# CPC PROTOCOL

## CHRONIC PROSTATITIS COHORT STUDY

## AMENDMENTS TO THE CPC STUDY PROTOCOL

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Second Edition: March 17, 1999

***Amendments to the CPC Study Protocol***

In response to input from the CPC External Advisory Committee and the CPCRN Steering Committee, the following amendments are being made to the CPC Study Protocol. These changes are effective immediately following the Steering Committee Meeting held on January 15,1999.

***Protocol Editions***

The Chronic Prostatitis Cohort (CPC) Study protocol describes the conduct of the multi-center, longitudinal study as the foundational tool to investigate a wide variety of scientific hypotheses about chronic prostatitis. The protocol was developed by the CPCRN (Chronic Prostatitis Collaborative Research Network), and will be maintained by the Data Coordinating Center (DCC) at the University of Pennsylvania over the course of the study through issuance of protocol revisions and amendments. The first edition of the protocol (dated 8/7/98) is being amended following extensive discussion by the Steering Committee during their January 1999 meeting. The revised edition of the CPC Study protocol (dated 3/17/99) will be referred to as the Second Edition.

**1.) DEFINITIONS**

**a.) PROSTATITIS**

The definition and classification of prostatitis symptoms for research studies established at the NIDDK consensus conference in 1996, (as originally summarized in the protocol) will be amended as follows:

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

| Text of Amendment: | Page 3. Replace lines # 31 – 41 with above text. |
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**b.) STANDARD UROLOGICAL PRACTICE**

The assumption of "standard urological practice" should be clarified. For example, a statement such as the following should precede the study criteria:

"Patients' clinical signs and symptoms will be assessed, documented and treated in a manner that is consistent with the standards of good urological practice. As such, each patient will be evaluated as deemed appropriate prior to consideration for CPC Study enrollment."

| Text of Amendment: | Page 5. Insert underlined sentence at line # 35. |
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## 2.) Study Criteria

a.) Inclusion Criteria

- Patients with symptoms of pain or discomfort in the pelvic region for at least three months duration within the last six months.

| Text of Amendment: | Page 5. Add underlined text to line # 44.<br>Page 13. Insert underlined text within line # 13. |
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b.) Exclusion Criteria

- Patients with a history of Genital Herpes will no longer be excluded from the CPC Study. (See Deferral Criteria.)

| Text of Amendment: | Page 6. Delete line # 31. Renumber subsequent Exclusion Criteria # 2 – # 9. |
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- Patients with the following Inflammatory Bowel Diseases: Crohn's Disease and Ulcerative Colitis, will be excluded from the CPC Study. Patients with Irritable Bowel Syndrome will not be excluded from the study.

| Text of Amendment: | Page 6. Replace line # 38 with text above. |
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c.) Deferral Criteria

- Patients who have been diagnosed with or treated for symptomatic Genital Herpes in the past twelve months will be deferred until they have been symptom free for a twelve-month period.

| Text of Amendment: | Page 6. Insert at line # 25 as Deferral Criteria # 6. |
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## 2.) SAMPLE SIZE/POWER CONSIDERATIONS FOR THE CPC STUDY

The Biostatistics group at the DCC should more fully describe the effects that can be demonstrated with this size cohort. For example, this same sample size will provide increased power for detecting longitudinal effects. See the following protocol sections.

### 2.4 SAMPLE SIZE/POWER CONSIDERATIONS FOR THE CPC STUDY

Each Clinical Research Center (CRC) will enroll approximately 35 patients with CP/CPPS into the CPC Study each year, beginning on November 9, 1998 (grant year 02), and continuing enrollment until August 31, 2001 (end of grant year 04). Assuming that each of the six (6) CRCs attain this accrual goal, the CPC Study will net 630 (35/yr. x 3 yrs. x 6 CRCs) patients with CP/CPPS. Although sample size justifications for such a multi-purpose cohort study require specifications of study design parameters for a wide variety of hypotheses, we considered investigating baseline associations in the CPC Study under a range of plausible study design characteristics (see Appendix A).

In addition to the measures for baseline comparisons described below, symptoms and other potentially time-dependent outcomes (*e.g.*, white blood cell counts) will be measured repeatedly over time (e.g., at the baseline visit, 1, 2, 3, 6, 9 and 12 months during the first year). It is expected that there may be trends towards improvement in symptoms due to an "intervention effect" of study participation, which will level off by three to six months after study initiation for each patient. Thus, once symptoms have stabilized within each patient, these repeated measurements may serve as replicates such that this cohort study design will have increased power to detect associations both among the individual components of the symptom index and between symptoms and these other measures. Appropriate clustered ("mixed effects") data models will be used to account for the within-patient replications in these analyses

### 2.4.1 Baseline Associations: *Binary Risk Factor*

Suppose the CPC Study patients are classified according to the presence or absence of a symptom (*e.g.*, pain exceeding a selected threshold) and a potential risk factor such as presence of a laboratory-based marker, such as elevated white count in EPS. Then, as displayed in Table 2 (Appendix A), assuming two-sided hypothesis testing at the 5% level, power of 80% for detecting odds ratios of 2.0 and 2.5, and proportions of patients with the symptom present ranging from 10% to 50%, the required sample size (after adjustment for clustering among clinical centers) ranges from 1,028 to 252. For example, these sample size projections in Table 2 indicate that baseline associations with odds ratios of 2.0 or greater can be detected with 80% power with a total sample size of 602 evaluable patients, provided that the selected symptom has a prevalence rate of at least 20%. For our proposed cohort size of 630 patients, if the prevalence of the selected symptom is less than 20%, these results in Table 2 indicate that the power may still approach 80% to detect associations with odds ratios somewhat larger than 2.5, even if the prevalence rate is only 10%.

### 2.4.2 Baseline Associations: *Continuous Risk Factor*

Suppose the CPC Study patients are classified according to the presence or absence of a symptom (*e.g.*,pain exceeding a selected threshold) and a potential risk factor measured on a continuous scale, such as the level of a laboratory-based marker, such as the white blood cell count in EPS. Then, as displayed in Table 3 (Appendix A), assuming two-sided hypothesis testing at the 5% level, power of 80% for detecting standardized effect sizes of 0.2, 0.3, 0.4 and 0.5, and proportions of patients with the symptom present ranging from 10% to 50%, the required sample size (after adjustment for clustering among clinical centers) ranges from 3,273 to 190. For example, these sample size projections in Table 3 indicate that for investigating standardized baseline mean differences of 0.4, a total sample size of 462 evaluable patients is required for symptoms with a prevalence of at least 20%, whereas a total sample size of 819 evaluable patients is required for symptoms with a prevalence of at least 10%. These results in Table 3 indicate that our proposed cohort size of 630 patients will be more than adequate to detect effect sizes of 0.3 s.d. units, provided the prevalence of the selected symptom is at least 30%, and effect sizes of 0.5 s.d. units, even if the prevalence of the selected symptom is only 10%. Conversely, these same calculations apply to analyses in which continuous symptom measures will be compared between two groups defined by a dichotomous baseline grouping measure.

### 2.4.3 Longitudinal Effects: Comparing Change Over Time

The primary rationale for collecting the longitudinal data within this CPC cohort study is to characterize the variability over time in the key symptoms and laboratory measures, in preparation for designing and conducting randomized clinical trials in patients with CP/CPPS. Since this CPC study design does not include a standard intervention, the resulting data will provide estimates for within-patient and between-patient variability in the natural treated (*viz*., usual care) history of CP/CPPS. Effects of limited institution-specific treatment trials will be accounted for in the statistical analyses by adjustments for clinical center effects and identification of treatment assignments. In addition, as mentioned above, evaluation of changes (if any) over time will allow assessment of the magnitude of an intervention effect, providing minimum estimates of placebo effects for future randomized trials.

Although specific longitudinal hypotheses have not been identified in advance, hypothesis-generating analyses focusing on differential patterns of change over time in symptoms or laboratory measures for subgroups identified by baseline factors will benefit from the increased statistical power due to the repeated measures and the within-patient correlations.

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| Text Amendment: | Page 7. Replace Section 2.4. Sample Size/Power |
| | Considerations for the CPC Study |
| | Page 7. Replace Section 2.4.1. Baseline Associations: |
| | Binary Risk Factor |
| | Page 8. Replace Section 2.4.2. Baseline Associations |
| | Continuous Risk Factors |
| | Page 8. Add Section 2.4.3. Longitudinal Effects: Comparing |
| | Change Over Time |

## 4) PATIENT RECRUITMENT

- The CPC Study will identify patients by referral source and zip code in order to more fully describe the study population.

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| Text of Amendment: | Page 9. Insert at line # 25. |

- In an effort to recruit minority patients, participating CPC Study clinical centers will seek the participation of primary care physicians, clinic sites and other referral sources not previously included in the CPC Study.

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| Text of Amendment: | Page 9. Insert at line # 22. |

## 5) LABORATORY PROCEDURES

- The FGT will be attempted one time only at Screening Visit #1 and at each subsequent clinic visit. Patients must be able to provide at least one of the following samples: EPS, VB3 or a semen sample, at SV1 or SV2, to be included in the study.

| Text of Amendment: | Page 10. Insert at line # 38. |
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- Patients are permitted to refuse to provide a semen sample. It is also acceptable if a patient is unable to provide a semen sample. However, patients not providing a semen sample, for whatever reason, must have provided at least one of either an EPS or VB3 sample.

| Text of Amendment: | Page 12. Add to line # 16. |
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- An alternative (to the Uricult paddle) laboratory plating procedure, will also be utilized at the clinical centers.

| Text of Amendment: | Page 11. Insert at line # 16. |
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**6) <u>DATA QUALITY CONTROL</u>**

The DCC is responsible for ensuring the quality of the data collected at each of the clinical centers through extensive data management techniques. These include the following:

h. Assemble a Quality Assurance/Quality Control Committee to monitor clinical center and DCC activities, and coordinate field visits.

| Text of Amendment: | Page 15. Add item h. to list at line # 19. |
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**7) <u>EXTERNAL ADVISORY COMMITTEE</u>**

The External Advisory Committee is comprised of the following physicians and researchers:

John N. Krieger, MD, Chairperson
Rodney U. Anderson, MD
Richard E. Berger, MD
Eric Bergstahl, MS
Claus Roerhborn, MD
Steve Tornetta

| Text of Amendment: | Page 19. Add list to line # 32. |
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