medicine, Groningen, The Netherlands

Queen's University
Kingston, Ontario, Canada

Stanford University Medical Center
Stanford, California

Temple University
Philadelphia, Pennsylvania


University of California at
Los Angeles, Los Angeles, CA

University of Maryland
Baltimore, Maryland

University of Mississippi
Jackson, Mississippi

University of Washington
Seattle, Washington

University of Washington School of
Medicine, Seattle, WA
University of Wisconsin
Madison, Wisconsin



Chronic Prostatitis is a common
condition that affects men of all
ages and ethnic groups.

We are interested in identifying
treatments for this condition.

**Will you help us make
this happen?**

Learn more about
this study's purpose by
visiting www.chronicprostatitis.org
or by visiting us on Facebook.

PLACE RETURN LABEL HERE

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Stanford University Medical Center
Stanford, California

Temple University
Philadelphia, Pennsylvania


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Los Angeles, Los Angeles, CA

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Baltimore, Maryland

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Stanford University Medical Center
Stanford, California

Temple University
Philadelphia, Pennsylvania


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Los Angeles, Los Angeles, CA

University of Maryland
Baltimore, Maryland

University of Mississippi
Jackson, Mississippi

University of Washington
Seattle, Washington

University of Washington School of
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Kingston, Ontario, Canada

Stanford University Medical Center
Stanford, California

Temple University
Philadelphia, Pennsylvania


University of California at
Los Angeles, Los Angeles, CA

University of Maryland
Baltimore, Maryland

University of Mississippi
Jackson, Mississippi

University of Washington
Seattle, Washington

University of Washington School of
Medicine, Seattle, WA
University of Wisconsin
Madison, Wisconsin



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PLACE RETURN LABEL HERE

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*

PROPOSED PARTICIPANT INFORMED CONSENT FORM

Chronic Prostatitis Clinical Research Network-2 (CPCR-2) RCT#1 PROTOCOL

A Randomized Multicenter Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of 10mg Alfuzosin in the Treatment of Chronic Prostatitis / Chronic Pelvic Pain Syndrome (CP/CPPS) in Recently-Diagnosed and/or Newly-Symptomatic Alpha-blocker Naïve Patients

You are being asked to participate in a research study because you have been newly diagnosed with Chronic Prostatitis and have been informed that you may be eligible for the investigational study known as: “A Randomized Multicenter Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of 10mg Alfuzosin in the Treatment of Chronic Prostatitis / Chronic Pelvic Pain Syndrome (CP/CPPS) in Recently-Diagnosed and/or Newly-Symptomatic Alpha-blocker Naïve Patients.” Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in the study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. If you decide to participate in the study, you will be asked to sign and date this form.

The CPCR-2 has been established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) to identify and study treatments for people with symptoms of CP/CPPS. It is hoped that such a research study will eventually lead to improvement in the treatment of CP/CPPS. This research study is being conducted at a number of medical centers including: Cleveland Clinic Florida; Harvard Medical School- Massachusetts General Hospital & Brigham & Women’s Hospital; Northwestern University Feinberg School of Medicine; Queen’s University; Stanford University Medical Center; Temple University; David Geffen School of Medicine at UCLA; University of Maryland; University of Mississippi Medical Center; University of Washington; and University of Washington- Harborview Medical Center/University of Sciences Malaysia.

What is the purpose of the study?

The purpose of this study is to investigate the efficacy and safety/tolerability of alfuzosin (trade name: Uroxatral®), a prescription medicine that is called an “alpha blocker”. Uroxatral® has been

approved by the United States Food and Drug Administration (FDA) to relieve the signs and symptoms of benign prostatic hyperplasia (BPH) or non-cancerous enlargement of the prostate. Uroxatral[®] works by relaxing the muscle surrounding the prostate, bladder neck, and prostatic urethra. Uroxatral[®] (and other similar alpha blocker drugs) have been used to treat CP/CPSP. This study will attempt to determine if Uroxatral[®] is effective in providing relief for CP/CPSP.

Who is being invited to participate in this study?

You will be invited to participate in this study if you are male, ≥ 18 years of age, have experienced symptoms of discomfort or pain in the pelvic region for at least a six (6) week interval, and have had symptoms bothersome enough in the past two years to prompt a doctor's visit. Approximately 270 participants with newly clinically diagnosed CP/CPSP 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. As part of the study you will be asked to complete the following:

Participate in Screening Visit 1

The Screening Visit will be an in-person visit where we will get your informed consent and provide you with more information about the study. You will be required to complete a medical history and a physical examination. The physical examination will include an abdominal examination, external genital exam, rectal exam, prostate exam, and perineal exam (area around the scrotum and anus). Urinalysis and a urine culture (examining a urine sample to detect the presence of blood, infection and other processes and doing a white blood cell count), as well as EPS (expressed prostatic secretion) specimen testing, which involves a rectal exam, will also be conducted. You will also be asked to complete questionnaires to assess your pain/discomfort, urinary symptoms and a Quality of Life (QOL) index.

Participate in Baseline Visit 2

If you qualify for the study and are interested in participating after the Screening Visit, you will be scheduled for the Baseline Visit. The completion of this visit defines enrollment in the study. During this visit, the research coordinator will review and confirm whether you are still eligible for the study. As in the Screening Visit 1, you will be asked to complete questionnaires to assess your pain/discomfort, urinary symptoms and a Quality of Life (QOL) index. Additional questionnaires about your depression/anxiety status and sexual function will also be administered at this time. All of these questionnaires will need to be completed at each subsequent Follow-up visit. You will then be randomly assigned to one of two treatment groups, half treated with medication and half treated with placebo. The medication you will receive 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. However, information regarding which treatment you are receiving will be made available to your physician in case of an emergency. The medication for weeks 1-6 will be given to you at this visit. One group will receive oral placebo (like a sugar pill); the other group will receive oral Uroxatral[®].

Take the study medication

You need to take one tablet from the bottle of study medication once a day. The research staff will provide you with specific instructions on how to take the study medication. You will take study medications daily for twelve (12) weeks. Medication for weeks 1-6 will be provided at the Baseline Visit 2. Medication for weeks 7-12 will be provided at the six-week follow-up visit.

Participate in Two Follow-up Clinic Visits

You will be required to participate in two (2) follow-up clinic visits at six (6) and (12) weeks after medication start. As described previously, you will be asked to fill out a number of questionnaires.

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 Uroxatral[®] to improve the symptoms of CP/CPPS. Even though you may receive Uroxatral[®] 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, we cannot say for certain that your participation will be of certain benefit.

What are the risks of participating in the study?

The side effects may include a lowering of blood pressure, dizziness, lightheadedness, syncope (fainting), postural hypotension (decrease in blood pressure when you sit or stand), fatigue, abdominal pain, dyspepsia (heartburn), constipation, nausea, bronchitis (bronchial tube inflammation), sinusitis (nasal infection), pharyngitis (infection or irritation of the pharynx and/or tonsils), and impotence.

The following adverse events have also been reported in post-marketing experience: skin rashes, pruritis, tachycardia (fast heart rate), chest pain, priapism (prolonged and painful erection of the penis).

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 CP/CPPS.

Voluntary Participation and Withdrawal/Early Trial Termination: 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. This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the FDA without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study Principal Investigator, or the FDA has decided to stop the study.

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 will be given a unique participant identification number. This number will be used to record your study information. You will never be tracked through the study by name, medical record number or any other personal identifier. A log of the participant names, participant ID numbers, and personal information (such as home address, telephone number, and emergency contact information) will be maintained in a locked area at the clinical site.

The University of Pennsylvania serves as the Data Coordinating Center (DCC) for this research study which means that the study information from all research centers, after being stripped of your identifying information, will be stored in secure electronic files at the University of Pennsylvania. All study data will be sent to the DCC by secured internet connection. Only authorized members of the research study will have permission to see this data. You further understand that authorized representatives of the Sponsor, the NIDDK, the NIH, (*insert your institution's name*), as well as the 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.

To help us protect your privacy, a Certificate of Confidentiality from the National Institutes of Health will be obtained. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. No voluntary disclosure of information that would identify you as a participant in this research study will be made, without your written consent.

Collection of Specimens: Your urine and EPS specimen samples will be collected for culture and analysis, as mentioned in the Screening Visit 1 section of this informed consent. These samples will be stripped of your name and any other identifying information. They will be connected to your study results only by your unique participant identification number. These specimens will not be stored.

Financial Costs and Compensation: You will not have to pay to be in this study. All procedures and tests will be covered by the study. You will receive no money for enrolling in this study. Uroxatral[®], the study medication, will be provided free of charge during your participation. [*This section should be customized per site. Parking/transportation reimbursement, if provided, should be itemized.*]

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]*. If you have an illness or injury during this research study that is not directly related to your participation in this study, you and/or your insurance provider or group will be responsible for the cost of the medical care of that illness or injury. *[Clinical sites should customize this section in accordance to their own institution's policies.]*

New Information: During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

Contact Persons for Study: If at any time you have questions, concerns, or comments about this study or a research-related injury, you should contact *[Insert Principal Investigator's name]* at *[Insert telephone number]*.

Institutional Review Boards/Subject Rights: The University of Pennsylvania *[Change to 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 would like more information or have questions about your rights as a research subject, you can contact the Office of Regulatory Affairs at the University of Pennsylvania by phoning (215) 898-2614. *[Change this to appropriate information for your clinical site's IRB]*

PARTICIPANT’S STATEMENT:

I have read the above information about the Uroxtral® Study. I have been given an opportunity to ask questions about it and to discuss it with [Insert Principal 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.

SIGNATURES

I have read and received a copy of this consent form. I understand that my signature below means that I voluntarily agree to participate in this study.

_____	_____	_____
Printed Name	Signature of Participant	Date

Complete ONLY if patient is unable to sign:

_____	_____	_____
Printed Name	Signature of Legally Authorized Representative (Note relationship with participant)	Date

Completed ONLY if patient or their legal representative is unable to read this consent form and an impartial witness is present for the entire discussion:

_____	_____	_____
Printed Name	Signature of Witness	Date

I certify that I have discussed the study purpose, potential benefits, and risks with the below named participant and/or his/her authorized representative, using language that is understandable and appropriate. 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.

_____	_____	_____
Printed Name	Signature of Person Obtaining Consent	Date

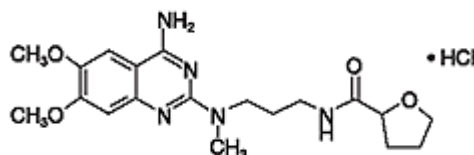
APPENDIX C: DRUG PRODUCT INSERT

UROXATRAL[®] Prescribing Information
(alfuzosin HCl extended-release tablets)

DESCRIPTION

Each UROXATRAL (alfuzosin HCl extended-release tablets) tablet contains 10 mg alfuzosin hydrochloride as the active ingredient. Alfuzosin hydrochloride is a white to off-white crystalline powder that melts at approximately 240°C. It is freely soluble in water, sparingly soluble in alcohol, and practically insoluble in dichloromethane.

Alfuzosin hydrochloride is (R,S)-N-[3-[(4-amino-6,7-dimethoxy-2-quinazoliny] methylamino] propyl] tetrahydro-2- furancarboxamide hydrochloride. The empirical formula of alfuzosin hydrochloride is C₁₉H₂₇N₅O₄•HCl. The molecular weight of alfuzosin hydrochloride is 425.9. Its structural formula is:



The tablet also contains the following inactive ingredients: colloidal silicon dioxide (NF), ethylcellulose (NF), hydrogenated castor oil (NF), hydroxypropyl methylcellulose (USP), magnesium stearate (NF), mannitol (USP), microcrystalline cellulose (NF), povidone (USP), and yellow ferric oxide (NF).

CLINICAL PHARMACOLOGY

The symptoms associated with benign prostatic hyperplasia (BPH) such as urinary frequency, nocturia, weak stream, hesitancy and incomplete emptying are related to two components, anatomical (static) and functional (dynamic). The static component is related to the prostate size. Prostate size alone does not correlate with symptom severity. The dynamic component is a function of the smooth muscle tone in the prostate and its capsule, the bladder neck, and the bladder base as well as the prostatic urethra. The smooth muscle tone is regulated by alpha-adrenergic receptors. Alfuzosin exhibits selectivity for alpha₁-adrenergic receptors in the lower urinary tract. Blockade of these adrenoreceptors can cause smooth muscle in the bladder neck and prostate to relax, resulting in an improvement in urine flow and a reduction in symptoms of BPH.

UROXATRAL (alfuzosin HCl extended-release) is a selective antagonist of post-synaptic alpha₁-adrenoreceptors, which are located in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra.

Pharmacokinetics

The pharmacokinetics of UROXATRAL have been evaluated in adult healthy male volunteers after single and/or multiple administration with daily doses ranging from 7.5 mg to 30 mg, and in patients with BPH at doses from 7.5 mg to 15 mg.

Absorption: The absolute bioavailability of UROXATRAL 10 mg tablets under fed conditions is 49%. Following multiple dosing of 10 mg UROXATRAL under fed conditions, the time to maximum concentration is 8 hours. C_{max} and AUC_{0-24} are 13.6 (SD = 5.6) ng/mL and 194 (SD = 75) ng·h/mL, respectively. UROXATRAL exhibits linear kinetics following single and multiple dosing up to 30 mg. Steady-state plasma levels are reached with the second dose of UROXATRAL administration. Steady-state alfuzosin plasma concentrations are 1.2- to 1.6- fold higher than those observed after a single administration.

Effect of Food: As illustrated in Figure 1, the extent of absorption is 50% lower under fasting conditions. Therefore, UROXATRAL should be taken immediately following a meal. (See **DOSAGE AND ADMINISTRATION**.)

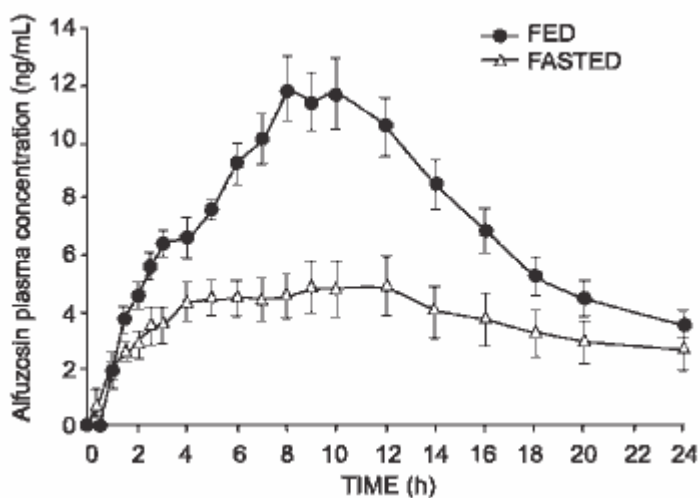


Figure 1 – Mean (SEM) Alfuzosin Plasma Concentration-Time Profiles after a Single Administration of UROXATRAL 10 mg tablets to 8 Healthy Middle-Aged Male Volunteers in Fed and Fasted States.

Distribution: The volume of distribution following intravenous administration in healthy male middle-aged volunteers was 3.2 L/kg. Results of *in vitro* studies indicate that alfuzosin is moderately bound to human plasma proteins (82% to 90%), with linear binding over a wide concentration range (5 to 5,000 ng/mL).

Metabolism: Alfuzosin undergoes extensive metabolism by the liver, with only 11% of the administered dose excreted unchanged in the urine. Alfuzosin is metabolized by three metabolic pathways: oxidation, O-demethylation, and N-dealkylation. The metabolites are not pharmacologically active. CYP3A4 is the principal hepatic enzyme isoform involved in its metabolism.

Excretion and Elimination: Following oral administration of ¹⁴C-labeled alfuzosin solution, the recovery of radioactivity after 7 days (expressed as a percentage of the administered dose) was 69% in feces and 24% in urine. Following oral administration of UROXATRAL 10 mg tablets, the apparent elimination half-life is 10 hours.

Special Populations

Elderly: In a pharmacokinetic assessment during phase 3 clinical studies in patients with BPH, there was no relationship between peak plasma concentrations of alfuzosin and age. However, trough levels were positively correlated with age. The concentrations in subjects ≥ 75 years of age were approximately 35% greater than in those below 65 years of age.

Patients with Renal Impairment: The pharmacokinetic profiles of UROXATRAL 10 mg tablets in subjects with normal renal function ($CL_{CR} > 80$ mL/min), mild impairment (CL_{CR} 60 to 80 mL/min), moderate impairment (CL_{CR} 30 to 59 mL/min), and severe impairment ($CL_{CR} < 30$ mL/min) were compared. These clearances were calculated by the Cockcroft-Gault formula. Relative to subjects with normal renal function, the mean C_{max} and AUC values were increased by approximately 50% in patients with mild, moderate, or severe renal impairment. (See **PRECAUTIONS, Special Populations**).

Patients with Hepatic Insufficiency: In patients with moderate or severe hepatic insufficiency (Child-Pugh categories B and C), the plasma apparent clearance (CL/F) was reduced to approximately one-third to one-fourth that observed in healthy subjects. This reduction in clearance results in three to four-fold higher plasma concentrations of alfuzosin in these patients compared to healthy subjects. Therefore, UROXATRAL is contraindicated in patients with moderate to severe hepatic impairment (See **CONTRAINDICATIONS**). The pharmacokinetics of UROXATRAL have not been studied in patients with mild hepatic insufficiency. (See **PRECAUTIONS, Special Populations**).

Drug-Drug Interactions

Metabolic interactions

CYP3A4 is the principal hepatic enzyme isoform involved in the metabolism of alfuzosin.

Potent CYP3A4 inhibitors

Repeated administration of 400 mg of ketoconazole, a potent inhibitor of CYP3A4, increased alfuzosin C_{max} 2.3-fold and AUC_{last} 3.2-fold following a single 10 mg dose of alfuzosin. Therefore, UROXATRAL should not be co-administered with potent inhibitors of CYP3A4 because exposure is increased, (e.g., ketoconazole, itraconazole, or ritonavir). (See **CONTRAINDICATIONS**).

Moderate CYP3A4 inhibitors

Diltiazem: Repeated co-administration of 240 mg/day of diltiazem, a moderately-potent inhibitor of CYP3A4, with 7.5 mg/day (2.5 mg three times daily) alfuzosin (equivalent to the exposure with UROXATRAL)

increased the C_{max} and AUC_{0-24} of alfuzosin 1.5- and 1.3-fold, respectively. Alfuzosin increased the C_{max} and AUC_{0-12} of diltiazem 1.4-fold. Although no changes in blood pressure were observed in this study, diltiazem is an antihypertensive medication and the combination of UROXATRAL and antihypertensive medications has the potential to cause hypotension in some patients. (See **WARNINGS**).

In human liver microsomes, at concentrations that are achieved at the therapeutic dose, alfuzosin did not inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6 or 3A4 isoenzymes. In primary culture of human hepatocytes, alfuzosin did not induce CYP1A, 2A6 or 3A4 isoenzymes.

Other interactions

Warfarin: Multiple dose administration of an immediate release tablet formulation of alfuzosin 5 mg twice daily for six days to six healthy male volunteers did not affect the pharmacological response to a single 25 mg oral dose of warfarin.

Digoxin: Repeated co-administration of UROXATRAL 10 mg tablets and digoxin 0.25 mg/day for 7 days did not influence the steady-state pharmacokinetics of either drug.

Cimetidine: Repeated administration of 1 g/day cimetidine increased both alfuzosin C_{max} and AUC values by 20%.

Atenolol: Single administration of 100 mg atenolol with a single dose of 2.5 mg of an immediate release alfuzosin tablet in eight healthy young male volunteers increased alfuzosin C_{max} and AUC values by 28% and 21%, respectively. Alfuzosin increased atenolol C_{max} and AUC values by 26% and 14%, respectively. In this study, the combination of alfuzosin with atenolol caused significant reductions in mean blood pressure and in mean heart rate. (See **WARNINGS**.)

Hydrochlorothiazide: Single administration of 25 mg hydrochlorothiazide did not modify the pharmacokinetic parameters of alfuzosin. There was no evidence of pharmacodynamic interaction between alfuzosin and hydrochlorothiazide in the 8 patients in this study.

Electrophysiology

The effect of 10 mg and 40 mg alfuzosin on QT interval was evaluated in a double-blind, randomized, placebo and active-controlled (moxifloxacin 400 mg), 4-way crossover single dose study in 45 healthy white male subjects aged 19 to 45 years. The QT interval was measured at the time of peak alfuzosin plasma concentrations. The 40 mg dose of alfuzosin was chosen because this dose achieves higher blood levels than those achieved with the co-administration of UROXATRAL and ketoconazole 400 mg. Table 1 summarizes the effect on uncorrected QT and mean corrected QT interval (QTc) with different methods of correction (Fridericia, population-specific, and subject-specific correction methods) at the time of peak alfuzosin plasma concentrations. No single one of these correction methodologies is known to be more valid. The mean change of heart rate associated with a 10 mg dose of alfuzosin in this study was 5.2 beats/minute and 5.8 beats/minute with 40 mg alfuzosin. The change in heart rate with moxifloxacin was 2.8 beats/minute.

Table 1. Mean QT and QTc changes in msec (95% CI) from baseline at Tmax (relative to placebo) with different methodologies to correct for effect of heart rate.

Drug/Dose	QT	Fridericia method	Population-specific method	Subject-specific method
Alfuzosin 10 mg	-5.8 (-10.2, -1.4)	4.9 (0.9, 8.8)	1.8 (-1.4, 5.0)	1.8 (-1.3, 5.0)
Alfuzosin 40 mg	-4.2 (-8.5, 0.2)	7.7 (1.9, 13.5)	4.2 (-0.6, 9.0)	4.3 (-0.5, 9.2)
Moxifloxacin * 400 mg	6.9 (2.3, 11.5)	12.7 (8.6, 16.8)	11.0 (7.0, 15.0)	11.1 (7.2, 15.0)

* Active control

The QT effect appeared greater for 40 mg compared to 10 mg alfuzosin. The effect of the highest alfuzosin dose (four times the therapeutic dose) studied did not appear as large as that of the active control moxifloxacin at its therapeutic dose. This study, however, was not designed to make direct statistical comparisons between the drugs or the dose levels. There has been no signal of Torsade de Pointes in the extensive post-marketing experience with alfuzosin outside the United States.

Clinical Studies

Three randomized placebo-controlled, double-blind, parallel-arm, 12-week studies were conducted with the 10 mg daily dose of alfuzosin. In these three studies, 1,608 patients [mean age 64.2 years, range 49-92 years; Caucasian (96.1%), Black (1.6%), Asian (1.1%), Other (1.2)] were randomized and 473 patients received UROXATRAL 10 mg daily. Table 1 provides the results of the three studies that evaluated the 10 mg dose.

There were two primary efficacy variables in these three studies. The International Prostate Symptom Score (IPSS, or AUA Symptom Score) consists of seven questions that assess the severity of both irritative (frequency, urgency, nocturia) and obstructive (incomplete emptying, stopping and starting, weak stream, and pushing or straining) symptoms, with possible scores ranging from 0 to 35. The second efficacy variable was peak urinary flow rate. The peak flow rate was measured just prior to the next dose in study 2 and on average at 16 hours post-dosing in studies 1 and 3.

There was a statistically significant reduction from baseline to last assessment (Week 12) in the IPSS versus placebo in all three studies, indicating a reduction in symptom severity (Table 2 and Figures 2, 3, and 4).

Table 2 — Mean Change (SD) from Baseline to week 12 in International Prostate Symptom Score in Three Randomized, Controlled, Double Blind Studies

Symptom Score	Study 1		Study 2		Study 3	
	Placebo (n=167)	UROXATRAL 10 mg (n=170)	Placebo (n=152)	UROXATRAL 10 mg (n=137)	Placebo (n=150)	UROXATRAL 10 mg (n=151)
Total symptom score						
Baseline	18.2 (6.4)	18.2 (6.3)	17.7 (4.1)	17.3 (3.5)	17.7 (5.0)	18.0 (5.4)
Change ^a	-1.6 (5.8)	-3.6 (4.8)	-4.9 (5.9)	-6.9 (4.9)	-4.6 (5.8)	-6.5 (5.2)
p-value	0.001		0.002		0.007	

^a Difference between baseline value and last value

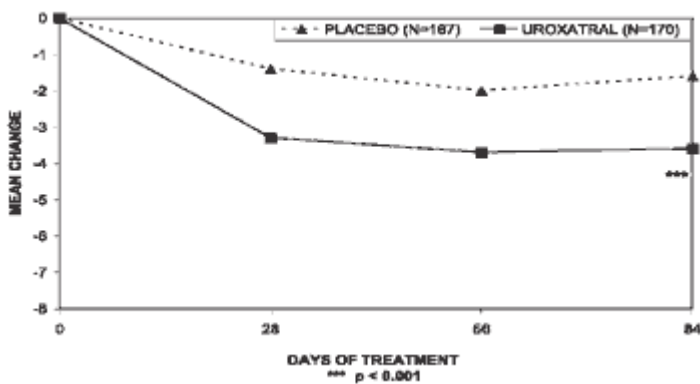


Figure 2 — Mean Change from Baseline in Total Symptom Score, by Visit: Study 1

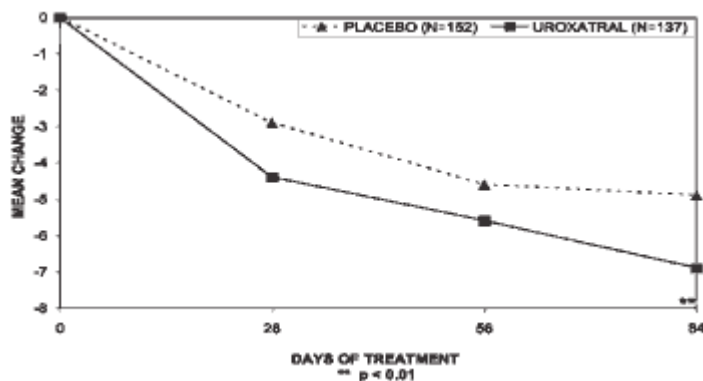


Figure 3 — Mean Change from Baseline in Total Symptom Score, by Visit: Study 2

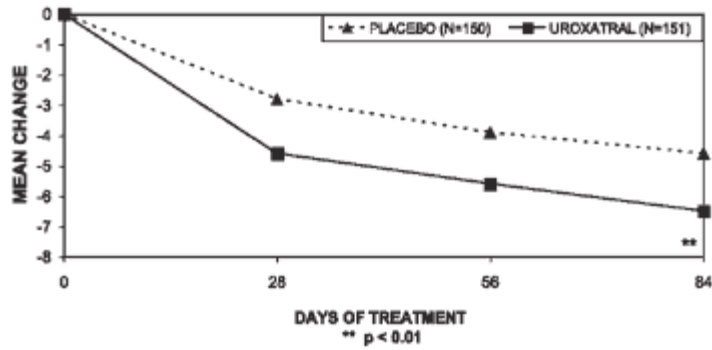


Figure 4 — Mean Change from Baseline in Total Symptom Score, by Visit: Study 3

Peak urinary flow rate was increased statistically significantly from baseline to last assessment (Week 12) versus placebo in studies 1 and 2 (Table 3 and Figures 5, 6, and 7).

Table 3 — Mean (SD) from Baseline in Peak Urine Flow Rate (mL/sec) in Three Randomized, Controlled, Double-Blind Studies

Symptom Score	Study 1		Study 2		Study 3	
	Placebo (n=167)	UROXATRAL 10 mg (n=170)	Placebo (n=147)	UROXATRAL 10 mg (n=136)	Placebo (n=150)	UROXATRAL 10 mg (n=136)
Mean Peak flow rate						
Baseline	10.2 (4.0)	9.9 (3.9)	9.2 (2.0)	9.4 (1.9)	9.3 (2.6)	9.5 (3.0)
Change ^a	0.2 (3.5)	1.7 (4.2)	1.4 (3.2)	2.3 (3.6)	0.9 (3.0)	1.5 (3.3)
p-value	0.0004		0.03		0.22	

^a Difference between baseline value and last value

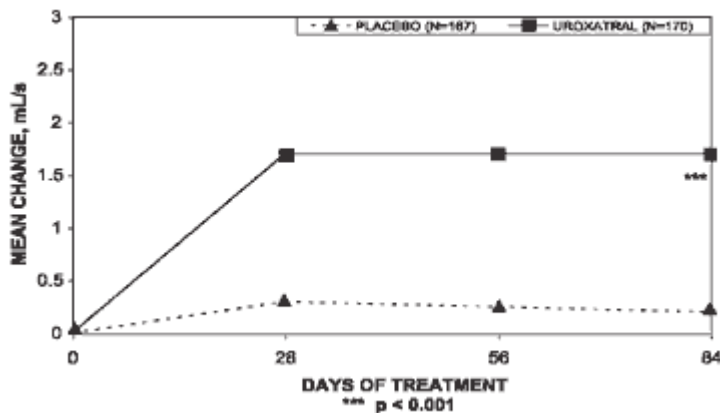


Figure 5 — Mean Change from Baseline in Peak Urine Flow Rate (mL/s), by Visit: Study 1

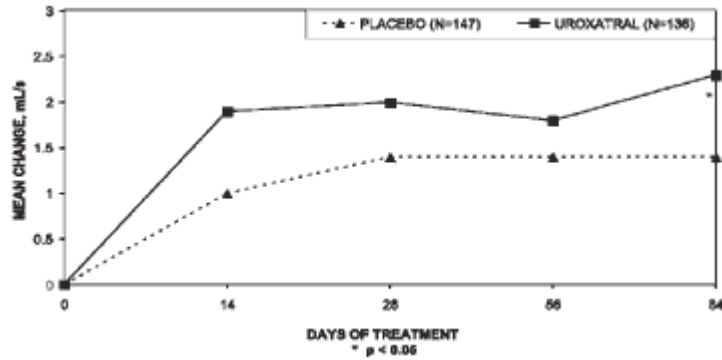


Figure 6 — Mean Change from Baseline in Peak Urine Flow Rate (mL/s), by Visit: Study 2

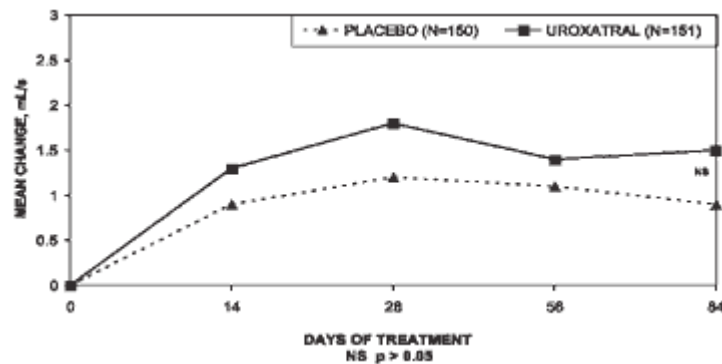


Figure 7 — Mean Change from Baseline in Peak Urine Flow Rate (mL/s), by Visit: Study 3

Mean total IPSS decreased at the first scheduled observation at Day 28 and mean peak flow rate increased starting at the first scheduled observation at Day 14 in studies 2 and 3 and Day 28 in study 1.

INDICATIONS AND USAGE

UROXATRAL (alfuzosin HCl extended-release tablets) is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia.

UROXATRAL is not indicated for the treatment of hypertension.

CONTRAINDICATIONS

UROXATRAL should not be used in patients with moderate or severe hepatic insufficiency, (Childs-Pugh categories B and C) since alfuzosin blood levels are increased in these patients. (See **CLINICAL PHARMACOLOGY, Patients with Hepatic Insufficiency subsection**).

UROXATRAL should not be co-administered with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, and ritonavir, since alfuzosin blood levels are increased. (See **CLINICAL PHARMACOLOGY**).

UROXATRAL (alfuzosin HCl extended-release tablets) is contraindicated in patients known to be hypersensitive to alfuzosin hydrochloride or any component of UROXATRAL tablets.

WARNINGS

Postural hypotension with or without symptoms (e.g., dizziness) may develop within a few hours following administration of UROXATRAL (alfuzosin HCl extended-release tablets). As with other alpha-blockers, there is a potential for syncope. Patients should be warned of the possible occurrence of such events and should avoid situations where injury could result should syncope occur. Care should be taken when UROXATRAL is administered to patients with symptomatic hypotension or patients who have had a hypotensive response to other medications.

PRECAUTIONS

General

Prostatic Carcinoma: Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently coexist. Therefore, patients thought to have BPH should be examined prior to starting therapy with UROXATRAL (alfuzosin HCl extended-release tablets) to rule out the presence of carcinoma of the prostate.

Drug-Drug Interactions: The pharmacokinetic and pharmacodynamic interactions between UROXATRAL and other alpha-blockers have not been determined. However, interactions may be expected, and UROXATRAL should NOT be used in combination with other alpha-blockers.

Coronary Insufficiency: If symptoms of angina pectoris should newly appear or worsen, UROXATRAL should be discontinued.

Hepatic Insufficiency: UROXATRAL should not be given to patients with moderate or severe hepatic insufficiency. (See **CONTRAINDICATIONS**). The pharmacokinetics of UROXATRAL have not been studied in patients with mild hepatic insufficiency (See **CLINICAL PHARMACOLOGY, Patients with Hepatic Insufficiency**).

Renal Insufficiency: Systemic exposure was increased by approximately 50% in pharmacokinetic studies of patients with mild, moderate, and severe renal insufficiency (See **CLINICAL PHARMACOLOGY, Special Populations**). In phase 3 studies, the safety profile of patients with mild (n=172) or moderate (n=56) renal impairment was similar to the patients with normal renal function in those studies. Safety data are available in only a limited number of patients (n=6) with creatinine clearance below 30 mL/min; therefore, caution should be exercised when UROXATRAL is administered in patients with severe renal insufficiency.

Patients with Congenital or Acquired QT Prolongation: In a study of QT effect in 45 healthy males (See **CLINICAL PHARMACOLOGY, Electrophysiology**), the QT effect appeared less with alfuzosin 10 mg than with 40 mg, and the effect of alfuzosin 40 mg did not appear as large as that of the active control moxifloxacin at its therapeutic dose. This observation should be considered in clinical decisions to prescribe UROXATRAL for patients with a known history of QT prolongation or patients who are taking medications known to prolong QT, although there has been no signal of Torsades de Pointe in the extensive post-marketing experience with alfuzosin outside the United States. There are no known PK/PD studies of the effects of other alpha blockers on cardiac repolarization.

Information for Patients

Patients should be told about the possible occurrence of symptoms related to postural hypotension, such as dizziness, when beginning UROXATRAL, and they should be cautioned about driving, operating machinery, or performing hazardous tasks during this period.

UROXATRAL should be taken with food and with the same meal each day.

Patients should be advised not to crush or chew UROXATRAL tablets.

Laboratory Tests

No laboratory test interactions with UROXATRAL tablets are known.

Pediatric Use

UROXATRAL is not indicated for use in children.

Geriatric Use

Of the total number of subjects in clinical studies of UROXATRAL, 48% were 65 years of age and over, whereas 11% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. (See **CLINICAL PHARMACOLOGY, Elderly subsection.**)

Carcinogenesis, Mutagenesis, and Impairment of Fertility

There was no evidence of a drug-related increase in the incidence of tumors in mice following dietary administration of 100 mg/kg/day alfuzosin for 98 weeks (13 and 15 times the level of exposure to humans based on AUC of unbound drug) in females and males, respectively. The highest dose tested in female mice may not have constituted a maximally tolerated dose. Likewise, there was no evidence of a drug-related increase in the incidence of tumors in rats following dietary administration of 100 mg/kg/day alfuzosin for 104 weeks (53 and 37 times the level of exposure to humans based on AUC of unbound drug) in females and males, respectively.

Alfuzosin showed no evidence of mutagenic effect in the Ames and mouse lymphoma assays, and was free of any clastogenic effects in the Chinese hamster ovary cell and in vivo mouse micronucleus assays. Alfuzosin treatment did not induce DNA repair in a human cell line.

There was no evidence of reproductive organ toxicity when male rats were given alfuzosin at daily oral (gavage) doses of up to 250 mg/kg/day for 26 weeks, which corresponds to levels of exposure several hundred times that in humans. No impairment of fertility was observed following oral (gavage) administration to male rats at doses of up to 125 mg/kg/day for 70 days. Estrous cycling was inhibited in rats and dogs at doses of 25 mg/kg and 20 mg/kg, respectively, corresponding to levels of systemic exposure (based on AUC of unbound drug) 12- and 18-fold higher, respectively, than in humans, although this did not result in impaired fertility in rats.

Pregnancy

Teratogenic Effects, Pregnancy and Lactation Category B. UROXATRAL is not indicated for use in women.

There was no evidence of teratogenicity or embryotoxicity in rats at maternal (oral gavage) doses up to 250 mg/kg/day, corresponding to systemic exposure levels 1,200-fold higher than in humans. In rabbits, up to the dose of 100 mg/kg/day (approximately 3 times the clinical dose by body surface area) given orally (via gavage), no evidence of fetal toxicity or teratogenicity was seen.

Gestation was slightly prolonged in rats with a maternal dose >5 mg/kg/day (oral gavage), which corresponds to systemic exposure levels (based on AUC of unbound drug) 12 times higher than human exposure levels, but there were no difficulties with parturition.

Nursing Mothers

UROXATRAL is not indicated for use in women.

ADVERSE REACTIONS

The incidence of treatment-emergent adverse events has been ascertained from 3 placebo-controlled clinical trials involving 1,608 men in which daily doses of 10 and 15 mg alfuzosin were evaluated. In these 3 trials, 473 men received UROXATRAL (alfuzosin HCl 10 mg extended-release tablets). In these studies, 4% of patients taking UROXATRAL (alfuzosin HCl extended-release tablets) 10 mg tablets withdrew from the study due to adverse events, compared with 3% in the placebo group.

Table 4 summarizes the treatment-emergent adverse events that occurred in $\geq 2\%$ of patients receiving UROXATRAL, and at an incidence numerically higher than that of the placebo group. In general, the adverse events seen in long-term use were similar in type and frequency to the events described below for the 3-month trials.

**Table 4 — Treatment-Emergent Adverse Events
Occurring in $\geq 2\%$ of UROXATRAL-Treated Patients
and More Frequently than with Placebo in 3-Month
Placebo-Controlled Clinical Studies**

Adverse Event	Placebo (n=678)	UROXATRAL (n=473)
Dizziness	19 (2.8%)	27 (5.7%)
Upper respiratory tract infection	4 (0.6%)	14 (3.0%)
Headache	12 (1.8%)	14 (3.0%)
Fatigue	12 (1.8%)	13 (2.7%)

The following adverse events, reported by between 1% and 2% of patients receiving UROXATRAL and occurring more frequently than with placebo, are listed alphabetically by body system and by decreasing frequency within body system:

Body as a whole: pain

Gastrointestinal system: abdominal pain, dyspepsia, constipation, nausea

Reproductive system: impotence

Respiratory system: bronchitis, sinusitis, pharyngitis

The following adverse events have also been reported in postmarketing experience: rash, tachycardia, chest pain, priapism.

Signs and Symptoms of Orthostasis in Clinical Studies: The adverse events related to orthostasis that occurred in the double-blind phase 3 studies with alfuzosin 10 mg are summarized in Table 5. Approximately 20% to 30% of patients in these studies were taking antihypertensive medication.

Table 5 — Number (%) of Patients with Symptoms Possibly Associated with Orthostasis in 3-Month Placebo-Controlled Clinical Studies

Symptoms	Placebo (n=678)	UROXATRAL (n=473)
Dizziness	19 (2.8%)	27 (5.7%)
Hypotension or postural hypotension	0	2 (0.4%)
Syncope	0	1 (0.2%)

Multiple testing for blood pressure changes or orthostatic hypotension was conducted in the three controlled studies at each scheduled clinic visit (Days 14, 28, 56, and 84). Patients with a decrease in systolic blood pressure of ≥ 20 mm Hg after 2 minutes standing following being supine were excluded from the three trials. These tests were considered positive for blood pressure decrease if (1) supine systolic blood pressure was ≤ 90 mm Hg, with a decrease ≥ 20 mm Hg versus baseline, and/or (2) supine diastolic blood pressure was ≤ 50 mm Hg, with a decrease ≥ 15 mm Hg versus baseline. The tests were considered positive for orthostatic hypotension if there was a decrease in systolic blood pressure of ≥ 20 mm Hg upon standing from the supine position during the orthostatic tests. According to these definitions, decreased systolic blood pressure was observed in none of the 674 placebo patients and 1 (0.2%) of the 469 UROXATRAL patients. Decreased diastolic blood pressure was observed in 3 (0.4%) of the placebo patients and in 4 (0.9%) of the UROXATRAL patients. A positive orthostatic test was seen in 52 (7.7%) of placebo patients and in 31 (6.6%) of the UROXATRAL patients.

No vital sign measurements were obtained following first dose administration in the phase 3 studies, except for a subset of patients in study 1 who had blood pressure measurements 12 to 16 hours after the first dose to assess the potential to produce orthostatic hypotension. None of these 35 UROXATRAL treated patients showed a positive test for systolic, diastolic or orthostatic blood pressure change.

OVERDOSAGE

Should overdose of UROXATRAL (alfuzosin HCl extended-release tablets) lead to hypotension, 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 the administration of intravenous fluids should be considered. If necessary, vasopressors should then be used, and the renal function should be monitored and supported as needed. Alfuzosin is 82% to 90% protein-bound; therefore, dialysis may not be of benefit.

DOSAGE AND ADMINISTRATION

The recommended dosage is one 10 mg UROXATRAL (alfuzosin HCl extended-release tablets) tablet daily to be taken immediately after the same meal each day. The tablets should not be chewed or crushed.

HOW SUPPLIED

UROXATRAL (alfuzosin HCl extended-release tablets) 10 mg is available as a round, three-layer tablet: one white layer between two yellow layers, debossed with X10. UROXATRAL is supplied as follows:

Package	NDC Number
Bottles of 30	0024-4200-30
Bottles of 100	0024-4200-10
Hospital Unit Dose (blister packs containing 10 cards of 10 tablets each)	0024-4200-20

Rx only.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Protect from light and moisture.

Keep UROXATRAL out of reach of children.

Distributed by:

sanofi~synthelabo

Sanofi-Synthelabo Inc., New York, NY 10016

UROXATRAL® is a registered trademark of Sanofi-Synthelabo.

USS-1

Revised June 2003

APPENDIX D: VISIT SCHEDULE

Form Name	-1 to -4 Weeks (Screening)	0 Weeks (Randomization)	6 Weeks (Follow-up)	12 Weeks (Follow-up)
	Visit 1 (B1 Clinic)	Visit 2 (B2 Clinic)	Visit 3 (Clinic)	Visit 4 (Clinic)
Prescreening/Screening/Baseline				
Pre-Screening Summary (PRESCR)				
Informed Consent (Administrative)	X			
Medical History (MEDHX)	X			
Eligibility Checklist (ELIG)	X	X		
NIH-Chronic Prostatitis Symptom Index (CPSI)	X	X	X	X
Randomization (RAND)		X		
Procedures and Labs				
Adverse Events/Serious Adverse Events (AE)		X	X	X
Demographics (DEMO)	X			
Dispensing Log (DISP)		X	X	
Drug Compliance (DCOMP)			X	X
EPS and Urine Testing (EUT)	X			
Physical Exam (EXAM)	X			
Urine Screening (URINE)	X			
Symptom Questionnaires				
Symptom Assessment (SYM)	X	X	X (GRA)	X (GRA)
Health Status Questionnaire® (SF-12)		X	X	X
The McGill Pain Questionnaire® (MPQ)		X	X	X
Hospital Anxiety and Depression Scale® (HADS)		X	X	X
The International Index of Erectile Function® (IIEF)		X	X	X
The Male Sexual Health Questionnaire (MSHQ)		X	X	X
Participant Expectations Questionnaire (EXP)		X		
PRN Forms				
Study Stop Point (SSTOP)	PRN	PRN	PRN	X
Treatment Stop Point (TSTOP)	PRN	PRN	PRN	X
Unmasking Record (UNMASK)	PRN	PRN	PRN	PRN
Administrative Forms				
Clinical Center Staff "Signature and Delegation of Responsibilities" Log (STAFFLOG)	X	PRN	PRN	PRN
Concomitant Medication (CMED)	X	X	X	X
Participant ID Assignment Log (PTLOG)	X			
Participant Contact Information (PTCONT)	X			
Participant Transfer (TRANS)	PRN	PRN	PRN	PRN
Study Drug Tracking Log (TRACK)		X	X	
Visit Checklist	X	X	X	X

APPENDIX E: CTCAE V3.0