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

Randomized Clinical Trial #2

A Randomized, Placebo-Controlled Multicenter Clinical Trial to Evaluate the Efficacy and Safety of Pregabalin for the Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS)

MANUAL OF PROCEDURES
(MOP)

Chronic Prostatitis Collaborative Research Network- 2
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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 participants with chronic prostatitis are Category 3[2] 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 participants 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.

The CPCRN-2 is currently recruiting participants for a randomized clinical trial (RCT#1) to evaluate the efficacy and safety of the alpha blocker pregabalin in the treatment of newly-diagnosed Chronic Prostatitis / Chronic Pelvic Pain Syndrome (CP/CPPS) participants. In this Manual of Procedures (MOP), we document the second randomized clinical trial (RCT#2) to be conducted by the CPCRN-2. This trial will focus on the recruitment of treatment-refractory Chronic Prostatitis / Chronic Pelvic Pain Syndrome (CP/CPPS) participants, with the objective to evaluate the efficacy and safety of pregabalin in the treatment of these participants. Pregabalin, a

structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), is manufactured and marketed by Pfizer, Inc as Lyrica®. Lyrica® is a new prescription medication approved for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN) and adjunctive treatment of partial onset seizures in adults with epilepsy.[4] Because the defining symptom of CP/CPPS is pain, a proposed mechanism for the etiology and pathogenesis of this condition is that of a neurogenic origin. The hypothesis then is that CP/CPPS participants may benefit from medications used to treat neuropathic pain.

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1 STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

1.1 Study Design and Objectives

This CPCRN-2 randomized clinical trial (RCT #2) will utilize a double-blinded, 2 arm design to evaluate the efficacy and safety of pregabalin in CP/CPPS participants, as compared to placebo.

The primary objectives of this trial are:

1. To compare six (6) weeks of treatment with pregabalin versus placebo in CP/CPPS participants with respect to the primary endpoint in the NIH-CPSI

2. To evaluate the safety and tolerability of six (6) weeks of pregabalin in CP/CPPS participants

1.2 Study Time Line and Endpoints (Include telephone visits)

This trial includes two phases- *Phase I* and *Phase II* and is comprised of both clinic and phone visits. Please refer to the ***Study Visit Schedule*** for the timing of the visits (Visits #1- 10). In Phase I, approximately 318 eligible participants will be randomized (2:1 randomization) to either pregabalin (utilizing a dose escalation of pregabalin from 150 mg to 300 mg and finally to 600 mg daily) or an identical looking placebo. Eligibility will be assessed through two baseline screening visits (Visit #1 and 2, two days to four weeks apart). Participants will be required to take study medication three times per day (tid) for a period of six (6) weeks, at which point they will then come in for their primary endpoint visit (Visit #5). Throughout the six weeks, the Research coordinator will contact the participant each time he adjusts his medication dose (or every two weeks from randomization). In total, it is anticipated that participant involvement in Phase I of the study will not exceed eleven weeks, from the first screening visit to the final telephone contact to assess that the participant has properly tapered down study medication.

All participants will complete the study at Visit #5. Participants returning for Visit 5 will be given the option to begin their medication taper down (proceed to Visit #6) or enroll in the open label (Phase II) portion of this trial (proceed to Visit #7). Depending on the respective scenario then, it is acceptable for a participant to either have Visits #1-6 completed or Visits #1-5, and #7-10 completed. Participant involvement in Phase II of the study will not exceed seven weeks.

The primary endpoint to be used for efficacy evaluation is the response rate, defined as a 6-point decrease from baseline to 6 weeks in the NIH-CPSI Total Score (scale of 0 - 43).[5] The responder criteria based on a 6-point decrease in the CPSI Total Score will allow detection of clinically detectable improvement in symptoms, as the goal is to identify treatment agents with solid clinical efficacy. As mentioned, the primary endpoint will be evaluated at Visit #5, and baseline NIH-CPSI Total Score at the second screening visit (Visit #2) will be used for all analyses. The NIH-CPSI Total Score assessed at Visit #1 will be only be used to determine participant eligibility. There are also a number of secondary endpoints that are described in the protocol.

1.3 General Protocol Policy

1.3.1 Changing the Protocol

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

1.3.2 Initiating a Protocol Change

Any member of the 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 #2 can be properly handled through a memo to each member of the Steering Committee. Proposed changes with a greater impact on the course of the CPCRN-2 RCT #2 will be presented to the Steering Committee via conference call or formal meeting to allow all members to benefit from the scientific debate generated in these discussions. Proposed changes can be implemented only after the Steering Committee reaches a majority vote and the NIDDK Project Officer approves 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. Protocol amendments will require approval from each sites' Institutional Review Board.

2 PARTICIPANT ENROLLMENT

2.1 Participant Population and Recruitment

2.1.1 Participant Population

This study will recruit men who have failed to respond to previous therapies for CP/CPPS (so-called "refractory participants"), including antibiotics. Thus the study protocol has been designed to test a new and novel therapy in a population of men with long-standing symptoms and who have failed previous treatments with standard CP/CPPS drugs. The study population will be drawn from participants presenting with symptoms of discomfort or pain in the pelvic region for at least a three month period within the last six months. Additionally, the participant's total overall score on the NIH-CPSI must be ≥15, with a non-zero pain domain score.

Each of the eleven (11) sites will randomize approximately 29 participants at a rate of two (2) participants per month. Recruitment will be conducted over a period of fifteen (15) months. Assuming a trial start date of February 15, 2005, recruitment will be completed by May 15, 2006. 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 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.

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. If allowed by the site's IRB, **exclusion** and **deferral** criteria may be reviewed with the participant 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 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.

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
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 (Krieger)
08= Queen's University
09= Stanford University
10= University of Maryland
11= University of Washington, Harborview (Berger)
18= University of Sciences Malaysia
19= King-Drew University

Participant ID Assignment Log Example

Clinical Center Code	Participant ID	Participant Initials	Participant Name
02	20001	JD	John Doe
02	20002	RS	Robert Smith
02	20003	MDC	Michael D. Cohen
02	20004	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 CPCRN-2 RCT#2; 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 CPCRN-2 RCT#2 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 this trial:

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 at least a moderate overall score on the NIH-CPSI (overall score ≥ 15 out of a potential of 0–43 points).
5. Participant must have had symptoms of discomfort or pain in the pelvic region for at least a three (3) month period within the last six (6) months.

6. Participant has a non-zero pain domain score on the NIH-CPSI at the time of enrollment.

2.5.2 Exclusion Criteria

Any participant satisfying one of the following criteria will <u>not</u> be eligible to participate in this trial:

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 a calculated creatinine clearance of <60 mL/min.
3. Participant has a platelet count <100,000/mm^3.
4. Participant is allergic to antiepileptic/antiseizure medications.
5. Participant has a known allergy or sensitivity to pregabalin (Lyrica®).
6. Participant is taking thiazolidinedione antidiabetic agents (i.e. rosiglitazone and pioglitazone).
7. Participant has New York Heart Association Class III or IV congestive heart failure.
8. Participant has a history of thrombocytopenia, or a bleeding diathesis.
9. Participant has a history of prostate, bladder or urethral cancer.
10. Participant has a history of alcohol abuse.
11. Participant has inflammatory bowel disease (such as Crohn's disease or ulcerative colitis, but not irritable bowel syndrome).
12. Participant has undergone pelvic radiation or systemic chemotherapy.
13. Participant has undergone intravesical chemotherapy.
14. Participant has been treated with intravesical BCG.
15. Participant has unilateral orchalgia without other pelvic symptoms.
16. Participant has an active urethral stricture.
17. Participant has a neurological disease or disorder affecting the bladder.
18. Participant has a neurological impairment or psychiatric disorder preventing his understanding of consent and his ability to comply with the protocol.

2.6 Deferral Criteria

2.6.1 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 previous gabapentin (Neurontin®) treatment within the past two (2) weeks.	Medication free for two (2) weeks.
2. Participant has had a urinary tract infection, with a urine culture value of >100,000 CFU/ml, within the past three (3) months, ***then***	Condition absent for three (3) months.
3. 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, ***then***	Condition absent for three (3) months.
4. If the participant has had a prostate biopsy in the past three (3) months, ***then***	Three (3) months from date of procedure.
5. If the participant has experienced symptoms of acute or chronic epididymitis within the past three (3) months, ***then***	Condition absent for three (3) months.
6. If the participant has been diagnosed with or treated for symptomatic genital herpes in the past twelve (12) months, ***then***	Twelve months from date diagnosed, and until they have been symptom free for a 12-month period (asymptomatic for 12 months).
7. If the participant has been taking prescription drugs with 5-alpha reductase activity (i.e. dutaserade or finasteride) in the past twelve (12) months, ***then***	Medication free for twelve (12) months.
8. Participant has started, stopped, or changed dose level of ANY prostatitis-specific medications within the past four (4) weeks.	Medication free for four (4) weeks
9. Participant has undergone TURP, TUIP, TUIBN, TUMT, TUNA, balloon dilation of the prostate, open prostatectomy or any other prostate surgery or treatment such as alcohol ablation or thermal therapy less than one (1) year ago.	Less than one year from date of procedure.

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.

2.7 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.

2.8 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 2-day hour VB2 culture, the creatinine clearance and platelet count. Only those participants, who have completed the entire screening phase and meet eligibility at <u>both</u> 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 ≥15 at both visits; an <u>average</u> score of baseline NIH-CPSI score of ≥15 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 **no**t 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.***

2.8.1 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 cell phone 215-531-0003, which will be available from 0900 to 2000 EST, Monday through Friday.

A member of the DCC team will 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.

2.9 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.

2.10 Participant Transfers

It is possible for a study participant to transfer to another CPCRN-2 RCT #2-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.

2.10.1 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.

2.10.2 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.

2.11 Study and Participant Documents

Study and participant documents must be made available to the CPCRN-2 RCT #2 Study Group, Pfizer, 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#2 Protocol/Amendments and Signature Page(s)
- RCT#2 Manual of Procedures and Signature Page
- RCT#2 Case Report Form Templates
- RCT#2 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 that 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. Note that use of historical data (standard of care physical exam and lab results up to 4 weeks prior to first visit) does not replace the need for having two screening visits.

If at any time during the screening process the participant 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 two (2) days and no more then 28 days 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
- Medical History [**MEDHX**]
- Eligibility Checklist [**ELIG**]
- NIH-CPSI [**CPSI**]
- Clinical Lab Results [**LABS**]
- Demographics [**DEMO**]
- EPS and Urine Testing [**EUT**]
- Physical Exam [**EXAM**]
- Urine Screening [**URINE**]
- Symptom Assessment [**SYM**], Q#4 not required at this visit
- Participant Contact Information [**PTCONT**]
- Participant ID Assignment Log [**PTLOG**]
- Visit Checklist [**VISIT1**]

Laboratory Procedures to be completed at this visit include a physical exam, a blood draw so that serum creatinine and platelet count can be measured. Urine and EPS samples will also be collected. 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 ***must*** be obtained. The participant must also attempt to provide an EPS and/or VB3 sample, but participants will not be excluded if they cannot provide either one of these samples.

The RC will review all over-the-counter and prescribed medications that the participant is currently taking and document in the source documents. The [***CMED*] *form is not being entered at visit 1 but over- the- counter drugs should be documented.***

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:

- Eligibility Checklist [**ELIG**]
- NIH-CPSI [**CPSI**]
- Randomization [**RAND**]
- Adverse Events/Serious Adverse Events [**AE**] – Pre-existing medical conditions (see note below)
- Concomitant Medications [**CMED**]
- Dispensing Log [**DISP**]
- Symptom Assessment Form [**SYM**], Q#4 is not required at this visit
- MOS SF-12 Health Status Questionnaire [**SF-12**]
- McGill Pain Questionnaire [**MCGILL**]
- Hospital Anxiety and Depression Scale [**HADS**]
- The Sexual Health Inventory for Men® [**SHIM]**
- Participant Expectations Questionnaire [**EXP**]
- Pain Medication Questionnaire **[PAIN]**
- Study Medication Tracking Log [**TRACK**]
- Visit Checklist [**VISIT2**]

The research staff will review the VB2 culture lab, Serum Creatinine, and Platelet count results from Screening Visit #1 to determine participant eligibility and record this on the [**ELIG**] form. The RC will have to calculate the creatinine clearance value based on the serum creatinine value. The participant's score on the [**CPSI**] will also be recorded on the [**ELIG**] form.

The RC will complete the **[CMED]** form and review any changes in the participant's medication use. Participants taking any medications to control their pelvic pain will need to complete the **[PAIN]** form.

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. You will have both blinded and open-label kits so it is important to not confuse the study kits. The open label kits are not participant specific and do not have a randomization number on them. It is also important that the RC check that the label on the blinded kit and the participant's 5-digit randomization number on the [**RAND**] form are the same and that the contents of the blinded kit is dispensed to the participant whose Participant ID is on the [**DISP**] form.

The study medication will be titrated over a 6-week period, as tolerated, to a maximum dose of 600 mg. Dosing will begin with 150 mg/daily, followed by 300 mg/daily, and a final dose of 600 mg/daily or maximally tolerated dose. Each blinded study kit will therefore have three bottles of study medication – one for each different dose. The bottles will have color coded labels A, B, and C. There will also be two taper down blister packets, labeled A and B. The RC will count the contents of each bottle and blister packet to confirm that they are as follows:

Bottle A: (50mg capsules)-150 capsules –"low dose"

Bottle B: (100mg capsules)-100 capsules- "medium dose"

Bottle C: (200mg capsules)-50 capsules- "high dose"

Blister packet A: (50mg capsules)-30 capsules

Blister packet B: (100mg capsules)-30 capsules

NOTE: Taper down blister packets are not distributed at this visit. They will be provided to the participant at Visit #5 (Primary Endpoint visit), only if the participant decides not to proceed with Phase II of the study.

The RC will instruct the participant to take one capsule three times daily; additional details on how to take the study medication will be provided in the Medication Manual developed by the University of Pennsylvania's Investigational Drug Service (IDS). The RC will also instruct the participant 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".

NOTE: Participants will be titrating study medication on their own so it is important they leave the clinic with a thorough understanding of how to do so.

NOTE: It should be emphasized that that there will be an excess of capsules from Bottle A and B if the dose titration proceeds as planned. Additional capsules are provided for those situations in which the participant cannot tolerate a scheduled dose and needs to be maintained at either the low or medium dose for the duration of the trial.

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. It is also important that the participant know that he needs to contact the RC if at any time he feels he needs to titrate to a lower dose of study medication because of side effects.

At this randomization visit, Visit #2, the RC will also begin recording all current pre-existing conditions reported by the participant. 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 will 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; ***with the exception of those associated with the disease under study.****

* Pre-existing conditions associated with CP symptomatology will NOT be recorded, as this information is captured by the NIH-CPSI at baseline and at all follow-up visits.

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
- Inparticipant 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 Phases of the trial. This includes one clinic visit at the end of the six (6) week treatment period for primary endpoint measurement (Visit #5). There are also two phone contacts in between, at week two (2) and week four (4) post-treatment

when the participant is titrating up in study medication (Visits #3 and #4 respectively). These visits are described further below.

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 Two (2)- Telephone Contact

Forms to be completed include:

- NIH-CPSI [**CPSI**]
- Adverse Events/Serious Adverse Events [**AE**]
- Concomitant Medications [**CMED**]
- Drug Compliance [**DCOMP**]
- Standard Telephone and Clinic Contact Summary **[STCONT]**
- Symptom Assessment Form [**SYM**]- including GRA
- Participant Daily Medication Diary **[PTDIARY]**
- Study Medication Tracking Log [**TRACK**]
- Visit Checklist [**VISIT3**]

NOTE: The research coordinator will complete all forms, including those normally participant-completed.

The purpose of this telephone contact is to determine patient adherence to the dosing schedule and drug compliance, and to assess patient tolerance to study dose. The research coordinator needs to ensure that any participant unable to tolerate the scheduled increase dose tapers down to the previous fixed dose. It is very important then that the RC will review with the participant any new adverse events which have occurred since Visit #2. All new adverse events as well as changes in pre-existing conditions while on study drug are to be recorded on the Adverse Event [**AE**] CRF.

NOTE: Previous fixed dose means that the participant continues to take three (3) capsules a day, but of a lower dose capsule. For example, if the participant cannot tolerate three (3) of the "medium" dose capsules, he will go back to taking three (3) of the "low" dose capsules, rather than two (2) of the "medium" dose capsules.

The RC will complete the **[CMED]** form and review any changes in the participant's medication use. The **[PAIN]** questionnaire is not completed during the phone visits, even if the participant is taking medications specifically for their pelvic pain. The **[PAIN]** questionnaire is to only be completed once at baseline and once at primary endpoint.

The research coordinator will ask the participant to answer the questions on both the [**CPSI**] and the GRA question on the **[SYM]** form- via interview format. The research coordinator will mark off the participant's answers to the questions directly on the case report form.

Completion of the **[DCOMP]** form will only be an estimate of compliance since the participant will not be returning any study medication during the telephone contacts. The only column that can be confirmed is the amount of study medication dispensed. If there appears to be an issue with study medication compliance, 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. For reference on completing this form, please refer to Section 5.4.5 of this MOP and as well as the sample **[DCOMP]** forms provided at RC training.

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 Four (4)- Telephone Contact

Forms to be completed at this visit include:

- NIH-CPSI [**CPSI**]
- Adverse Events/Serious Adverse Events [**AE**]
- Concomitant Medications [**CMED**]
- Drug Compliance [**DCOMP**]
- Standard Telephone and Clinic Contact Summary **[STCONT]**
- Symptom Assessment Form [**SYM**]- including GRA
- Participant Daily Medication Diary **[PTDIARY]**
- Study Medication Tracking Log [**TRACK**]
- Visit Checklist [**VISIT4**]

This second telephone contact will proceed similarly to Visit #3, with the same forms being completed. The only difference is that the patient is now titrating from the "medium" dose up to the "high" dose.

When completing the **[DCOMP]** form, note that this is not to be cumulative for all weeks one (1) through four (4). The research coordinator is only assessing compliance between weeks two (2) through four (4).

The RC will review the Visit #4 checklist [**VISIT4**] form to ensure that all required forms and procedures were completed and schedule Visit #5 according to the participant's follow-up contact schedule.

3.2.5 Visit # 5 - Week Six (6)- Primary Endpoint Visit

Forms to be completed at this visit include:

- NIH-CPSI [**CPSI**]
- Adverse Events/Serious Adverse Events [**AE**]
- Concomitant Medications [**CMED**]

- Dispensing Log **[DISP]**
- Drug Compliance [**DCOMP**]
- EPS and Urine Testing **[EUT]** only if your site is doing the optional second collection of these samples
- Standard Telephone and Clinic Contact Summary **[STCONT]**
- Symptom Assessment Form [**SYM**]- including GRA
- MOS SF-12 Health Status Questionnaire [**SF-12**]
- McGill Pain Questionnaire **[MCGILL**]
- Hospital Anxiety and Depression Scale [**HADS**]
- The Sexual Health Inventory for Men® **[SHIM**]
- Participant Expectations Questionnaire **[EXP]**
- Pain Medications Questionnaire **[PAIN]**
- Participant Daily Medication Diary **[PTDIARY]**
- Study Medication Tracking Log [**TRACK**]
- Visit Checklist [**VISIT5**]

This is the final Clinic Visit for Phase I of the trial, and also the primary endpoint visit. At this visit, the RC will review with the participant any new adverse events which have occurred since Visit #4. 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**] form

The RC will complete the [**CMED**] form and review any changes in the participant's medication use. As in the baseline randomization visit (Visit #2), if the participant is taking any medications specifically for their pelvic pain, he will need to complete the **[PAIN]** questionnaire.

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

The RC will assess study medication compliance by collecting all three study medication bottles 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**]. Please refer to Section 5.4.5 of this MOP as well as the sample [**DCOMP**] forms provided at RC training.

The RC will review the Visit #5 checklist [**VISIT5**] form to ensure that all required forms and procedures were completed. At this visit, participants will be given the option of taking active therapy for an additional 6 weeks (Phase II of the trial). The exception would be those participants that encountered a Serious Adverse Event while on study treatment in Phase I but did not withdraw from the trial. Participants will remain blinded to the initial treatment assignment they were on in Phase I of the trial.

Those individuals proceeding to Phase II of the trial will be given the contents of an open-label kit. Note that all of these kits are identical and are not participant-specific (i.e. with no

randomization numbers) so you can issue any of the kits to the participant. Similar to the blinded kits, there are three bottles of study medication and two taper-down packets.

NOTE: Those participants going on to Phase II of the trial will not have a Visit #6 (Phone Contact), but will instead proceed directly to Visit #7 (Phone). Please mark Visit #6 as "MISSING" in the DMS. A pop-up window will appear asking whether the participant is enrolling in Phase II of the trial or not.

Those individuals who opt not to go on to Phase II of the trial will be given their taper down blister packets. Please make sure to distribute the packets from the blinded kit that matches the participant's 5-digit randomization number. The research coordinator should instruct the individual to start with packet B, then packet A. Again, one capsule should be taken three times a day.

NOTE: For those participants already on the medium dose ("B" or 100mg dose TID), they only need to take taper packet A. For those participants already on the low dose ("A" or 50 mg dose TID), they do not need to taper down.

A Study Stop **[SSTOP]** and Treatment Stop **[TSTOP]** form will also be completed for this participant at this visit.

3.2.6 Visit #6 – Week Seven (7)

Forms to be completed at this visit include:

- NIH-CPSI [**CPSI**]
- Adverse Events/Serious Adverse Events [**AE**]
- Concomitant Medications [**CMED**]
- Standard Telephone and Clinic Contact Summary **[STCONT]**
- Symptom Assessment Form [**SYM**]- including GRA
- Participant Daily Medication Diary **[PTDIARY]**
- Study Medication Tracking Log [**TRACK**]
- Visit Checklist [**VISIT6**]

This telephone contact is only for those participants NOT going on to Phase II of the trial. At the end of the one-week taper down, the participant will be contacted by telephone to confirm completion of study drug taper. The Research coordinator will also continue to record the participant's concomitant medication use on the **[CMED]** form, as well as monitor any adverse events that have newly occurred, changed, or been resolved on the Adverse Event [**AE**] CRF. The NIH-CPSI and the GRA question on the **[SYM]** form will also be completed.

The RC will review the Visit #6 checklist [**VISIT6**] form to ensure that all required forms and procedures were completed

3.2.7 Visit #7 – Week Seven (7)

Forms to be completed at this visit include:

- NIH-CPSI [**CPSI**]
- Adverse Events/Serious Adverse Events [**AE**]
- Concomitant Medications [**CMED**]
- Drug Compliance [**DCOMP**]
- Standard Telephone and Clinic Contact Summary **[STCONT]**
- Symptom Assessment Form [**SYM**]- including GRA
- Participant Daily Medication Diary **[PTDIARY]**
- Study Medication Tracking Log [**TRACK**]
- Visit Checklist [**VISIT7**]

This visit is only for participants going on to Phase II of the trial, and will proceed the same as all the other telephone contacts in Phase I. Please refer to Visits #3 and #4 above. All participants will be undergoing another scheduled titration because participants will still be blinded to which study treatment they were initially on. Once again, the RC will determine patient adherence to the dosing schedule and drug compliance, and to assess patient tolerance to study dose. Any adverse events will need to be tracked on the Adverse Event [AE] CRF.

NOTE: There is a more rapid titration in the open-label. Participants will only be on the low ("A" or 50 mg TID) and medium ("B" or 100 mg TID) doses for one week each, instead of two weeks as in Phase I.

The RC will review the Visit #7 checklist [**VISIT7**] form to ensure that all required forms and procedures were completed and schedule Visit #8 according to the participant's follow-up contact schedule.

3.2.8 Visit #8 – Week Eight (8)

Forms to be completed at this visit include:

- NIH-CPSI [**CPSI**]
- Adverse Events/Serious Adverse Events [**AE**]
- Concomitant Medications [**CMED**]
- Drug Compliance [**DCOMP**]
- Standard Telephone and Clinic Contact Summary **[STCONT]**
- Symptom Assessment Form [**SYM**]- including GRA
- Participant Daily Medication Diary **[PTDIARY]**
- Study Medication Tracking Log [**TRACK**]

- Visit Checklist [**VISIT8**]

This visit is another telephone contact with the participant, taking place two weeks after the Visit #5 Clinic visit to assess adherence and tolerance to titration to the medium ("B" or 100 mg TID) dose.

The RC will review the Visit #8 checklist [**VISIT8**] form to ensure that all required forms and procedures were completed and schedule Visit #9 according to the participant's follow-up contact schedule.

3.2.9 Visit # 9 - Week Twelve (12)

Forms to be completed at this visit include:

- NIH-CPSI [**CPSI**]
- Adverse Events/Serious Adverse Events [**AE**]
- Concomitant Medications [**CMED**]
- Drug Compliance [**DCOMP**]
- Dispensing Log **[DISP]**
- Standard Telephone and Clinic Contact **[STCONT]**
- Symptom Assessment Form [**SYM**]- including GRA
- MOS SF-12 Health Status Questionnaire [**SF-12**]
- McGill Pain Questionnaire **[MCGILL**]
- Hospital Anxiety and Depression Scale [**HADS**]
- The Sexual Health Inventory for Men® [**SHIM**]
- Study Stop Point [**SSTOP**]
- Treatment Stop Point [**TSTOP**]
- Participant Daily Medication Diary **[PTDIARY]**
- Study Medication Tracking Log [**TRACK**]
- Visit Checklist [**VISIT9**]

This is the final clinic visit, at the end of the six week open label. At this visit, the RC will review with the participant any new adverse events which have occurred since Visit #8. 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. The RC will complete the [**CMED**] form and review any changes in the participant's medication us.

The participant will complete all the symptom questionnaires with the exception of the Participant Expectations **[EXP]** and Pain Medication **[PAIN]** questionnaires.

The participant will return the study medication bottles 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.

The participant will leave this visit with the two taper-down packets and instructions on how to perform the taper-down. Distribution of the taper-down packets will be recorded on the **[DISP]** form.

The RC will review the Visit #9 checklist [**VISIT9**] form to ensure that all required forms and procedures were completed and schedule Visit #10 according to the participant's follow-up contact schedule.

3.2.10 Visit #10 – Week Thirteen (13)

Forms to be completed at this visit include:

- NIH-CPSI [**CPSI**]
- Adverse Events/Serious Adverse Events [**AE**]
- Concomitant Medications [**CMED**]
- Standard Telephone and Clinic Contact Summary **[STCONT]**
- Symptom Assessment Form [**SYM**]- including GRA
- Participant Daily Medication Diary **[PTDAIRY]**
- Visit Checklist [**VISIT10**]

This visit is the final contact with the patient. At the end of the one-week taper down, the participant will be contacted by telephone to confirm completion of study drug taper. The Research coordinator will also continue to record the participant's concomitant medication use on the **[CMED]** form, as well as monitor any adverse events that have newly occurred, changed, or been resolved on the Adverse Event [**AE**] CRF. The NIH-CPSI and the GRA question on the **[SYM]** form will also be completed.

The RC will review the Visit #10 checklist [**VISIT10**] form and ensure that all required forms and procedures were completed.

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 pregabalin, 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 pregabalin 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 participant 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 participant is in immediate risk of death from the event);
- Results in in-participant 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 participant 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 inparticipant 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 participant/event ***outcome or action*** criteria, usually associated with events that pose a threat to a participant'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 participant 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 Pfizer 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 is responsible of both the relationship and expectedness assessment.

The Sponsor shall also notify FDA by telephone or by facsimile transmission of any *unexpected* and *serious* (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.

Any relevant follow up information should be transmitted to the FDA in no event later than 15 calendar days. The DCC will disseminate these IND safety reports to the investigational sites and the Sponsor will notify Pfizer corporate pharmacovigilance at the same time.

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
- other medically important event including "syncope"

Note: As a convention for pregabalin studies, syncope (actual loss of consciousness) is to be considered as serious adverse event under the category of medically important event.

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

NIH/NIDDK

- Notifies FDA
- Notifies Pfizer corporate pharmacovigilance
- IND safety report should be transmitted to FDA and Pfizer at the same time.
- Keep Pfizer CPV informed of any significant safety issues, events, or results, and DSMB recommendations in evaluating the relationship with study drug and in evaluating the expectedness according to the current investigator's brochure.

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 Pfizer

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 CPCRN-2 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#2 (Protocol – CP02):

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, 18 and 19.

Visit Number: Visit numbers have been identified in the protocol when specific events happen during the course of the study. Visit numbers range from 01-10

CRF Date: This is the date of the case report form is completed, in most cases, the date of the visit/contact.

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
Concomitant Medications	CMED
NIH – Chronic Prostatitis Symptom Index	CPSI
Clinical Lab Results	LABS
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
McGill Pain Questionnaire® (MPQ)	MCGILL
Medical History	MEDHX
Pain Medication Questionnaire	PAIN
Participant Expectations Questionnaire	EXP
Physical Exam	EXAM
Pre-Screening Summary	PRESCR
Randomization	RAND
Sexual Inventory of Men ®	SHIM
Standard Telephone and Clinic Contact Summary	STCONT
Study Stop Point	SSTOP
Symptoms Assessment	SYM
Treatment Stop Point	TSTOP
Unmasking Record	UNMASK
Urine Screening	URINE

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 13 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 through #13. 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.

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" (code"1") 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.

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.

REMINDER: If participant is taking medication for pain, they need to complete the Pain Medication Questionnaire [PAIN], at Visit #2 and Visit #5.

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. 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.

Concomitant Medications [CMED]

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

Document the names, dosages and frequencies of other medications the participant is taking and include them in your listing.

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

When: Visit #2 through #10

General Directions

The information on this form is obtained from the participant's interview and the participant's completed the Participant Daily Medication Diary **[PTDIARY**] form and is used to track all concomitant medications being used during the course of the study. Starting at Visit #2, the participant records all medications being used, any new medications started, dosage changes and any medications stopped at any time up to Visit #10.

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

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

Drug Name: The drug name, as recorded on the Participant Daily Medication Diary [**PTDIARY**].

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

Frequency Taken: Select the *most specific response* possible, based on the information obtained from the **[PTDIARY]**.

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

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

Start Date: Date participant started taking a new medication or changed a dosing level of a medication he is already taking. If the participant is unsure of the start date, have him use his best judgment in recalling the month and the year. Based on information recorded at a previous visit, if the participant is still continuing to take the medication, mark (X) in the box instead of providing a date.

Stop Date: Date participant stopped taking the medication. If the participant is still continuing to take the medication, mark (X) in the box instead of providing a date.

Exclusionary Medications: Answer yes or no based on the eligibility requirements and as per PI discretion.

Restricted Medications: Answer yes or no based on the eligibility requirements and as per PI discretion.

For Pelvic/Bladder Pain: Answer yes or no based on whether or not the drug was taken specifically for pelvic/bladder pain. If yes, the Pain Medication Questionnaire [PAIN] form will need to be completed as well, if this is indicated at Visits #2 or #5.

For Urinary Frequency/Urgency: Answer yes or no based on whether or not the drug was taken for specifically for urinary frequency/urgency.

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 through #10.

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 Clinical Laboratory Results [LABS]

Purpose: To collect study-specific laboratory blood tests to determine the eligibility of the participant for the study and if the results are outside of the normal ranges of the institution.

Who: RC completed, based on lab reports

When: Visit 1

General Directions:

What is being measured is serum creatinine and platelet count. The serum creatinine value will be used to calculate the participant's creatinine clearance. Only the Cockcroft-Gault (CG) equation is to be used for this calculation. The formula is provided on the worksheet section of this form. For those sites whose laboratory provides a calculated creatinine clearance value as

part of their report- please confirm that the CG equation was used to derive the value. For each of these laboratory values, the PI is to determine whether the value is clinically significant, based on the laboratory's normal reference ranges.

Laboratory results/reports are to be kept as source documentation and maintained in the participant's study folder. This [LABS] form is to be signed and dated by the PI. The PI ID is also to be included.

Q#1 Please record the Serum Creatinine (mg/dL) results in the "test result" column. The date this specimen was drawn and whether it is Clinically Significant needs be recorded for this question as well.

Q#2 Please see the "Worksheet Section" of this form to determine the Creatinine Clearance. Once you have completed the worksheet section, please record the Creatinine Clearance value, date of specimen (when specimen was drawn) and indicate whether it is clinically significant

Q#3 Please record the date the platelets were drawn in the "Date of Specimen" column, the results in the "Test Results" column and indicate if it was clinically significant or not in the "Clinically Significant" column.

5.4.4 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.

5.4.5 Dispensing Log [DISP]

Purpose: To record study medications dispensed to a participant (for bottles and taper packets)

Who: RC completed

When: Visits #2, #5, and #9- Note that this is now a single form and can be completed outside of visit packets

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 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 (Question #2).

5.4.6 Drug Compliance [DCOMP]

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

Who: RC completed

When: Visits #3, #4, #5, #7, #8, and #9- Note that this is now a single form and can be completed outside of visit packets.

General Directions

This form is being completed during both Clinic Visits (#5 and 9) and Telephone Contacts (Visits #3, 4, 7, and 8). When being completed during Telephone contacts, this form may have totals recorded that are a "best estimate" because no study drug is being returned. The only definite entries are those for Questions 2a, 3a , and 4a- asking for how many capsules of each dose were dispensed. The RC will need to take the participant's word on how many capsules were used (taken) to complete Questions 2d, 3d, and 4d. Given the ability of participants to adjust their medications based on tolerance, the questions asking about the amount of capsules that "should have been used" can be a highly variable number. The corresponding dose changes may result in the participant not using all the study medication anticipated but still remaining 100% compliant. However, the sum of Questions #2e,3e, and 4e should add up to 42 capsules (14 days x 3 capsules/day).

The scenario below illustrates how this might work out over the course of two weeks- Completed at Visit #4 (Week 4). Please also refer to all the **[DCOMP]** example sheets provided at RC training.

> Assumption is that the participant wasn't able to titrate up to the medium dose ("B" or 100 mg TID) for the scheduled two weeks. Instead the patient only took the medium dose for 4 days and then dropped back down to the low dose ("A" or 50 mg TID) for the remaining 10 days. Knowing this, the amount of 100 mg capsules that should have been

used is then "12" (4 days x 3 capsules /day) rather than "42" (14 days x 3 capsules /day).The remaining "30" (10 days x 3 capsules /day) taken would be the 50 mg dose. Therefore, this participant still remains 100% compliant.

This form is not meant to be cumulative across all visits, but meant to measure compliance between visits.

At Clinic Visits #5 and 9, participants will have returned their study medication for a count. At this point, there will be definitive numbers to calculate the participant's drug compliance.

Qxn #1: Confirm the current treatment point.

Qxns #s 2 and 3:

- Ask the participant about lost or damaged study drug as well as missed doses (refer to Standard Telephone and Clinic Contact **[STCONT]** forms) each time the [**DCOMP]** form is completed. *During the titration periods, also ask about any dose changes up to an increased dose or down to a decreased dose due to the participant's tolerance of study drug.
- In box A, document the amount of the drug dispensed (total from Study Medication Dispensing Log **[DISP]** forms).
- 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 and corresponding doses (according to dose level) taken each day 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.

Qxn #4: 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.

5.4.7 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 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. *NOTE: For this Protocol, the overall score of* ***greater than or equal to 15*** *is the requirement for entry in this tria* **.**

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 #7a asks for an actual urine count in CFU/ml (quantitative) as opposed to a qualitative description such as "No growth". "No growth" descriptors on the lab results should be denoted as "0" on Qx #7a. In the instance where more than one Gram negative or enterococcus species is identified in the VB2 sample, please record the highest bacterial count from the [EUT] form.

Qx#8: The ability to answer this exclusion criterion will require the results from the [LABS] form. The calculated creatinine must be less than 60 mL/min.

Q#9: The ability to answer this exclusion criterion will require the results from the [LABS] form. The platelet count must be less than 100,000/mm^3.

Qx #34: This question must be answered at both Visits 1 and 2. This question must have a "yes" response for a successful randomization.

5.4.8 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. Only gram negative species are listed.

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. Please record the highest count on Qx #7a of the [ELIG] form.

NOTE: For VB2, if there is any culture count ≥ 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.

5.4.9 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, #5, and #9

5.4.10 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, #5, and #9

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 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, #5, and #9

5.4.12 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".

5.4.13 Pain Medication Questionnaire [PAIN]

Purpose: To obtain information about the participant's access to and experience with how well their pain medications manage their pain

Who: Participant completes

When: Visits #2 and #5

5.4.14 Participant Expectations Questionnaire [EXP]

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 and Visit #5

General Directions

This form will not be administered until the participant has been randomized and provided with study drug, to assure the participant that their responses do not influence whether they will receive active drug or placebo. The RC will NOT review this form with the participant; rather, the participant 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: This form can only be completed in the Data Management System (DMS) after the month being reported is over. For example, if this report is for the month of August, data entry can only be done on September 1st or thereafter.

Qx #2: Data sources reviewed for the pre-screening process can include any records for new participants at the clinical center, established participants, and/or any other participant/hospital record resources permitted for review by each Clinical Center's institution and within the bounds of applicable HIPAA regulations. The total for this question is included in Table 1 in the cumulative total for "Total Data Sources Reviewed" column of the CPCRN RCT#2 reports.

Qx #3: This total is the sum of the number of Pt.s not contacted from the records reviewed due to any of the reasons listed in the question below.

Qx#4a: This total reflects the number of subjects who were NOT determined as potential participants due to reasons apparent from the record review. For example, these could be subjects who do not meet the age requirements, do not have symptoms related to CP., or are currently taking the study agent.

Qx#4b: This total is the sum of subjects from the record review whom the Principal Investigator has determined are not potential participants. This can be due to reasons such as potential conflicting health concerns or any other reason the Investigator may find it unsafe for the subject to participate.

Qx#4c: This total is the sum of all other subjects gathered from the record review who are NOT determined to be potential participants for any other reason

Qx #5: This is the total number of subjects contacted for the first time by all methods for the month being reported. If a participant was contacted in a previously reported month, but could not confirm participation then and they were contacted again during the month being reported, they are NOT included again in this total. The total for this question is included in Table 1 in the cumulative total for the "Total Contacted" column of the CPCRN RCT#2 reports.

Qx#5a: This total includes subjects who were contacted by phone by the clinical center staff as well as subjects who called the clinical center.

Qx#5b: This total includes the number of subjects seen by the clinical center staff. For example, these may be subjects who were referred, new subjects who have contacted the clinical center, or established participants at the clinical center.

Qx#5c: This total includes subjects who have been contacted directly and personally by a written letter, e mail, or other written correspondence.

Qx#5.1: This total includes all subjects who have been contacted directly and are no longer being considered as potential participants. For example, this may include subjects seen in the clinic after an initial telephone contact and who do not meet criteria to be potential participants. This total also includes subjects who may have been initially contacted in a previous month, but were not yet prescreened. The total for this question is included in Table 1 in the cumulative total for the "Prescreening Failure" column of the CPCRN RCT#2 reports.

Qx#5.2 This total includes all subjects who have been contacted, but have not yet decided if they will or will not participate in the prescreening/screening process. For example, this may include participants who have been directly informed of the study, but have not replied as to whether or not they will agree to be prescreened. If a subject has not yet made a decision in the month following the month when they were initially recorded on the Prescreening Summary form (for example, decision pending in both July and August) they will only be included in this total for their initial contact month (July). When a decision has been made, either by the subject (about participation or non-participation) or the RC (that the subject has been lost to follow-up) the subject will be added to the appropriate total. This total is included in the cumulative total of the "Decision for Participation Pending" column of Table 1 in the CPCRN RCT#2 reports.

Qx #6: This total includes all participants who agreed to participate in prescreening/screening in the month being reported. If a subject has agreed to participate but has not yet been screened, that subject will not be included in this total, but in the total for question 6a. This total is included in the cumulative total of the "Total Agreed to Participate" column of Table 1 in the CPCRN RCT#2 reports.

Qx#6a: This total includes the number of subjects who agreed to participate in the prescreening/screening process and scheduled a contact/visit, but have not yet had their screening visit. This total is included in the "Screening Visit Scheduled" column of Table 1 in the CPCRN RCT#2 reports.

Qx #7: This total includes the number of subjects who have been directly contacted and declined to participate in the prescreening/screening process. This total is included in the "Total Declined to Participate" column of Table 1 in the CPCRN RCT#2 reports.

Qx#8a: This question is a "catch-all" for any subjects who declined to participate in the prescreening/screening process, but for whom none of the reasons listed below apply. It simply means that the subject is not interested in participating in the study.

The scenario of a participant signing informed consent, completing visit one, and then deciding not to further participate in the trial will be considered a Screening failure, and is not to be recorded on the [PRESCR] form. An [ELIG] form for this participant will need to be data-entered in the CP02 database.

5.4.17 Randomization [RAND]

Purpose: To ensure that a potential participant is eligible for CPCRN-2 RCT#2 (Protocol – CP02) 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 The Sexual Health Inventory for Men®

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

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

When: Visits #2, #5, and #9

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.

5.4.19 Standard Telephone and Clinic Contact Summary [STCONT]

Purpose: To collect information on study drug a compliance as well as a self-reported symptom assessment

Who: RC Completes

When: Visits #3 through #10

General Instructions:

Qxns # 1 and 2 capture information regarding a change in dosage during the titration up to the maximum tolerable dose, the taper-down off of the study medication, and (if necessary) a reduction in dose from a higher dose that the participant can not tolerate.

Qxns # 4 and 5 are not answered during the taper down visits (Visits #6 and 10)

5.4.20 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 #9, 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 #9, 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 #9 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.

5.4.21 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 #1through #10.

General Directions

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

Qx #4: This Global Response Assessment (GRA) question is ONLY completed at the treatment/follow-up visits.

5.4.22 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 #9, 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 #9 or as needed.

General Directions

Qx #3: Unacceptable medications as per eligibility requirement and per PI discretion.

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.

5.4.23 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.

5.4.24 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. It if 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
Participant Daily Medication Diary	PTDIARY
Clinic Correspondence Log	CCORRESP
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
Visit #5 Checklist	VISIT5
Visit #6 Checklist	VISIT6
Visit #7 Checklist	VISIT7
Visit #8 Checklist	VISIT8
Visit #9 Checklist	VISIT9
Visit #10 Checklist	VISIT10

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#2 (Protocol – CP02) 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 Participant Daily Medication Diary [PTDIARY]

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

Who: Participant-completed at home.

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

General Directions:

At Visit #2 the RC provides the participant with ***enough*** booklets for ***each*** week of the treatment phase of the study until Visit #6. At Visit #5 the RC then gives the participant enough booklets for either: the taper-down period (if the participant chooses **NOT** to continue into Phase II), **OR** the twelve weeks until Visit #9 (if the participant **DOES** choose to continue into Phase II). At Visit #9, the RC will then give the participant enough booklets for the taper-down period.

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

Instructions on exclusionary and cautionary medications are to be provided to the participant.

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

Referring to the photocopy of their medications, the participant is instructed to record new medications, changes in medications, and medications stopped each day.

If the participant has stopped taking a medication in between visits, they should record the stop date in the margin.

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

5.5.3 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.

5.5.4 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 participant information and CRF's between clinic sites in the event that a participant relocates to another CPCRN-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 2 Week Phone 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 4 Week Phone 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.

5.5.13 Visit #5 Checklist [VISIT5]

Binder: Case Report Form Binder

The Visit #5 Checklist [**VISIT5**] form lists all the forms and tests to be completed for Visit #5, 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.

5.5.14 Visit #4 Checklist [VISIT6]

Binder: Case Report Form Binder

The Visit #6 Checklist [**VISIT6**] form lists all the forms and tests to be completed for Visit #6, the 7 Week Phone visit. This form *must* be completed for every participant, and filed in the participant's study binder, if the participant is **not** continuing to Phase II.

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.

5.5.15 Visit #7 Checklist [VISIT7]

Binder: Case Report Form Binder

The Visit #7 Checklist [**VISIT7**] form lists all the forms and tests to be completed for Visit #7, the 7 Week Phone visit. This form *must* be completed for every participant, and filed in the participant's study binder, if the participant **is** continuing on to Phase II.

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.

5.5.16 Visit #8 Checklist [VISIT8]

Binder: Case Report Form Binder

The Visit #8 Checklist [**VISIT8**] form lists all the forms and tests to be completed for Visit #8, the 8 Week Phone 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.

5.5.17 Visit #9 Checklist [VISIT9]

Binder: Case Report Form Binder

The Visit #9 Checklist [**VISIT9**] form lists all the forms and tests to be completed for Visit #9, 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.

5.5.18 Visit #10 Checklist [VISIT10]

Binder: Case Report Form Binder

The Visit #10 Checklist [**VISIT10**] form lists all the forms and tests to be completed for Visit #10, the 13 Week Phone visit. This form *must* be completed for every participant, and filed in the participant's study binder, if the participant **is** continuing to Phase II.

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 second 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) participants 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 #2.

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 CPCRN2 – Protocol 2 Data Management System (DMS).

7.2 CPCRN2 Main Menu

Purpose: To allow access to CPCRN2 DMS system CC applications and CRFs for each protocol.

Users: Clinical center personnel:

- Data Management/Data Entry Personnel
- Research Coordinator

User Actions:

Open the "CPCRN2 – 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 "CP02" Button to open the "CPCRN2 Protocol 2 (CP02): Clinical Center Menu". The database logon dialog box will open.

Log on the database

1. Enter Username [Assigned by DCC helpdesk support]
2. Enter Password [Assigned by DCC helpdesk support]
   NOTE: Do not share USERNAME and PASSWORD information. The DMS tracks user actions based on this access information.
3. Enter Database **[PROD]**
4. Press "Connect" button
5. The **CPCRN2—Protocol 2 (CP02)** Menu appears
6. Dialog box displays user name and role
7. Press OK button

7.3 CPCRN2—Protocol 2 (CP02) 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.

2. Eligibility and Randomization

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

3. 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**], Dispensing Log **[DISP]**, Study Drug Compliance **[DCOMP]** 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, DISP, DCOMP and UNMASK entry.

4. 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.

5. **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.
6. **Reports Menu:** Opens the Reports Menu Application
7. **Cancel:** Exits the CPCRN2 – Protocol 2 (CPCRN2 CP02) 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 (2). 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.
2. **Enter the Participant Initials**
   a. Participant Initials must be 2 to 3 uppercase letters.
   b. Error message is given if less than 2 or more than 3 letters are entered or any character that is not a letter is entered.
   c. Warning message given for duplicate initials.
3. **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.
4. **Enter the Participant Birth Date**
5. **Enter the Participant Gender**
6. **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.

7. <u>Warning message given for duplicate SID.</u>

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. <u>Enter participant ID</u>

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.

2. <u>Enter participant initials</u>

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

b. If initials do not match, then an error message will be generated and user will not be able to proceed until the correct initials are entered.

3. Enter Clinical Center Number

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

4. Enter Visit Number

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

5. All four fields are mandatory.

6. 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.

7. 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**], Concomitant Medications **[CMED]**, 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 reports forms with multiple pages, the option to either proceed and move forward to next page of the form or move back to the preceding page is available. These buttons are not available during Verification.
j. Upon completing data entry for each case report form a Commit button will allow the entries for that form to be saved and moved onto the next. The verification process is completed with an Update button, which updates the data in the DMS.
k. The date cannot be changed after it has been saved (committed or updated).
l. After the last form has been entered, the entry process can be repeated for the next participant.
m. You will have the option of exiting the entry process at any time. The data entered on any unsaved forms will be lost.

8. 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).

9. 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.

10. 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.

11. 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:

1. Enter the participant ID

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

2. Enter participant initials

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

3. Enter Clinical Center Number

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

4. **Enter Visit Number**

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

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

6. **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**], Dispensing Log **[DISP]**, Study Drug Compliance **[DCOMP]** 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.

7. **After choosing to proceed:**

   a. The system will open the entry screens for each form in the appropriate order.
   b. If a form has been previously entered or marked as missing, a message will be issued indicating the form status. After acknowledging any form status messages, the next form is presented.
   c. The form entry screens will look like the Case Report Forms (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).

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

   a. Enter all data on the forms into the appropriate fields.

   b. The data fields fall into the following categories: alphabetic letter, alphanumeric, categorical, date, numeric, time, and free text. Specifications for these fields are described in the Data Field Specifications section.

   c. For case report forms with multiple pages, the option to either proceed and move forward to next page of the form or move backwards to the preceding page is available (for First Entry not for Verification).

d. Upon completing data entry for each case report form a Commit button will allow the entries for that form to be saved and move onto the next form.
e. The data cannot be changed after it has been saved.
f. After the last form has been entered, the entry process can be repeated for the next participant.

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

10. <u>Special Requirements for Adverse Events/Serious Adverse Events</u> [AE]**, <u>Concomitant Medications</u>** [CMED] **<u>and EPS and Urine Testing</u>** [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 **<u>cannot</u>** be deleted (or added). If this number is incorrect or has to be changed, record entry will have to be restarted.
c. Any number of records can be entered, but the number has to match the number of records initially indicated.

11. <u>Navigation</u>:

a. Mouse navigation is limited to use with the buttons and for revisiting fields in Adverse Events/Serious Adverse Events [AE], **Concomitant Medications** [CMED] **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).

12. <u>Verification</u>:

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 Adverse Events and Serious Adverse Events [**AE**], Concomitant Medications **[CMED]** and EPS and Urine Testing **[EUT]**; 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 CTC AE codes.

Users: Clinical center personnel
Research Coordinator

User Actions:

Choose "CRFs and References":

-- A portal will list the study documents, CRFs, and CTC AE 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:

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

1. **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 he same as the assigned to the center, an error message is given.
2. **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 data must be after the study start date and prior to the date of entry. If not, an error message is given.
3. **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.

4. **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.
5. **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.
6. **All five fields (Clinical Center Number, CRF Date, Month, Year, and RC ID) are mandatory.**

5. **After entering the mandatory fields, choose:**
   a. Proceed to enter the Pre-screening Summary [**PRESCR**] form, or
   b. Cancel to exit Pre-screening Summary.
6. **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), and
k. *Verified By:* The user name/ID of the person verifying the randomization number (should be the same as Randomized By).
j. *Date Ineligible:* The date that Screening and Eligibility CRF data indicated that the participant was marked as an ineligible participant.

3. <u>Form Status:</u>

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.

NOTE: This function also available via Web URL:
http://ssd2.cceb.med.upenn.edu/crcu_html/crcu_med_ref.htm

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 with be recorded as a "1" in the DMS. An unchecked value will be recorded as a NULL with the DMS. The check boxes may be checked using the keyboard space bar or (if the cursor is on the check box) the mouse. When the cursor is on the check box, it may not be readily apparent, so a message will be displayed in the lower left of the application window and the check box will be highlighted in red.

Date Fields

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

Numeric Field

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

Time Field

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

Free Text Fields

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

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

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

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.

Types of messages

a. Data entry messages that indicate data types and ranges for field entry.
b. Messages indicating the status of completing some application processes.
c. Messages indicating the number of choices in a list box.
d. Messages indicating the number of records returned from the DMS or number of records available to the application.

Dialog Boxes

1. *Location:* Messages pop up in dialog boxes.
2. *Required User Action*:
   - User should record all Error Messages indicating problems communicating with the DMS and report these problems to the help desk.
   - User must acknowledge the message by pressing the dialog box Ok button.

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 where pressed.
4) Messages indicating the status of completing some application processes.

7.14 CRCU Software Systems Help Desk

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.

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.uppcrn.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 SDCC Project Manager immediately. The Sponsored Project Help Desk will then take the necessary actions to deactivate that user's database account.

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 Time).

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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
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 #2
CPC	Chronic Prostatitis Cohort
CPCRN	Chronic Prostatitis Collaborative Research Network
CPCRN-2	the Second Chronic Prostatitis Collaborative Research Network
CPCRN-2 RCT #2	the second Randomized Controlled 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
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

ACRONYMS / ABBREVIATIONS	
HADS	Hospital Anxiety and Depression Scale
HIPPA	Health Insurance Portability and Accountability Act of 1996
IC	Interstitial Cystitis
IDS	Investigational Drug Service
IIEF	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 Indentifer
PRESCR	Pre-Screening Log
PRN	As Needed
PROGRESS	Progress Notes
PTCONT	Participant 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
RCT	Randomized Clinical Trial
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

ACRONYMS / ABBREVIATIONS	
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
VB-2	Voided Bladder Urine-2
VB-3	Voided Bladder Urine-3

MANUAL OF PROCEDURE

AGREEMENT PAGE

CPCRN-2 RCT #2

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: VISIT SCHEDULE

CPCRN 2

Randomized Clinical Trial #2 (Protocol – CP02)

Forms and Visit Schedule

	Phase I						Phase II			
	-1 to -4 Weeks (Screening)	0 Weeks (Random-ization)	2 Weeks (Follow-up)	4 Weeks (Follow-up)	6 Weeks (Follow-up)	7 Weeks (Follow-up)	7 Weeks (Follow-up)	8 Weeks (Follow-up)	12 Weeks (Follow-up)	13 Weeks (Follow-up)
Form Name	Visit 1 (B1 Clinic)	Visit 2 (B2 Clinic)	Visit 3 (Phone)	Visit 4 (Phone)	Visit 5 (Clinic)	Visit 6 (Phone)	Visit 7 (Phone)	Visit 8 (Phone)	Visit 9 (Clinic)	Visit 10 (Phone)
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	X	X	X	X	X	X
Randomization (RAND)		X								
Procedures and Labs										
Adverse Events/Serious Adverse Events (AE)		X	X	X	X	X	X	X	X	X
Concomitant Medications (CMED)		X	X	X	X	X	X	X	X	X
Clinical Lab Results (LABS)	X									
Demographics (DEMO)	X									
Dispensing Log (DISP)		X			X				X	
Drug Compliance (DCOMP)			X	X	X		X	X	X	
EPS and Urine Testing (EUT)	X				X					
Physical Exam (EXAM)	X									
Standard Telephone and Clinic Contact Summary (STCONT)			X	X	X	X	X	X	X	X
Urine Screening (URINE)	X									
Symptom Questionnaires										
Symptom Assessment (SYM)	X	X	X (GRA)	X (GRA)	X (GRA)	X (GRA)	X (GRA)	X (GRA)	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	

Forms and Visit Schedule

	Phase I						Phase II			
	-1 to -4 Weeks (Screening)	0 Weeks (Random-ization)	2 Weeks (Follow-up)	4 Weeks (Follow-up)	6 Weeks (Follow-up)	7 Weeks (Follow-up)	7 Weeks (Follow-up)	8 Weeks (Follow-up)	12 Weeks (Follow-up)	13 Weeks (Follow-up)
Form Name	Visit 1 (B1 Clinic)	Visit 2 (B2 Clinic)	Visit 3 (Phone)	Visit 4 (Phone)	Visit 5 (Clinic)	Visit 6 (Phone)	Visit 7 (Phone)	Visit 8 (Phone)	Visit 9 (Clinic)	Visit 10 (Phone)
The Sexual Health Inventory for Men® (SHIM)		X			X				X	
Participant Expectations Questionnaire (EXP)		X			X					
Pain Medication Questionnaire (PAIN)		X			X					
PRN Forms										
Study Stop Point (SSTOP)	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	X	
Treatment Stop Point (TSTOP)	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	X	
Unmasking Record (UNMASK)	PRN	PRN	PRN	PRN	PRN	PRN				
Administrative Forms										
Clinical Center Staff "Signature and Delegation of Responsibilities" Log (STAFFLOG)	X	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	
Participant Daily Medication Diary (PTDIARY)	X	X	X	X	X	X	X	X	X	
Participant ID Assignment Log (PTLOG)	X									
Participant Contact Information (PTCONT)	X									
Participant Transfer (TRANS)	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	
Study Drug Tracking Log (TRACK)		X	X	X	X	X	X	X	X	
Visit Checklist	X	X	X	X	X	X	X	X	X	

APPENDIX B: LYRICA® DRUG PACKAGE INSERT

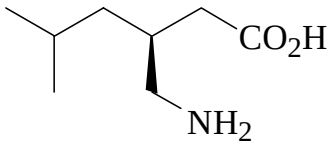
LYRICA

LYRICA® (pregabalin) 25, 50, 75, 100, 150, 200, 225, and 300-mg Capsules

CV

DESCRIPTION

Pregabalin is described chemically as (*S*)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23. The chemical structure of pregabalin is:



Pregabalin is a white to off-white, crystalline solid with a pK_{a1} of 4.2 and a pK_{a2} of 10.6. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is – 1.35.

LYRICA (pregabalin) Capsules are supplied as imprinted hard-shell capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg of pregabalin, along with lactose monohydrate, cornstarch, and talc as inactive ingredients. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells. The imprinting ink contains shellac, black iron oxide, propylene glycol, and potassium hydroxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

LYRICA (pregabalin) binds with high affinity to the alpha$_2$-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha$_2$-delta subunit may be involved in pregabalin's antinociceptive and antiseizure effects in animal models. *In vitro*, pregabalin reduces the calcium-dependent release of several neurotransmitters, possibly by modulation of calcium channel function.

While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to $GABA_A$, $GABA_B$, or benzodiazepine receptors, does not augment $GABA_A$ responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

Pharmacokinetics

Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours.

Absorption and Distribution

Following oral administration of pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is ≥90% and is independent of dose. Following single- (25 to 300 mg) and multiple- dose (75 to 900 mg/day) administration, maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated

administration, steady state is achieved within 24 to 48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data.

The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in C_{max} of approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats.

Metabolism and Elimination

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CLcr) (see **Special Populations**, **Renal Impairment and DOSAGE AND ADMINISTRATION**, **Patients with Impaired Renal Function**).

Special Populations

Race: In population pharmacokinetic analyses of the clinical studies in various populations, the pharmacokinetics of pregabalin were not significantly affected by race (Caucasians, Blacks, and Hispanics).

Gender: Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and pregabalin drug exposure is similar between genders.

Renal Impairment and Hemodialysis: Pregabalin clearance is nearly proportional to creatinine clearance (CLcr). Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified (see **DOSAGE AND ADMINISTRATION**, **Patients with Renal Impairment**).

Elderly: Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CLcr. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see **DOSAGE AND ADMINISTRATION**, **Patients with Renal Impairment**).

Pediatric Pharmacokinetics: Pharmacokinetics of pregabalin have not been adequately studied in pediatric patients.

Drug Interactions:

In Vitro Studies: Pregabalin, at concentrations that were, in general, 10-times those attained in clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. The potential of pregabalin to induce these enzymes has not been studied *in vitro*.

In Vivo Studies: The drug interaction studies described in this section were conducted in healthy adults, and across various patient populations.

Gabapentin: The pharmacokinetic interactions of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single-dose administration of

100-mg pregabalin and 300-mg gabapentin and in 18 healthy subjects following concomitant multiple-dose administration of 200-mg pregabalin every 8 hours and 400-mg gabapentin every 8 hours. Gabapentin pharmacokinetics following single- and multiple-dose administration were unaltered by pregabalin coadministration. The extent of pregabalin absorption was unaffected by gabapentin coadministration, although there was a small reduction in rate of absorption.

Oral Contraceptive: Pregabalin coadministration (200 mg three times a day) had no effect on the steady-state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 μg, respectively) in healthy subjects.

Lorazepam: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of lorazepam single-dose pharmacokinetics and single-dose administration of lorazepam (1 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Oxycodone: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of oxycodone single-dose pharmacokinetics. Single-dose administration of oxycodone (10 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Ethanol: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of ethanol single-dose pharmacokinetics and single-dose administration of ethanol (0.7 g/kg) had no effect on the steady-state pharmacokinetics of pregabalin.

Phenytoin, carbamazepine, valproic acid, and lamotrigine: Steady-state trough plasma concentrations of phenytoin, carbamazepine and carbamazepine 10,11 epoxide, valproic acid, and lamotrigine were not affected by concomitant pregabalin (200 mg three times a day) administration.

Population pharmacokinetic analyses in patients treated with pregabalin and various concomitant medications suggest the following:

Therapeutic class	Specific concomitant drug studied
Concomitant drug has no effect on the pharmacokinetics of pregabalin	
Hypoglycemics Diuretics	Glyburide, insulin, metformin, Furosemide
Antiepileptic Drugs	Tiagabine
Concomitant drug has no effect on the pharmacokinetics of pregabalin and pregabalin has no effect on the pharmacokinetics of concomitant drug	
Antiepileptic Drugs	Carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid

CLINICAL STUDIES

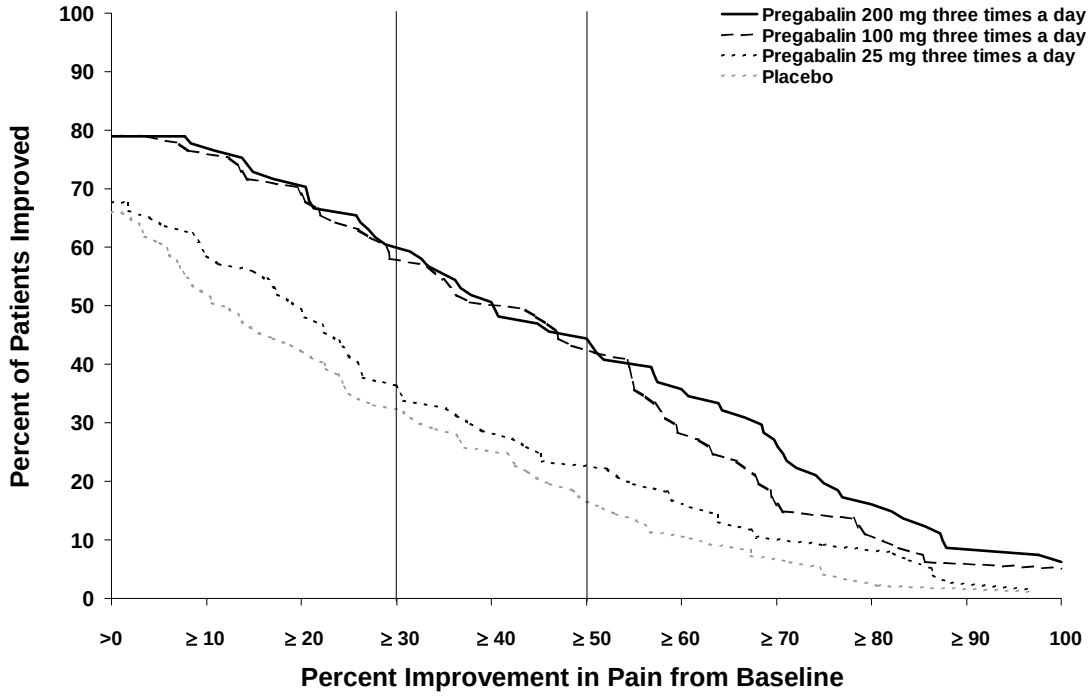
Neuropathic pain associated with diabetic peripheral neuropathy

The efficacy of the maximum recommended dose of LYRICA for the management of neuropathic pain associated with diabetic peripheral neuropathy was established in three double-blind, placebo-controlled, multicenter studies that enrolled 729 patients with three times a day dosing, two of which studied the maximum recommended dose.
Studies DPN 1 and DPN 2 enrolled a total of 483 patients of which 89% completed the studies. Patients enrolled had Type 1 or 2 diabetes mellitus with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for 1 to 5 years. The patients had a minimum mean baseline pain score of ≥4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). The baseline mean pain scores across the two studies ranged from 6.1 to 6.7. Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to pregabalin. Patients recorded their pain daily in a diary.

Study DPN 1: This 5-week study of 337 patients (240 pregabalin and 97 placebo) compared LYRICA 25, 100, or 200 mg three times a day with placebo. Treatment with LYRICA 100 and 200 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. There was no evidence of a greater effect on pain scores of the 200 mg three times a day dose than the 100 mg three times a day dose, but

there was evidence of dose dependent adverse effects (see **ADVERSE REACTIONS**). For various degrees of improvement in pain from baseline to study endpoint, Figure 1 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

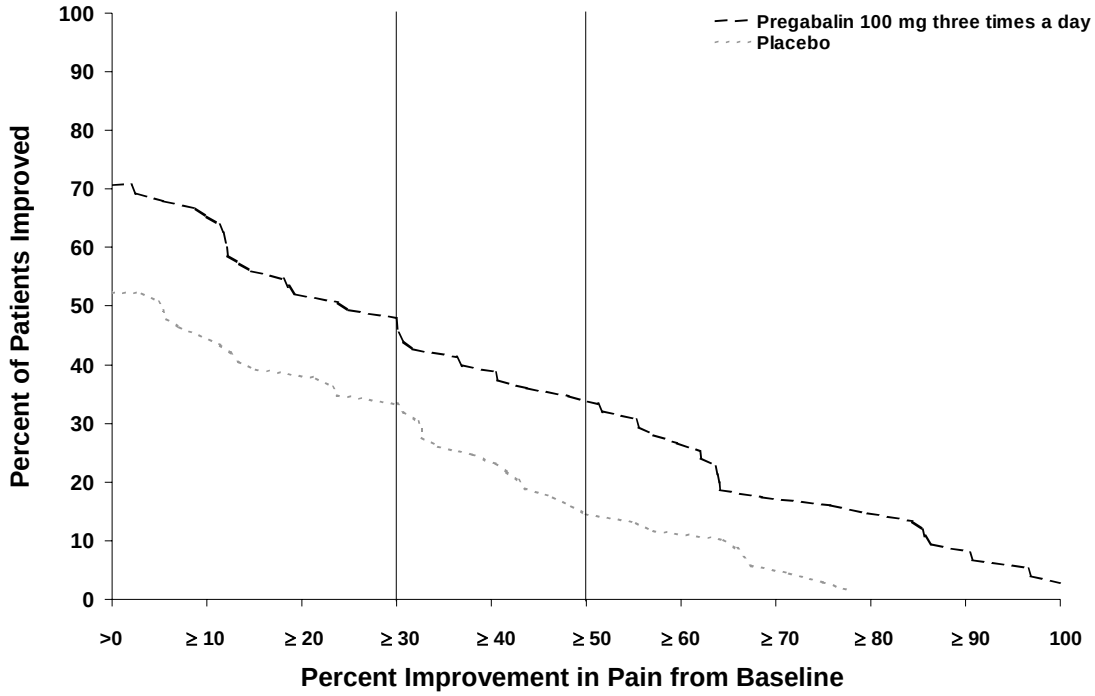
Figure 1: Patients Achieving Various Levels of Pain Relief



Study DPN 2: This 8-week study of 146 patients (76 pregabalin and 70 placebo) compared LYRICA 100 mg three times a day with placebo. Treatment with LYRICA 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figure 2 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not

complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 2: Patients Achieving Various Levels of Pain Relief

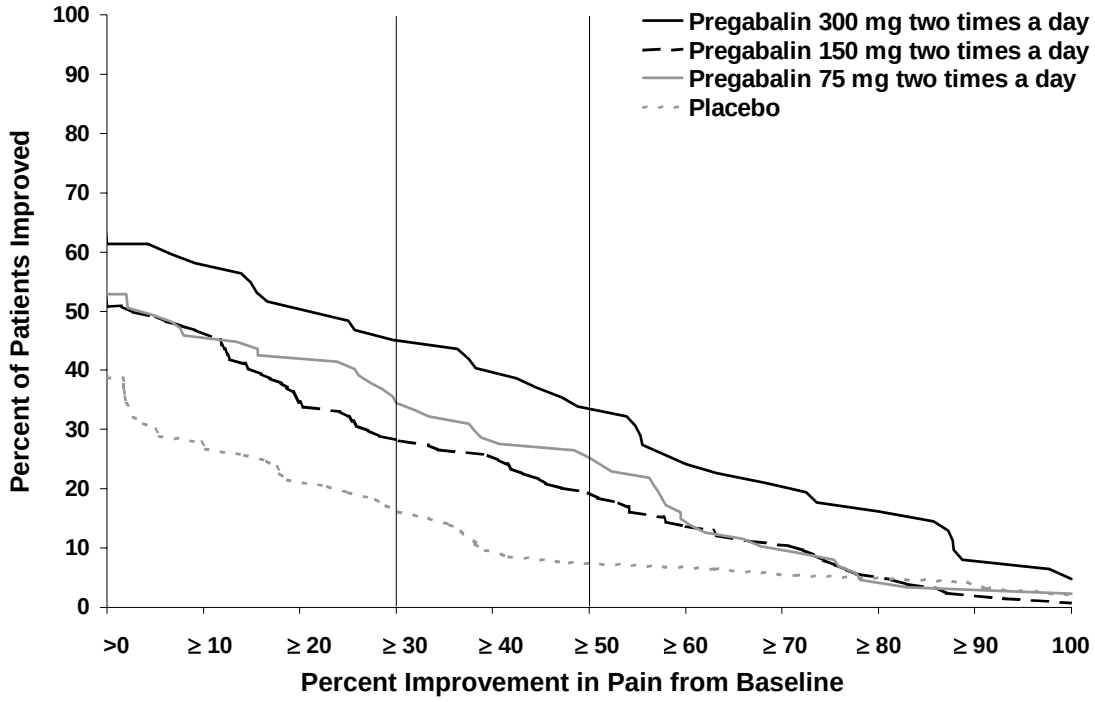


Postherpetic Neuralgia

The efficacy of LYRICA for the management of postherpetic neuralgia was established in three double-blind, placebo-controlled, multicenter studies. These studies enrolled 779 patients, of whom 566 completed the studies. These patients had neuralgia persisting for at least 3 months following healing of herpes zoster rash and a minimum baseline score of ≥4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). The baseline mean pain scores across the 3 studies ranged from 6 to 7. Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to pregabalin. Patients recorded their pain daily in a diary.

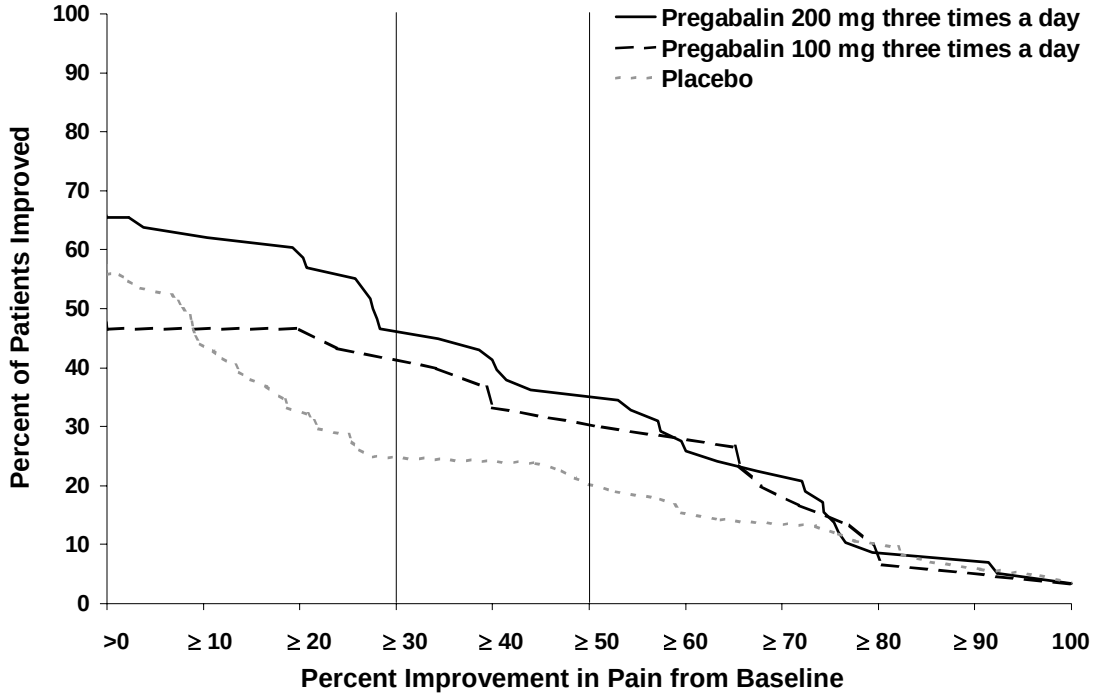
Study PHN 1: This 13-week study of 368 patients (275 pregabalin and 93 placebo) compared LYRICA 75, 150, and 300 mg twice daily with placebo. Patients with creatinine clearance (CLcr) between 30 to 60 mL/min were randomized to 75 mg, 150 mg, or placebo twice daily. Patients with creatinine clearance greater than 60 mL/min were randomized to 75 mg, 150 mg, 300 mg or placebo twice daily. In patients with creatinine clearance greater than 60 mL/min treatment with all doses of LYRICA statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Despite differences in dosing based on renal function, patients with creatinine clearance between 30 to 60 mL/min tolerated LYRICA less well than patients with creatinine clearance greater than 60 mL/min as evidenced by higher rates of discontinuation due to adverse events. For various degrees of improvement in pain from baseline to study endpoint, Figure 3 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 3: Patients Achieving Various Levels of Pain Relief



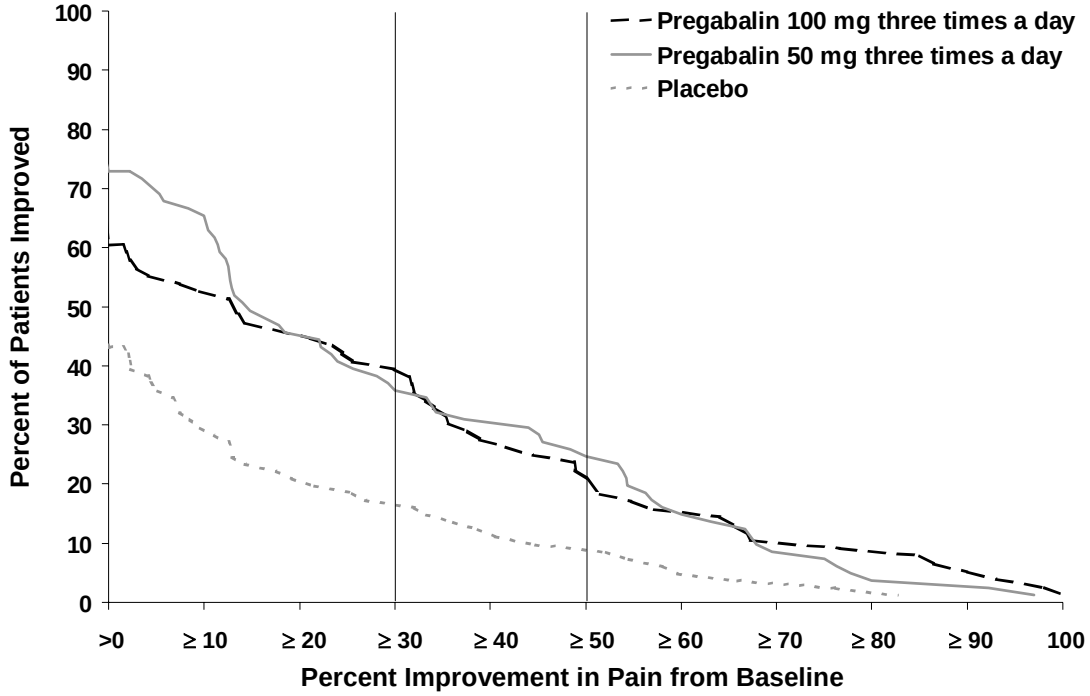
Study PHN 2: This 8-week study of 173 patients (89 pregabalin and 84 placebo) compared LYRICA 100 or 200 mg three times a day with placebo, with doses assigned based on creatinine clearance. Patients with creatinine clearance between 30 to 60 mL/min were treated with 100 mg three times a day, and patients with creatinine clearance greater than 60 mL/min were treated with 200 mg three times daily. Treatment with LYRICA statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figure 4 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 4: Patients Achieving Various Levels of Pain Relief



Study PHN 3: This 8-week study of 238 patients (157 pregabalin and 81 placebo) compared LYRICA 50 or 100 mg three times a day with placebo with doses assigned regardless of creatinine clearance. Treatment with LYRICA 50 and 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Patients with creatinine clearance between 30 to 60 mL/min tolerated LYRICA less well than patients with creatinine clearance greater than 60 mL/min as evidenced by markedly higher rates of discontinuation due to adverse events. For various degrees of improvement in pain from baseline to study endpoint, Figure 5 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 5: Patients Achieving Various Levels of Pain Relief



Epilepsy

The efficacy of LYRICA as adjunctive therapy in partial onset seizures was established in three 12-week, randomized, double-blind, placebo-controlled, multicenter studies in 1052 adult patients. Patients were enrolled who had partial onset seizures with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant antiepileptic drugs (AEDs). Patients taking gabapentin were required to discontinue gabapentin treatment 1 week prior to entering baseline. During an 8-week baseline period, patients had to experience at least 6 partial onset seizures with no seizure-free period exceeding 4 weeks. The mean duration of epilepsy was 25 years in these 3 studies and the mean and median baseline seizure frequencies were 22.5 and 10 seizures per month, respectively. Approximately half of the patients were taking 2 concurrent AEDs at baseline. Among the LYRICA-treated patients, 80% completed the double-blind phase of the studies.

Table 1 shows median baseline seizure rates and median percent reduction in seizure frequency by dose.

Table 1: Seizure Response in Controlled, Add-On Epilepsy Studies

Daily Dose of Pregabalin	Dosing Regimen	N	Baseline Seizure Frequency/mo	Median % Change from Baseline	p-value, vs. placebo
Study E1					
Placebo	BID	100	9.5	0	
50 mg/day	BID	88	10.3	-9	0.4230
150 mg/day	BID	86	8.8	-35	0.0001
300 mg/day	BID	90	9.8	-37	0.0001
600 mg/day	BID	89	9.0	-51	0.0001
Study E2					
Placebo	TID	96	9.3	1	
150 mg/day	TID	99	11.5	-17	0.0007
600 mg/day	TID	92	12.3	-43	0.0001
Study E3					
Placebo	BID/TID	98	11	-1	
600 mg/day	BID	103	9.5	-36	0.0001
600 mg/day	TID	111	10	-48	0.0001

In the first study (E1), there was evidence of a dose-response relationship for total daily doses of Lyrica between 150 and 600 mg/day; a dose of 50 mg/day was not effective. In the first study (E1), each daily dose was divided into two equal doses (twice a day dosing). In the second study (E2), each daily dose was divided into three equal doses (three times a day dosing). In the third study (E3), the same total daily dose was divided into two equal doses for one group (twice a day dosing) and three equal doses for another group (three times a day dosing). While the three times a day dosing group in Study E3 performed numerically better than the twice a day dosing group, this difference was small and not statistically significant.

A secondary outcome measure included the responder rate (proportion of patients with ≥50% reduction from baseline in partial seizure frequency). The following figure displays responder rate by dose for two of the studies.

Figure 6. Responder rate by study

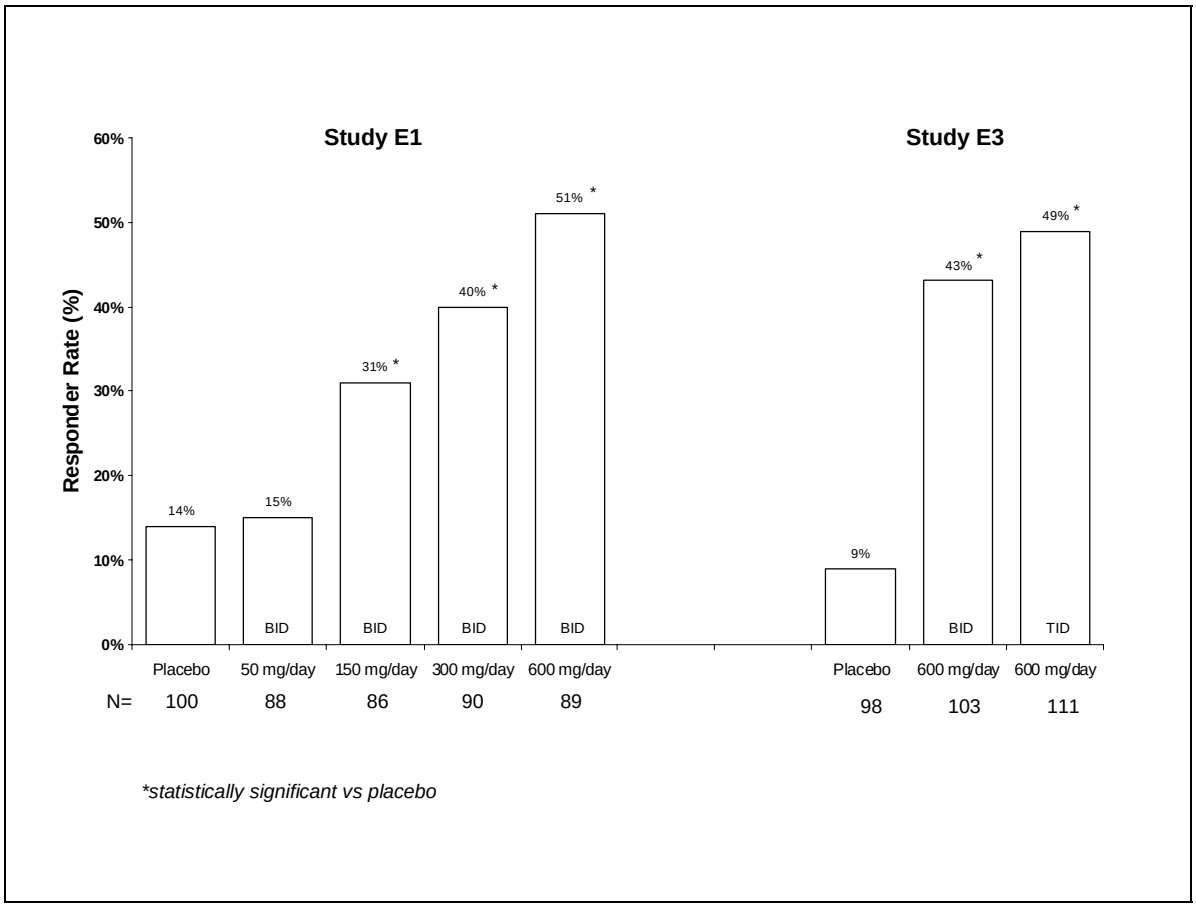
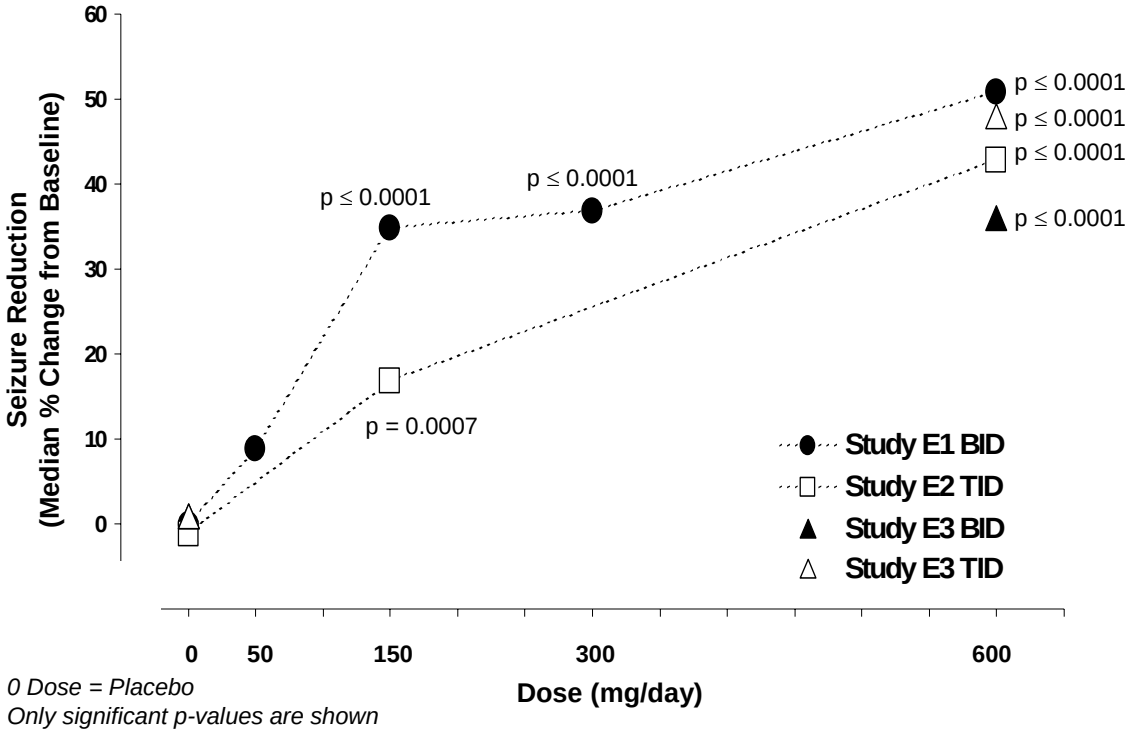


Figure 7. Seizure Reduction by Dose (All Partial Onset Seizures) for Studies E1, E2, and E3



Subset evaluations of the antiseizure efficacy of LYRICA showed no clinically important differences as a function of age, gender, or race.

INDICATIONS AND USAGE

LYRICA is indicated for management of

- Neuropathic pain associated with diabetic peripheral neuropathy
- Postherpetic neuralgia

LYRICA is indicated as adjunctive therapy for adult patients with partial onset seizures.

CONTRAINDICATIONS

LYRICA is contraindicated in patients with known hypersensitivity to pregabalin or any of its components.

WARNINGS

Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, pregabalin should be withdrawn gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If pregabalin is discontinued this should be done gradually over a minimum of 1 week.

Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies of pregabalin, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility**). The clinical significance of this finding is unknown. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients >12 years of age, new or worsening-preexisting tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with LYRICA, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

PRECAUTIONS

Dizziness and Somnolence

Pregabalin causes dizziness and somnolence. Patients should be informed that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery (see **PRECAUTIONS-Information for Patients**).

In the pregabalin controlled trials, dizziness was experienced by 29% of pregabalin-treated patients compared to 9% of placebo-treated patients; somnolence was experienced by 22% of pregabalin-treated patients compared to 8% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse events most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse events in short-term, controlled studies, dizziness persisted until the last dose in 31% and somnolence persisted until the last dose in 46% of patients.

Ophthalmological Effects

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision (6%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued pregabalin treatment due to vision-related events (primarily blurred vision).

Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated and 2% of placebo-treated patients.

Although the clinical significance of the ophthalmologic findings is unknown, patients should be informed that if changes in vision occur, they should notify their physician. If visual disturbance persists, further assessment should be considered. More frequent assessment should be considered for patients who are already routinely monitored for ocular conditions **(**See **PRECAUTIONS-Information for Patients)**.

Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, and diarrhea. Pregabalin should be tapered gradually over a minimum of 1 week rather than discontinued abruptly.

Weight Gain

Pregabalin treatment caused weight gain. In pregabalin controlled clinical trials of up to 13 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin-treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.2%) withdrew from controlled trials due to weight gain. Pregabalin associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema (see **Precautions-Peripheral Edema**).

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

Among diabetic patients, pregabalin-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin for at least 2 years, the average weight gain was 5.2 kg.

While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1C}).

Peripheral Edema

Pregabalin treatment caused edema, primarily described as peripheral edema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

In controlled clinical trials the incidence of peripheral edema was 6% in the pregabalin group compared with 2% in the placebo group. In controlled clinical trials, 0.6% of pregabalin patients and no placebo patients withdrew due to peripheral edema.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with pregabalin only, and 19% (23/120) of patients who were on both pregabalin and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on pregabalin only; and 7.5% (9/120) of patients on both drugs.

As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering LYRICA and these agents.

Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status**,** LYRICA should be used with caution in these patients.

Creatine Kinase Elevations

Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by

malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Laboratory Changes

Decreased Platelet Count

Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of 20 x 10^3/μL, compared to 11 x 10^3/μL in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and <150 x 10^3/μL. In randomized controlled trials, pregabalin was not associated with an increase in bleeding related adverse events.

ECG Changes

PR Interval Prolongation

Pregabalin treatment was associated with mild PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3-6 msec at pregabalin doses ≥300 mg/day. This mean change difference was not associated with an increased risk of PR increase ≥25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse events of second or third degree AV block.

Subgroup analyses did not identify an increased risk of PR prolongation in patients with baseline PR prolongation or in patients taking other PR prolonging medications. However, these analyses cannot be considered definitive because of the limited number of patients in these categories.

Information for Patients

Patients should be counseled that LYRICA may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive, operate complex machinery, or engage in other hazardous activities until they have

gained sufficient experience on pregabalin to gauge whether or not it affects their mental, visual, and/or motor performance adversely.

Patients should be counseled that LYRICA may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician (see **PRECAUTIONS**).

Patients should be advised to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, or diarrhea.

Patients should be counseled that LYRICA may cause edema and weight gain.

Patients should be advised that concomitant treatment with LYRICA and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure.

Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence.

Patients should be told to avoid consuming alcohol while taking LYRICA, as LYRICA may potentiate the impairment of motor skills and sedation of alcohol.

Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy.

Men being treated with LYRICA who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain (see **PRECAUTIONS, Carcinogenesis and Impairment of Fertility**).

Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with LYRICA. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with LYRICA was observed in clinical trials (see **Animal Toxicology**).

Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LYRICA.

Drug Interactions

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. In vitro and in vivo studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs (see **CLINICAL PHARMACOLOGY**).

Pharmacodynamics

Multiple oral doses of pregabalin were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when pregabalin was co-administered with those drugs. No clinically important effects on respiration were seen (see **PRECAUTIONS, Dizziness and Somnolence and Information for Patients**).

Animal Toxicology

Dermatopathy

Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the

maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies.

Ocular Lesions

Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) ≥2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for two years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD.

Mutagenesis

Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro*, was not clastogenic in mammalian systems *in vitro* and *in vivo*, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Impairment of Fertility

In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3-4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

In addition, adverse effects on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD.

In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established.

Human Data

In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo- and pregabalin-treated subjects in mean percent sperm with normal motility was <4% and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied.

Pregnancy

Pregnancy Category C

Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) ≥5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at ≥1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established.

When pregnant rabbits were given pregabalin (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD.

In a study in which female rats were dosed with pregabalin (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at ≥ 100 mg/kg and offspring survival was decreased at ≥ 250 mg/kg. The effect on offspring survival was pronounced at doses ≥1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at ≥250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD.

There are no adequate and well-controlled studies in pregnant women. LYRICA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effects of pregabalin on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures ≥50 times the mean human exposure ($AUC_{(0-24)}$ of 123 μg·hr/mL) at the maximum recommended clinical dose of 600 mg/day.

Use in Nursing Mothers: It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of pregabalin in pediatric patients have not been established.

In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses ≥50 mg/kg. The neurobehavioral changes persisted in animals tested after cessation of dosing and, thus, were considered to represent long-term effects.

The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established.

Geriatric Use

In controlled clinical studies of LYRICA in neuropathic pain associated with diabetic peripheral neuropathy, 306 patients were 65 to 74 years of age, and 88 patients were 75 years of age or older.

In controlled clinical studies of LYRICA in neuropathic pain associated with postherpetic neuralgia, 282 patients were 65 to 74 years of age, and 379 patients were 75 years of age or older.

In controlled clinical studies of LYRICA in epilepsy, there were only 10 patients 65 to 74 years of age, and 2 patients who were 75 years of age or older.

No overall differences in safety and efficacy were observed between these patients and younger patients. Even though the incidence of adverse events did not increase with age, greater sensitivity of some older individuals cannot be ruled out. LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function.

Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment, as noted in the **DOSAGE AND ADMINISTRATION** section.

ADVERSE REACTIONS

In all controlled and uncontrolled trials across various patient populations during the premarketing development of pregabalin, more than 10,000 patients have received pregabalin. Approximately 5000 patients were treated for 6 months or more, over 3100 patients were treated for 1 year or longer, and over 1400 patients were treated for at least 2 years.

Adverse Events Most Commonly Leading to Discontinuation in All Controlled Clinical Studies

In controlled trials of all populations combined, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the adverse events most frequently leading to discontinuation were dizziness (4%) and somnolence (3%). In the placebo group, 1% of patients withdrew due to dizziness and <1% withdrew due to somnolence. Other adverse events that led to discontinuation from controlled trials more frequently in the pregabalin group compared to the placebo group were ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, and peripheral edema (1% each)

Most Common Adverse Events in All Controlled Clinical Studies

In controlled trials of all patient populations combined, dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and "thinking abnormal" (primarily difficulty with concentration/attention) were more commonly reported by subjects treated with pregabalin than by subjects treated with placebo (≥5% and twice the rate of that seen in placebo).

Controlled Studies with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Adverse Events Leading to Discontinuation

In clinical trials in patients with neuropathic pain associated with diabetic peripheral neuropathy, 9% of patients treated with pregabalin and 4% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse events were dizziness (3%) and somnolence (2%). In comparison, <1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin group than in the placebo group, were asthenia, confusion, and peripheral edema. Each of these events led to withdrawal in approximately 1% of patients.

Most Common Adverse Events

Table 2 lists all adverse events, regardless of causality, occurring in ≥1% of patients with neuropathic pain associated with diabetic neuropathy in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse events with a maximum intensity of "mild" or "moderate".

Table 2 . Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	**75 mg/day [N=77] %**	**150 mg/day [N=212] %**	**300 mg/day [N=321] %**	**600 mg/day [N=369] %**	**All PGB* [N=979] %**	**Placebo [N=459] %**
Body as a whole						
Asthenia	4	2	4	7	5	2
Accidental injury	5	2	2	6	4	3
Back pain	0	2	1	2	2	0
Chest pain	4	1	1	2	2	1
Face edema	0	1	1	2	1	0
Digestive system						
Dry mouth	3	2	5	7	5	1
Constipation	0	2	4	6	4	2
Flatulence	3	0	2	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	4	6	9	12	9	2
Weight gain	0	4	4	6	4	0
Edema	0	2	4	2	2	0
Hypoglycemia	1	3	2	1	2	1
Nervous system						
Dizziness	8	9	23	29	21	5
Somnolence	4	6	13	16	12	3
Neuropathy	9	2	2	5	4	3
Ataxia	6	1	2	4	3	1
Vertigo	1	2	2	4	3	1
Confusion	0	1	2	3	2	1
Euphoria	0	0	3	2	2	0
Incoordination	1	0	2	2	2	0

Table 2 . Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	**75 mg/day [N=77] %**	**150 mg/day [N=212] %**	**300 mg/day [N=321] %**	**600 mg/day [N=369] %**	**All PGB* [N=979] %**	**Placebo [N=459] %**
Thinking abnormal[a]	1	0	1	3	2	0
Tremor	1	1	1	2	1	0
Abnormal gait	1	0	1	3	1	0
Amnesia	3	1	0	2	1	0
Nervousness	0	1	1	1	1	0
Respiratory system						
Dyspnea	3	0	2	2	2	1
Special senses						
Blurry vision[b]	3	1	3	6	4	2
Abnormal vision	1	0	1	1	1	0

*PGB: pregabalin

[a] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

[b] Investigator term; summary level term is amblyopia

Controlled Studies in Postherpetic Neuralgia

Adverse Events Leading to Discontinuation

In clinical trials in patients with postherpetic neuralgia, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse events were dizziness (4%) and somnolence (3%). In comparison, less than 1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring in greater frequency in the pregabalin group than in the placebo group, were confusion (2%), as well as peripheral edema, asthenia, ataxia, and abnormal gait (1% each).

Most Common Adverse Events

Table 2 lists all adverse events, regardless of causality, occurring in ≥ 1% of patients with neuropathic pain associated with postherpetic neuralgia in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. In addition, an event is included, even if the incidence in the all pregabalin group is not greater than in the placebo group, if the incidence of the event in the 600 mg/day group is more than twice that in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse events with a maximum intensity of "mild" or "moderate".

Table 3 . Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	**75 mg/d [N=84] %**	**150 mg/d [N=302] %**	**300 mg/d [N=312] %**	**600 mg/d [N=154] %**	**All PGB* [N=852] %**	**Placebo [N=398] %**
Body as a whole						
Infection	14	8	6	3	7	4
Headache	5	9	5	8	7	5
Pain	5	4	5	5	5	4
Accidental injury	4	3	3	5	3	2
Flu syndrome	1	2	2	1	2	1
Face edema	0	2	1	3	2	1
Digestive system						
Dry mouth	7	7	6	15	8	3
Constipation	4	5	5	5	5	2
Flatulence	2	1	2	3	2	1
Vomiting	1	1	3	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	0	8	16	16	12	4
Weight gain	1	2	5	7	4	0
Edema	0	1	2	6	2	1
Musculoskeletal system						
Myasthenia	1	1	1	1	1	0
Nervous system						
Dizziness	11	18	31	37	26	9

Table 3 . Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	**75 mg/d [N=84] %**	**150 mg/d [N=302] %**	**300 mg/d [N=312] %**	**600 mg/d [N=154] %**	**All PGB* [N=852] %**	**Placebo [N=398] %**
Somnolence	8	12	18	25	16	5
Ataxia	1	2	5	9	5	1
Abnormal gait	0	2	4	8	4	1
Confusion	1	2	3	7	3	0
Thinking abnormal[a]	0	2	1	6	2	2
Incoordination	2	2	1	3	2	0
Amnesia	0	1	1	4	2	0
Speech disorder	0	0	1	3	1	0
Respiratory system						
Bronchitis	0	1	1	3	1	1
Special senses						
Blurry vision[b]	1	5	5	9	5	3
Diplopia	0	2	2	4	2	0
Abnormal vision	0	1	2	5	2	0
Eye Disorder	0	1	1	2	1	0
Urogenital System						
Urinary Incontinence	0	1	1	2	1	0

*PGB: pregabalin

[a] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

[b] Investigator term; summary level term is amblyopia

Controlled Add-On Studies in Epilepsy

Adverse Events Leading to Discontinuation

Approximately 15% of patients receiving pregabalin and 6% of patients receiving placebo in add-on epilepsy trials discontinued prematurely due to adverse events. In the pregabalin treatment group, the adverse events most frequently leading to discontinuation were dizziness (6%), ataxia (4%), and somnolence (3%). In comparison, <1% of patients

in the placebo group withdrew due to each of these events. Other adverse events that led to discontinuation of at least 1% of patients in the pregabalin group and at least twice as frequently compared to the placebo group were asthenia, diplopia, blurred vision, thinking abnormal, nausea, tremor, vertigo, headache, and confusion (which each led to withdrawal in 2% or less of patients).

Most Common Adverse Events

Table 4 lists all dose-related adverse events, regardless of causality, occurring in at least 2% of all LYRICA-treated patients. Dose-relatedness was defined as the incidence of the adverse event in the 600 mg/day group was at least 2% greater than the rate in both the placebo and 150 mg/day groups. In these studies, 758 patients received pregabalin and 294 patients received placebo for up to 12 weeks. Because patients were also treated with 1 to 3 other AEDs, it is not possible to determine whether the following adverse events can be ascribed to pregabalin alone, or the combination of pregabalin and other AEDs. A majority of pregabalin-treated patients in these studies had adverse events with a maximum intensity of “mild” or “moderate”.

Table 4. Dose-related treatment-emergent adverse event incidence in controlled trials in Epilepsy (Events in at least 2% of all LYRICA-treated patients and the adverse event in the 600 mg/day group was ≥2% the rate in both the placebo and 150 mg/day groups

Body System - Preferred Term	**150 mg/d** [N = 185] %	**300 mg/d** [N = 90] %	**600 mg/d** [N = 395] %	**All PGB*** [N = 670][a] %	**Placebo** [N = 294] %
Body as a Whole					
Accidental Injury	7	11	10	9	5
Pain	3	2	5	4	3
Digestive System					
Increased Appetite	2	3	6	5	1
Dry Mouth	1	2	6	4	1
Constipation	1	1	7	4	2
Metabolic and Nutritional Disorders					
Weight Gain	5	7	16	12	1
Peripheral Edema	3	3	6	5	2
Nervous System					
Dizziness	18	31	38	32	11
Somnolence	11	18	28	22	11
Ataxia	6	10	20	15	4
Tremor	3	7	11	8	4
Thinking Abnormal[b]	4	8	9	8	2
Amnesia	3	2	6	5	2
Speech Disorder	1	2	7	5	1
Incoordination	1	3	6	4	1
Abnormal Gait	1	3	5	4	0
Twitching	0	4	5	4	1
Confusion	1	2	5	4	2
Myoclonus	1	0	4	2	0
Special Senses					
Blurred Vision[c]	5	8	12	10	4
Diplopia	5	7	12	9	4
Abnormal Vision	3	1	5	4	1

*PGB: pregabalin

a Excludes patients who received the 50 mg dose in Study E1.

b Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

c Investigator term; summary level term is amblyopia.

Adverse events occurring in ≥ 2% of patients with partial onset seizures in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group, but did not show dose-relatedness, include the following:

asthenia, infection, chest pain, vomiting, nervousness, nystagmus, paresthesias, visual field defect.

Other Adverse Events Observed During the Clinical Studies of LYRICA (pregabalin)

Following is a list of treatment-emergent adverse events reported by patients treated with LYRICA during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: **frequent** adverse events are those occurring on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those occurring in 1/100 to 1/1000 patients; **rare** events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the **WARNINGS** and **PRECAUTIONS** sections.

Body as a Whole – *Frequent:* Abdominal pain, Allergic reaction, Fever, *Infrequent:* Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction, Suicide attempt, *Rare:* Anaphylactoid reaction, Ascites, Granuloma, Hangover effect, Intentional Injury, Retroperitoneal Fibrosis, Shock, Suicide

Cardiovascular System –*Infrequent:* Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope; *Rare:* ST Depressed, Ventricular Fibrillation

Digestive System – *Frequent*: Gastroenteritis, Increased appetite; *Infrequent:* Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema; *Rare:* Aphthous stomatitis, Esophageal Ulcer

Hemic and Lymphatic System – *Frequent:* Ecchymosis; *Infrequent:* Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; *Rare:* Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocythemia

Metabolic and Nutritional Disorders – *Rare:* Glucose Tolerance Decreased, Urate Crystalluria

Musculoskeletal System – *Frequent*: Arthralgia, Leg cramps, Myalgia, Myasthenia; *Infrequent:* Arthrosis; *Rare:* Generalized Spasm

Nervous System – *Frequent:* Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching; *Infrequent:* Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia, *Rare:* Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Guillain Barre syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Psychotic depression, Schizophrenic reaction, Torticollis, Trismus

Respiratory System –*Rare:* Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn

Skin and Appendages – *Frequent:* Pruritus, *Infrequent:* Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; *Rare:* Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Petechial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule

Special senses– *Frequent:* Conjunctivitis, Diplopia, Otitis media, Tinnitus; *Infrequent:* Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; *Rare:* Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis

Urogenital System – *Frequent*: Anorgasmia, Impotence, Urinary frequency, Urinary incontinence, *Infrequent*: Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, *Rare*: Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis

Comparison of Gender and Race

The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: LYRICA is a Schedule V controlled substance.

In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, Lyrica (450mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30mg, single dose). In controlled clinical studies in over 5500 patients, 4 % of Lyrica-treated patients and 1 % of placebo-treated patients overall reported euphoria as an adverse event, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea (see **PRECAUTIONS**, Abrupt Discontinuation), suggestive of physical dependence.

Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior).

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

There is limited experience with overdose of pregabalin. The highest reported accidental overdose of pregabalin during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse events experienced by patients exposed to higher doses (≥900 mg) were not clinically different from those of patients administered recommended doses of pregabalin.

Treatment or Management of Overdose

There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with pregabalin.

Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

DOSAGE AND ADMINISTRATION

LYRICA™ is given orally with or without food.

Neuropathic pain associated with diabetic peripheral neuropathy

The maximum recommended dose of LYRICA is 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Dosing should begin at 50 mg three times a day (150 mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function (see **Patients with Renal Impairment)**.

Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse effects, treatment with doses above 300 mg/day are not recommended (see **ADVERSE REACTIONS**).

When discontinuing LYRICA, taper gradually over a minimum of 1 week.

Postherpetic neuralgia

The recommended dose of LYRICA is 75 to 150 mg two times a day, or 50 to 100 mg three times a day (150 to 300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Dosing should begin at 75 mg two times a day, or 50 mg three times a day (150 mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function (see **Patients with Renal Impairment)**.

Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 300 mg/day, and who are able to tolerate LYRICA, may be treated with up to 300 mg two times a day, or 200 mg three times a day (600 mg/day). In view of the dose-dependent adverse effects and the higher rate of treatment discontinuation due to adverse events, dosing above 300 mg/day should be reserved only for those patients who have on-going pain and are tolerating 300 mg daily (see **ADVERSE REACTIONS**).

When discontinuing LYRICA, taper gradually over a minimum of 1 week.

Epilepsy

LYRICA at doses of 150 to 600 mg/day has been shown to be effective as adjunctive therapy in the treatment of partial onset seizures in adults. The total daily dose should be divided and given either two or three times daily. Both the efficacy and adverse event profiles of LYRICA have been shown to be dose-related. In general, it is recommended that patients be started on a total daily dose no greater than 150 mg/day (75 mg two times a day, or 50 mg three times a day). Based on individual patient response and tolerability, the dose may be increased to a maximum dose of 600 mg/day.

The effect of dose escalation rate on the tolerability of LYRICA has not been formally studied.

The efficacy of add-on LYRICA in patients taking gabapentin has not been evaluated in controlled trials. Consequently, dosing recommendations for the use of LYRICA with gabapentin cannot be offered.

When discontinuing LYRICA, taper gradually over a minimum of 1 week.

Patients with Renal Impairment:

In view of dose-dependent adverse events and since LYRICA is eliminated primarily by renal excretion, the dose should be adjusted in patients with reduced renal function. Dosage adjustment in patients with renal impairment should be based on CLcr, as indicated in Table 3. To use this dosing table, an estimate of the patient's CLcr in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

$$CL_{Cr} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \; (\times \; 0.85 \text{ for female patients})$$

For patients undergoing hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see Table 3).

Table 5 : Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose (mg/day)[a]			Dose Regimen
≥60	150	300	600	BID or TID
30-60	75	150	300	BID or TID
15-30	25-50	75	150	QD or BID
<15	25	25-50	75	QD
Supplementary dosage following hemodialysis (mg)[b]				
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg				

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.

[a] Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

[b] Supplementary dose is a single additional dose.

HOW SUPPLIED

25-mg capsules:

White, hard-gelatin capsule printed with black ink “Pfizer“ on the cap, “PGN 25” on the body; available in:

Bottles of 90: NDC0071-1012-68

50-mg capsules:

White, hard-gelatin capsule printed with black ink “Pfizer“ on the cap, “PGN 50” and an ink band on the body, available in:

Bottles of 90: NDC0071-1013-68

75-mg capsules:

White/orange hard gelatin capsule printed with black ink “Pfizer“ on the cap, “PGN 75” on the body; available in:

Bottles of 90: NDC0071-1014-68

100-mg capsules:

Orange, hard-gelatin capsule printed with black ink “Pfizer“ on the cap, “PGN 100” on the body, available in:

Bottles of 90: NDC0071-1015-68

150-mg capsules:
White hard gelatin capsule printed with black ink “Pfizer“ on the cap, “PGN 150” on the body, available in:
Bottles of 90 : NDC0071-1016-68

200-mg capsules:

Light orange hard gelatin capsule printed with black ink “Pfizer“ on the cap, “PGN 200” on the body, available in:
Bottles of 90: NDC0071-1017-68

225-mg capsules:

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300-mg capsules:
White/orange hard gelatin capsule printed with black ink “Pfizer“ on the cap, “PGN 300” on the body, available in:
Bottles of 90: NDC0071-1018-68

Storage

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

Rx Only

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