CHRONIC PROSTATITIS COHORT (CPC) STUDY PROTOCOL

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PROTOCOL

1. BACKGROUND

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

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

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

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

1. *Acute bacterial prostatitis* is an acute infection of the prostate.
2. *Chronic bacterial prostatitis* is a recurrent infection of the prostate.
3. *Chronic nonbacterial prostatitis/chronic pelvic pain syndrome* (CPPS), where there is no demonstrable infection. Subgroups of this class are:
   - 3.1 *Inflammatory chronic pelvic pain syndrome*, where white cells are found in the semen, 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.

Patients in Categories 1-3 are characterized by chronic pain; however, unlike patients in Category 1 & 2, patients with Category 3 prostatitis do not have any detectable infection of the prostate as determined by conventional microbiological techniques. Abnormalities in the EPS are the primary

objective features of Category 3 prostatitis and chronic pain is the primary subjective symptom. The majority of patients with chronic prostatitis are Type 3. (3)

The occurrence and persistence of pain as a primary presenting symptom is an important aspect of both diagnosis and outcome evaluation. In the recent review article in *Pain* by Egan and Krieger (6), they note that "chronic abacterial prostatitis is remarkably similar to chronic pain syndromes", and accordingly they make the case for therapy based on multidisciplinary approaches to pain management, rather than the traditional 'organ system' approach. Many therapies have been tried for chronic prostatitis, with a primary focus on improving bladder outlet resistance. However, the general consensus among clinical urology research investigators conducting therapy trials involving chronic prostatitis patients is well reflected in the recent summary of Nickel and Sorensen (4) that

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

In response to these growing concerns about the diagnosis and treatment of Chronic Prostatitis, the NIDDK funded the Chronic Prostatitis Clinical Research Network (CPCRN), comprised of six (6) Clinical Research Centers (CRCs) and a Data Coordinating Center (DCC), effective October 1, 1997. The primary research questions to be addressed by the CPCRN will encompass the diagnosis, etiology, natural history and prognosis, and the development of treatment strategies focused on Chronic Abacterial Prostatitis - Chronic Pelvic Pain Syndrome (CPPS). In support of these broad research goals, the CPCRN formed Working Groups to coordinate the development of a longitudinal Chronic Prostatitis Cohort (CPC) Study, the development and validation of a symptom severity index for CPPS, as well as other laboratory and clinical outcome measures. Ultimately, the goals of the CPCRN are to conduct well-controlled, multicenter epidemiological studies and therapeutic trials aimed at providing definitive answers to the unresolved questions of diagnosis and treatment of CPPS.

2. STUDY DESIGN: THE CHRONIC PROSTATITIS COHORT (CPC)

The CPCRN identified the formation of a multi-center, longitudinal Chronic Prostatitis Cohort (CPC) Study as the foundational tool to investigate a wide variety of scientific hypotheses. This CPC Study is designed to investigate the characteristics of patients with symptomatology consistent with CP/CPPS and to determine the treated history of CP. During an initial year of protocol development, the CPCRN will develop valid and reliable symptom severity indexes, outcome measures, diagnostic tools and responsive quality of life measures, so that meaningful natural history and prognostic hypotheses can be explored. The Clinical Research Centers (CRCs) will then begin recruiting patients using broad inclusion/exclusion criteria, to participate in a longitudinal cohort study, while receiving usual care for their CP/CPPS condition. Extensive patient data will be collected at baseline screening and follow-up visits and entered into a centralized database. The target accrual of patients is approximately 35 patients per year at 6 clinical centers, resulting in 210 patients enrolled into the CPC per year. Over the course of 3 years of accrual, this will result in a cohort of approximately 630 patients.

Six Clinical Centers will enroll patients into the CPC Study:

1. Brigham and Women's Hospital & Massachusetts General Hospital, Harvard University Medical School, Boston, MA 02115
2. Temple University Hospital, Temple University, Philadelphia, PA 19140
3. University of Maryland Medical System, University of Maryland School of Medicine, Baltimore, MD 21201

4. Northwestern University Medical School, Northwestern University, Chicago, IL 60611
5. Harbor - UCLA Medical Center, University of California at Los Angeles, Los Angeles, CA 90024
6. Kingston General Hospital, Queen's University, Kingston, Ontario, Canada K7L 2V7

2.1 SPECIFIC AIMS

The goal of the Chronic Prostatitis Cohort (CPC) Study is to assemble and follow a cohort of patients with Chronic Pelvic Pain Syndrome (CPPS). The specific aims are to

i) better define the condition Chronic Prostatitis (CP) or Chronic Pelvic Pain Syndrome (CPPS);
ii) develop techniques to aid in the diagnosis of CP;
iii) characterize the patient with CP;
iv) study the natural history and prognosis of patients with CP;
v) set the stage to conduct epidemiological studies to address etiologic hypotheses;
vi) set the stage to begin clinical trials and offer effective therapy for CP.

To implement this CPC Study, a centralized, standardized registry containing data on patients at baseline screening and longitudinal follow-up will include demographic and diagnostic information, dietary habits, patient and family medical history, symptoms, and treatments and their outcomes. In addition, serum and prostatic fluid specimens will be stored in specimen banks for future use by qualified investigators.

2.2 STUDY TIME FRAME

A pilot study to test patient recruitment and screening procedures at the Clinical Research Centers (CRCs), data collection and data entry procedures, and internet communications between the CRCs and the DCC will begin on October 12, 1998. (Two patients in each of the 6 Clinical Centers will be recruited for the pilot study). The full-scale CP Cohort study will begin on November 9, 1998, and recruitment of approximately 630 patients will continue for 3 years until 2001.

2.3 STUDY POPULATION

The study population of particular interest is the group of male patients with symptomatology consistent with Chronic Prostatitis (CP) or Chronic Pelvic Pain Syndrome (CPPS). Any potential study participant must meet a set of basic criteria before being considered a candidate for the complete screening process. 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.

2.3.1 *Inclusion Criteria*

Any patient satisfying all of the following criteria will pass the screening for inclusion:

1. Male.

2. Having symptoms of discomfort or pain in the pelvic region for at least three months duration within the last six months.

2.3.2 *Deferral Criteria*

There are several physical conditions for which a patient will be deferred from entry into the CPC Study. Once it is formally ascertained that the condition is not present or has subsided, the patient will be reconsidered for entry into the CPC Study. The following list identifies the conditions for deferment and the criteria that a patient must meet in order to be evaluated further for entry into the study:

1. If a patient has been treated with antimicrobial agents within the last three months, he will be deferred until he has been treatment free for three months. This period of time will include the three months prior to screening.

2. If a patient has had a positive urine culture in the past 3 months (as reported by the patient), or has had a positive urine culture laboratory value of >100,000 CFU/ml, the patient will be deferred until he is without the condition for 3 months;

3. If a patient has any of the following sexually transmitted diseases; Gonorrhea, Chlamydia, Mycoplasma, Trichomonas, he will be deferred until he has been off treatment and symptom free for three months.

4. If a patient has had a prostate biopsy within the last three months, he will be deferred until three months from the date of the procedure.

5. If a patient has been told by a health care professional that he had epididymitis within the last three months, he will be deferred until he has been off treatment and symptom free for three months.

6. If a patient has been diagnosed with or treated for symptomatic Genital Herpes in the past twelve months, he will be deferred until he has been symptom free for a twelve-month period.

2.3.3 *Exclusion Criteria*

Any patient satisfying any one of the following criteria will not be eligible to participate in the CPC Study. Exclusion criteria will not be ongoing throughout the study. Patients experiencing any of the exclusion criteria during the follow-up phase of the study will continue to be tracked and included in the cohort study. However, it will be noted in follow-up data if a patient has developed any of the exclusion criteria.

1. Patients with a history of prostate, bladder or urethral cancer.

2. Patients with the following Inflammatory Bowel Diseases: Crohn's Disease and Ulcerative Colitis, <u>will be excluded</u> from the CPC Study. Patients with Irritable Bowel Syndrome <u>will not be excluded</u> from the study.

3. Patients who have been treated with BCG.

4. Patients with unilateral orchalgia, without pelvic symptoms.

5. Patients with an active urethral stricture.

6. Patients with a neurological disease or disorder affecting the bladder.

7. Patients with a history of TURP, TUIP, TUIBN, TUMT, TUNA, balloon dilation, or any other prostate surgery or treatment such as cryotherapy or thermal therapy.

8. Patients with a history of pelvic radiation, systemic or intravesical chemotherapy.

9. Patients with a neurological impairment or psychiatric disorder preventing their understanding of consent and their ability to comply with the protocol.

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.

2.5 INFORMED CONSENT

At the start of Screening Visit #1, after the Research Coordinator (RC) determines that a patient meets the inclusion criteria, but prior to the thorough screening process, an informed consent will be obtained from each patient. The parent or guardian of patients under 18 years of age will be asked to sign the informed consent form. Only one informed consent will be required for each patient. That is, at Screening Visit #1, the patient will provide informed consent for the baseline screening procedures, as well as for all follow-up procedures. Prior to obtaining a patient's informed consent, participants will be informed of all aspects of the study, including baseline screening procedures, follow-up procedures, assurance of patient confidentiality, and potential risks and benefits to the patient (see Appendix B).

3. STUDY PLAN

The CPC Study comprises two distinct phases for each participating patient: i) the *screening phase* and ii) the *longitudinal follow-up phase* (see Appendix C). The screening phase, which assesses a patient's eligibility to participate in the CPC Study, comprised of two to three clinic visits scheduled as closely together as possible. Ideally, all screening clinic visits will be completed in a 2-3 week period. Screening criteria must be completed within 30 days of the initial visit in order for a patient to remain eligible for study participation. Any patient failing any of the inclusion or exclusion criteria will be treated according to usual clinical care, but will not be eligible to participate in the follow-up phase. Any patient passing all of the inclusion, deferral and exclusion criteria will receive all baseline screening tests/procedures and will be eligible to participate in the longitudinal follow-up phase. Patients participating in this phase will be followed until the close of the CPC Study, with six contacts during year 01, four by telephone (at 1, 2, 3, and 9 months post-screening) and two times by a physician's office visit (at 6 and 12 months post-screening). Duration of follow-up will vary depending upon the patient's study enrollment date. In subsequent years, patients will be followed by two physician visits and two telephone contacts. The phone calls will take place during months 3 and 9 of every patient-year, and the clinic visits on months 6 and 12 of every patient-year (see Appendix D).

3.1 PATIENT RECRUITMENT

Patient recruitment will be conducted through the urology clinic at each of the participating Clinical Research Centers (CRCs). Patients referred to the CRCs with symptoms suggestive of CP/CPPS will be introduced to the CPC Study by the Research Coordinator and by a one-page flyer describing the study (see Appendix E). In an effort to recruit minority patients, participating CPC Study centers will seek the participation of primary care physicians, clinic sites and other referral sources not previously included in the CPC Study network. Potentially eligible patients will then be asked whether they are interested in participating in the study. The CPC Study will identify patients by referral source and zip code in order to more fully describe the study population.

3.2 PATIENT SELECTION

Initially every potential study participant will undergo a series of screening procedures that take approximately 2 - 3 weeks to complete. The screening phase entails at least two clinic visits. The screening process may take three visits, depending on procedure completion. The data collected and diagnostic procedures completed during this phase are identified below (see Sections 3.2.1 and 3.2.2), in the order in which they will be obtained or undergone. The order of the procedures identified below has been selected to ensure that eligibility criteria checked by non-invasive methods precede those checked by more invasive methods, and to provide a balance of patient comfort and timeliness.

3.2.1 *Screening Visit #1*

During each patient's first screening visit, he will complete the following questionnaires and undergo the following examinations. If a patient fails any of the study eligibility criteria, based on the data collected during this visit, he would not be required to complete the physical examination, urinalysis, or urine culture for the purposes of the study. If a patient meets all of the eligibility criteria checked during this screening visit, the following forms and procedures will be completed and the patient will proceed to Screening Visit #2.

1. *Inclusion/Exclusion/Deferral Criteria.*
Each patient will complete a preliminary screening form that checks whether he meets the initial inclusion/exclusion/deferral criteria. Each patient will provide the research staff with his age and an assessment of his pain/discomfort.

2. *Patient Contact Information.*
Patients will be asked to provide the clinical center with their address, phone umber, primary care physician, and the name and address of two other contacts. This information will be stored at the CRC only and available only to pertinent study personnel.

3. *1-day Voiding Log supplies and directions.*
Each patient will be provided with a voiding log. The patient will be asked to select a typical day, record the date, and then record the time and amount of each urination during a complete 24 hour time period. The patient will be asked to return the completed log at Screening Visit #2.

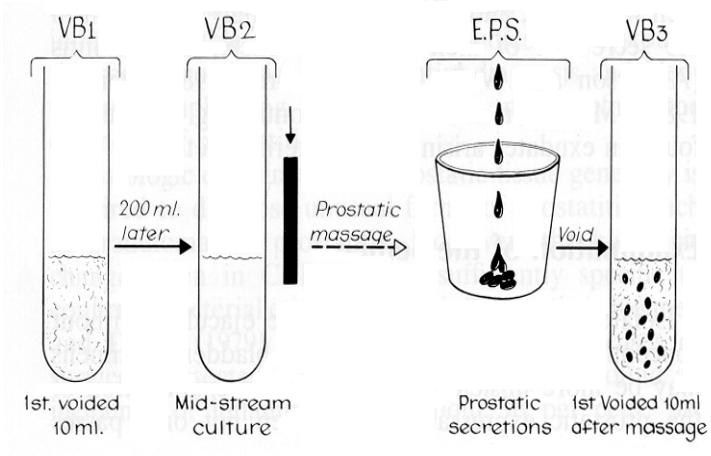
4. *Patient Medical History.*
Each patient will provide the research staff with his general medical history and specific genitourinary medical history. In particular, the patient will be asked to provide information regarding his disease and surgical histories.

5. *Patient Symptom/Impact/General Quality of Life Index*
Each patient will provide the research staff with an assessment of his discomfort/pain by completing the chronic prostatitis symptom index and a condition specific impact index. In addition, patients will complete the SF-12, a general Quality of Life Index.

6. *Prior Prostatitis Diagnoses and Treatments.*
Each patient will provide the research staff with information regarding procedures and treatments for chronic prostatitis symptoms.

7. *Physical Examination.*
Each patient will undergo a focused physical examination. This examination will include an abdominal exam, external genital exam, rectal exam, prostate exam, and perineal exam.

8. *Urinalysis, urine and EPS specimens for microscopy and culture.*
Each patient will provide the research staff with 3 urine specimens and an EPS (expressed prostatic secretion) specimen for analysis and culture. The urine specimen will be collected via the classic “four-glass test” described in Meares and Stamey (7). 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.



The results from the EPS culture and the post-EPS urine (VB_3), if available, will be compared with the findings from the 1st voided urine (VB_1) and the midstream urine (bladder specimen or (VB_2). A macroscopic urinalysis will be completed to quantify hemoglobin, protein, and glucose levels, and a microscopic urinalysis will be completed to quantify white blood cells, red blood cells and yeast. All specimens will be cultured for 5 days, with results recorded at 48 hours and 5 days. Although the urinalysis will be performed at the respective CRC, all centers will be required to use the same brand of dipstick (see Appendix F). An alternative (to the Uricult paddle) laboratory plating procedure, will also be utilized at the clinical centers.

9. *Serum Sample collection*.
Up to 10 mls of venous blood (which amounts to approximately 1 tube of blood), will be collected from each patient. The specimen will be stored at the CRC Laboratory in the frozen serum bank for future research use (see Appendix G).

10. *Visit close-out.*
   i. Appointment scheduling. An appointment will be made for Screening Visit #2.

   ii. Concomitant medications. Each patient will receive instructions from the RC to bring to Screening Visit #2 all of the over-the-counter and prescribed medications that he is currently taking.

3.2.2 *Screening Visit #2*

During this screening visit, each patient will complete the questionnaires and/or undergo the examinations described below.

1. *1-Day Voiding Log*.
The research staff will collect each patient's 1-day voiding log, and check for its completeness.

2. *Epidemiologic Questionnaire.*
Each patient will provide the research staff with his demographic information, including date of birth (age), race, marital status, socioeconomic status, level of education, dietary habits and sexual history.

3. Concomitant Medications.
The research staff will record the types of medications currently being taken by the patient. In addition, during the visit the patient will be asked to self-report any additional concomitant

medications. Patients will be asked to recall their medications if they fail to bring them to the second screening visit.

4. *Uroflow study.*
Uroflow is the only noninvasive urodynamic test available. It is a reflection of the final result of the act of voiding and is therefore influenced by a number of variables. These include the effectiveness of muscular contraction, completeness of sphincter relaxation, and the patency of the urethra (see Appendix G).

5. *Urethral Swab.*
A urethral swab will aid in assessment of urethral infection as a possible contaminant of subsequent cultures (see Appendix G).

6. *Semen Sample.*
Analysis of seminal plasma is an important tool in the evaluation of cytokines as a possible immunologic response in the CP syndrome (see Appendix G). 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.

7. *Visit close-out.*
Appointment scheduling. An appointment will be made to follow-up the patient approximately one month after the completion of this screening visit. This follow-up contact will be a telephone call.

3.3 PATIENT FOLLOW-UP SCHEDULE

3.3.1 *Follow-up Telephone Contacts (Months 1, 2, 3, 9, 15, 21, 27 and 33)*.

During months 1, 2, 3, 9, 15, 21, 27 and 33, every patient will receive a follow-up telephone contact from the RC, beginning one month after the completion of his final screening visit. Duration of follow-up will vary depending on patient enrollment date. During this contact, each patient will provide the research staff with information on his status since the last contact. The following form will be completed during this contact:

1. *Symptom/Impact/General Quality of Life Index.* Each patient will provide the research staff with an assessment of his discomfort/pain by completing the chronic prostatitis symptom index, impact index and the SF-12.

2. Appointment scheduling. An appointment will be made for the next scheduled contact.

3.3.2 *Brief Clinic Visit (Month 6, 18, and 30)*

During months 6, 18, and 30, after initial enrollment in the follow-up phase, the patient will have a clinic visit, in which he will provide the research staff with the requested information and undergo the procedures identified below.

1. *Symptom/Impact/General Quality of Life Index.* This form is described under Screening Visit #1. (See section 3.2.1)

2. *Interim Health Care Assessment*. The research staff will request information regarding any non-chronic prostatitis related medical events, surgical procedures and hospitalizations that occurred since the last clinic visit. The patient will also provide the research staff with information regarding recent prostatitis treatment.

3. *Urinalysis, urine and EPS microscopy*. This form is described under Screening Visit #1.

4. *Physical exam*. The patient will have a focused physical exam as indicated by the physician.

5. *Visit close-out.*

   i) Appointment scheduling. An appointment will be made for the next scheduled contact.

3.3.3 Yearly Clinic Visit (Month 12, 24 and 36)

During months 12, 24 and 36 after initial enrollment in the follow-up phase, the patient will have an annual clinic visit, in which he will provide the research staff with the requested information and undergo the procedures identified below.

1. *1-day Voiding Log*. The research staff will collect each patient's 1-day voiding log, and check for its completeness.

2. *Symptom/Impact/General Quality of Life Index*. This form is described under Screening Visit #1.

3. *Interim Health Care Assessment*. The research staff will request information regarding any non-chronic prostatitis related medical events, surgical procedures and hospitalizations that occurred since the last clinic visit. The patient will also provide the research staff with information regarding recent prostatitis treatment.

4. *Physical exam*. The patient will have a focused physical exam as indicated by the physician.

5. *Urinalysis, urine and EPS specimens for microscopy and culture*. This form is described under Screening Visit #1.

6. *Visit close-out.*

   i) Appointment scheduling. An appointment will be made for the next scheduled contact.

3.3.4 *Patient Follow-up*

Each of the six clinical centers in the CPC Study will have the same target accrual of patients per year. The success of the study depends heavily on the ability of clinical centers to retain enrolled patients throughout their follow-up phase. The DCC will monitor enrollment and timeliness of

follow-up for all patients; however, the onus of keeping patients interested in the study resides in the hands of the clinical center staff. Clinical centers may offer a designated phone line for study patients and easy access to study personnel and medical information as incentives to continued participation in the study.

4. HUMAN SUBJECTS

4.1 STUDY POPULATION

Any male patient presenting with symptoms of pain and/or discomfort in the pelvic region which persist for at least 3 months, within the last six months, will be considered a candidate for enrollment into the study. The study population of particular interest is the group of patients with symptomatology consistent with CP.

4.2 RECRUITMENT AND CONSENT PROCEDURES

Patient recruitment will be conducted through referrals to the urology clinic at each of the participating CRCs. Patients may be self-referred or referred through their primary physician (either solicited or unsolicited by the urology clinic). Patients referred to the clinics with symptoms suggestive of the CP/CPPS will be introduced to the CPC Study by the CRC Research Coordinator and by a one-page flyer describing the study (see Appendix E). Potentially eligible patients will then be asked whether they are interested in participating in the study.

If the patient expresses interest in participating, and passes the initial inclusion criteria, the patient will be asked to sign one informed consent form, providing consent for both the screening procedures and the follow-up procedures. Prior to signing the informed consent, the Research Coordinator will go over the consent form orally with the patient, and answer any questions that the patient has concerning participation in the CPC Study. The original signed consent form will be kept in a separate file at the Clinical Center, while a copy of the signed consent form will be given to the patient.

4.3 PATIENT CONFIDENTIALITY

Extensive efforts will be made to ensure that the patient's confidentiality is maintained. Each patient will be assigned a unique study identification number. A log of the patient names, patient ID numbers, and pertinent registration information (*e.g.* home address, telephone number, and emergency contact person) will be maintained in a locked file cabinet at each Clinical Center. The staff at the Data Coordinating Center will not have access to this log. Only the patient ID number will be given to the Data Coordinating Center staff and entered into the CPC Study. Any communication between the Data Coordinating Center staff and the Clinical Center staff regarding patient data will occur via this patient ID number.

4.4 INFORMED CONSENT

Each Clinical Center will prepare an informed consent form following the guidelines of their local Institutional Review Board (IRB). The form will, at a minimum, contain a description of the potential risks, benefits, and expense to the subject, and identify risk management procedures and the risk-benefit ratio.

5. DATA COORDINATION AND STATISTICAL ANALYSIS

5.1 DATA COORDINATION

The Data Coordinating Center (DCC) will coordinate all activities pertaining to i) development, production, testing and distribution of data forms; ii) collection, entry, verification and validation of data;

and iii) data management and quality assurance. Data management issues, especially those concerning data quality and integrity in multicenter trials as discussed extensively in Meinert (8) DeMets (9) Neaton (10) and Bailey(11), will be addressed. Appendix H illustrates data and specimen flow and reporting patterns between the Clinical Centers and the DCC. The DCC, in collaboration with the CRC Principal Investigators (PI), has developed a set of case report forms that will be tested, and altered accordingly, during the Pilot Study. The DCC will develop and maintain a computerized Data Management System for the CPC Study that will be deployed in each of the Clinical Centers.

5.1.1 Data Quality Control

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

a. Distributing the Protocol, Manual of Operations, and all study reports,
b. Designing and maintaining a complete set of case report forms,
c. Reviewing all forms for completeness,
d. Performing thorough validation and querying processes,
e. Tracking laboratory forms and specimens,
f. Participating in official NIH site visits of all CRCs, to be conducted yearly, and
g. Maintaining complete documentation of the data quality process.
h. Assemble a Quality Assurance/Control Committee to monitor clinical center and DCC activities, and coordinate field visits.

The DCC will also be subject to official NIH site visits, to ensure that the data management techniques are valid and complete.

5.2 STATISTICAL ANALYSIS

The PI and Co-investigators of the DCC will provide overall leadership for the biostatistical and epidemiological study design issues, the selection of relevant comparison subgroups and variables, and the choice of the statistical analysis plans, in close cooperation with the Steering Committee and study investigators. The general biostatistical strategies that will be used to meet the specific aims of the CPC Study are outlined below**.** Details of sample size calculations related to specific hypotheses are outlined in Section 2.4 and Appendix A.

5.2.1 General Methods for Statistical Analysis

A brief overview of some of the statistical methods that may be used at the time of analysis, both for descriptive purposes and in more comprehensive analysis of the primary research questions, is summarized in the following sections. It is recognized that these methods may be revised and additional ones considered as the details of the specific analyses are developed.

Standard descriptive statistics will be used to describe baseline characteristics and follow-up measures, both overall and within comparison subgroups. Summary statistics such as means, medians, standard deviations, and ranges will be produced for measured variables. Frequencies will be tabulated for categorical and ordinal variables. Graphical methods will be used extensively to examine distributions, identify potential influential points, and guide in data transformations if warranted. For outcomes collected longitudinally, and to examine associations among various measures, scatterplots and grouped boxplots will be produced to examine assumptions of linearity, symmetry, and heteroscedascity.

5.2.2 *Baseline Descriptive Analyses*

Estimates of the distribution of age, race, and other demographic characteristics of CP patients, both overall and stratified by levels of baseline severity and CP diagnostic classification, will be produced. Summary statistics for selected characteristics of family medical history and personal medical history, as well as symptoms, diagnostic procedures and treatments, will also be generated. Analyses will be conducted both combined across centers and separately for each Clinical Center, in order to evaluate center to center differences in patient populations. Due to the observational nature of these data, hypothesis tests for differences in the distribution of baseline characteristics across disease categories will be conducted within a general randomization model framework. This framework includes the Mantel-Haenszel test, as well as its generalizations to incorporate ordinal factors and ordinal response variables, implemented easily within SAS PROC FREQ. Therefore a wide range of questions involving differences of patient characteristics among CP diagnostic classification levels, adjusted for clinical center effects, can be addressed. These methods, as well as examples of their use in similar studies, are described in (12-14) and (15)

5.2.3 *Baseline Association Patterns*

Investigation of the potential relationships between medical history factors, diagnostic procedure results, symptoms, and the CP symptom index will be explored initially within a descriptive framework, producing correlation coefficients and contingency table measures of association, depending on the measurement scale of the variables under consideration (binary, nominal, or ordinal). Furthermore, the relative importance of each factor among a reduced set of selected variables will be assessed within the framework of a variational model, such as a multiple logistic regression model, multiple logit model or an ordinal logit model. These methods have been described and illustrated extensively in the text by Agresti (16), and have been expanded to accommodate adjustments for clustering within clinics for binary response data in (17-22) and for nominal and ordinal scale data in (23,24). In particular, the GEE methodology outlined in (18-20) and implemented within the SAS macro documented in (21) has been used successfully within the DCC to develop predictive models to assess the relative effects of multiple risk factors adjusted for clustering of observations within patients or clinics.

5.2.4 *Longitudinal Profiles*

The treated history of CP patients will be investigated within a longitudinal study design in which each patient is re-evaluated at successive follow-up intervals (see follow-up schedule in Appendix D). A wide range of hypotheses concerning changes over time in these CP patients are of interest. In general, analyses will focus on within-patients patterns of change over time and differences in these patterns of change between groups defined by relevant diagnostic and risk factor information. Models for longitudinal changes will include adjustment for other baseline factors and covariates, such as baseline severity on the CP symptom index.

Statistical methods appropriate for the analyses of these data will include growth curve and profile analysis methods tailored for both continuous and categorical longitudinal data (25). In particular, predictive models investigating sources of variation in the CP symptom index for patients with varying lengths of follow-up can be implemented within the GEE framework outlined in (18)and (19). Regression diagnostics will be used for all models to assess model adequacy and examine potential outlying or influential datapoints. The sample sizes outlined in Appendix A have been designed to provide adequate power to detect baseline associations. For outcomes measured repeatedly over time, the power for comparisons among groups will depend on the frequency of follow-up, degree of patient withdrawal and actual patterns of change over time, but will in general be greater than for the cross-sectional analyses.

For some outcome variables, time-to-event methods may be appropriate and will use standard survival analysis methods including Kaplan-Meier plots, logrank tests, and Cox proportional hazards modeling (26).

5.2.5 Missing Data and Incomplete Follow-up

It is expected that 20-30% of patients may withdraw prior to the final assessment at 3 years of follow-up. In addition, length of follow-up will differ among patients depending on the time of study entry. For example, patients entered into the study during the first year will have considerably more return visits than those entered near the end of the study. The statistical methods for longitudinal data analysis outlined above allow for staggered entry and differential lengths of follow-up among patients. However, careful attention will be paid to the varying length of follow-up among patient subgroups, especially those defined by baseline severity, in order to evaluate any potential bias introduced by differential follow-up among patient subgroups. The characteristics of patients without complete follow-up will be examined. All attempts will be made to keep missing data to a minimum and all available data on all patients will be used for the primary analyses.

5.2.6 Interim Analyses

In addition to the on-going monitoring of data quality conducted as part of standard data management procedures (as cited in Section 5.1), two interim analyses of the accruing data will be conducted prior to completion of data collection and follow-up on all patients. The purpose of these analyses is to provide initial information on baseline and follow-up data and allow assessment of assumptions regarding baseline distributions of demographic and disease-related parameters. Since this is an observational cohort study, no formal methods of adjustment for comparisons using sequential methods for study monitoring will be used. However, issues both of multiple comparisons and reduced power will be considered in the evaluation of results. The first of these analyses will be conducted when complete baseline data are available on approximately one half of the projected total number of patients (approximately 315). This analysis is expected to occur mid-way through Year 02 (May, 2000) of accrual and will focus on overall baseline distributions of patient characteristics, especially characteristics related to disease severity. The second interim analysis will be conducted when at least one year of longitudinal follow-up is available on these patients and will provide initial analyses of patterns of change and variability over time in preparation for design of future studies including potential clinical trials. It is expected that the second interim analysis will take place around May, 2001. The final analysis of all baseline and follow-up data on all patients will begin when accrual and follow-up on the full cohort are complete around March, 2002, to allow 6 months for the primary analyses to be completed before the end of the funding period.

6. STUDY ORGANIZATION

The CPC Study organization includes 6 Clinical Research Centers, a Data Coordinating Center, a Steering Committee, an External Advisory Committee, NIDDK Project Staff, and several working subcommittees. The responsibilities of each component are described below.

6.1 CLINICAL RESEARCH CENTERS

The responsibilities of each Clinical Center include:

1. Recruiting and following patients throughout the course of the five-year study.
2. Confirming eligibility of each patient based on the study criteria identified in the protocol.
3. Adhering to study protocol in the implementation of procedures and the acquisition of data.
4. Collecting data of high quality.

5. Collaborating with other study investigators in the development of the manual of operations, acquisition of high quality data, and the analysis and publication of study results.

6.2 DATA COORDINATING CENTER

The Data Coordinating Center will provide administrative, biostatistical, epidemiological and data management leadership for the CPC Study in the design/conduct of collaborative research programs. Additional responsibilities include:

1. Preparation of the study protocol, manual of operations, and questionnaires, based on collaboration with the Steering Committee and NIDDK Project Scientists.
2. Provision of overall leadership in the biostatistical and epidemiological study designs for etiologic, diagnostic, natural history and prognostic studies.
3. Collaboration with other study investigators in the development and testing of data questionnaires and study procedures.
4. Development of data and specimen tracking procedures.
5. Provision of an efficient data management system, accessible through the popular world wide web (www) technology.
6. Development of validation protocols to study objective laboratory-based findings.
7. Training of Clinical Research Center staff and monitoring clinic performance in overall study procedures.
8. Coordination of Steering Committee and External Advisory Committee meetings.
9. Preparation of detailed reports regarding patient recruitment and retention, data collection activities, and interim results to the External Advisory Committee.
10. Collaboration with study investigators in the analysis and publication of study results.

6.3 STEERING COMMITTEE

The Steering Committee is the primary governing body of the CPC Study. Steering Committee members include the NIDDK Project Scientists, and the principal investigators from each of the Clinical Research Centers and the Data Coordinating Center. Although other study investigators will often attend meetings, all major scientific decisions will be made by the Steering Committee (one vote for each member). The primary responsibilities of the Steering Committee include:

1. Identifying the specific aims of the study.
2. Determining study eligibility criteria.
3. Developing the study plan.
4. Developing the study protocol and manual of operations, and participating in forms development.
5. Overseeing standardized implementation of the study protocol.
6. Establishing subcommittees, as needed.
7. Reviewing and approving all publications based on any data collected for the CPC Study.
8. Monitoring overall study quality control.
9. Approving outside study investigators for access to data and stored specimens for their own epidemiological and clinical studies.
10. Establishing the time line for the study.
11. Establishing the goals and the agenda for Steering Committee meetings.

6.3.1 Basic Science Studies

Clinical centers will conduct basic science research projects in support of the overall goals of the CPCRN. These studies will be conducted in parallel to the CPC Study. As preliminary data from basic science projects are analyzed, opportunities to expand the most promising investigations to more of the clinical centers will be explored. Based on these results, targeted studies addressing etiologic, diagnostic and prognostic issues will be proposed utilizing the CPC Study and appropriately selected control groups.

6.3.2 Publication Policies

From within the membership of the CPCRN, a Publications, Presentations, & Ancillary Studies (PP&AS) Committee will be formed to address issues regarding the presentation and dissemination of study information. The preparation of all publications or presentations must be assigned by the Steering Committee to specifically appointed writing committees. The authorship policy of the CPC Study is to recognize all participants of the CPC professional staff, as well as to recognize individual effort. The Chairman of the PP&AS Committee will establish a schedule and formal review process for all materials submitted, according to specific guidelines described in the Manual of Operations and Procedures.

6.3.3 Ancillary Studies

Any ancillary study must be undertaken with careful consideration of its impact on the objectives of the CPC Study. To protect the integrity of the major study, a proposal to conduct an ancillary study must be reviewed by the PP&AS Committee before its initiation. Guidelines describing the format, submission and approval process for ancillary studies are outlined in detail in the Manual of Operations and Procedures.

6.4 EXTERNAL ADVISORY COMMITTEE

The External Advisory Committee (EAC) is an independent advisory group composed of experts in relevant medical, statistical, and bioethical fields. The primary responsibility of the Committee is to periodically review the progress of the CPC Study, and provide advice to the NIDDK Project Scientists regarding the scientific merit of the study. The EAC is comprised of the following physicians and researchers:

John N. Kreiger, MD, Chairperson
Rodney U. Anderson, MD
Richard E. Berger, MD
Eric Bergstahl, MS
Claus Roehrborn, MD
Steven Tornetta

6.5 NIDDK PROJECT SCIENTIST

The NIDDK Project Scientist's primary responsibility is to provide scientific support in all aspects of the CPC Study, including protocol development, quality control, interim data monitoring, final data analysis and interpretation, preparation of publications, and performance monitoring.

6.6 WORKING SUBCOMMITTEES

The Steering Committee establishes working subcommittees as needed to carry out various tasks to achieve the specific aims. Subcommittees established thus far, include Committee on the CPC Protocol, Committee on Symptom Index Development, Laboratory Measures Committee, and Basic Science Projects Committee.

7. PROJECT COLLABORATORS

7.1 CLINICAL CENTER INVESTIGATORS

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