MULTIDISCIPLINARY APPROACH TO PELVIC PAIN (MAPP)

TRANS-MAPP EPIDEMIOLOGY AND PHENOTYPING (EP) STUDY PROTOCOL

Sponsored by: The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), Department of Health and Human Services (DHHS)

PROTOCOL – VERSION 5

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1 INTRODUCTION

1.1 Overview

Urological Chronic Pelvic Pain Syndromes (UCPPS) are characterized by pelvic pain with concurrent urinary symptoms. Broadly, UCPPS comprise Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS) in men and women, and Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) in men. IC is a debilitating bladder disorder characterized by urinary urgency, frequency, and pain. The presentation of symptoms can be quite variable among patients, suggesting that IC is a multi-factorial syndrome with several proposed etiologies, some of which may be interrelated.[1] PBS, as defined by the International Continence Society, is "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology."[2] PBS is a clinical description of disease based on the patient's symptoms, and does not depend on urodynamic or cystoscopic findings. These symptoms may be related to IC, although diagnostic criteria are still lacking for this entity, and the relationship between PBS and IC is not clear. For clarity and compliance with current nomenclature, this protocol will use the term IC/PBS. CP/CPPS or NIH type IIIA/IIIB prostatitis is also characterized by pelvic pain and voiding symptoms, in the absence of proven urinary tract infection or other obvious pathology. CP/CPPS is also a clinical description based on symptoms, and does not depend on urodynamic or cystoscopic findings.

1.2 Burden of Urological Chronic Pelvic Pain

As with many chronic pain disorders, UCPPS are poorly understood and characterized, and treatment is mostly empirical and unsatisfactory. Estimates of prevalence of the syndromes vary widely. In 1990, IC was thought to affect as many as 500,000 U.S. citizens, with 25% of the patients under age 25.[3] Estimates in 2002, using expanded definitions of IC/PBS, now exceed 10 million.[4] Quality of life for patients with IC/PBS can be worse than for patients with end-stage renal disease.[5] As for IC/PBS, estimates of the prevalence of CP/CPPS vary similarly: community based surveys demonstrated a prevalence of 8%,[6] and can be as high as 11.5% in men younger than age 50.[7]

1.3 Mission and Structure of the MAPP Research Network

The NIDDK-funded Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network is focused on a broader approach to the study UCPPS than previously undertaken. A wide range of scientific discovery projects, moving beyond the previous traditional bladder- and prostate-focused efforts, are conducted at six Discovery Sites. Investigations include the relationship between UCPPS and other chronic pain conditions, including fibromyalgia (FM), chronic fatigue (CF) syndrome, and irritable bowel syndrome (IBS), innovative epidemiological studies, search for clinically important biomarkers, investigation of bacterial, viral and other infectious causative/exacerbating agents, novel brain imaging studies, and animal studies to better understand the pathophysiology of these often disabling syndromes.

In addition to the six Discovery Sites, the MAPP research network includes a Data Coordinating Core (DCC), responsible for providing biostatistical expertise, promoting network-wide quality assurance standards, including a comprehensive data management system (DMS), and providing comprehensive project and administrative support. The MAPP research network also includes a Tissue Analysis and Technology Core (TATC), responsible for providing tissue and other sample collection, banking, analyses, and coordination with the NIDDK Biorepository. Further details of the structure of the MAPP network are provided in Section 8.

1.4 Overarching Hypotheses and Aims of the MAPP Research Network‡

1. The coordinated, multisite efforts of the MAPP Research Network will allow the creation of a large database of individuals with UCPPS, measured at baseline and followed longitudinally for one year, as well as asymptomatic and disease comparator controls (e.g., CFS, FM, IBS) measured only at baseline, who will be extensively phenotyped for a number of symptom-based and biological domains. This large longitudinal dataset will, for the first time, allow identification of biologically-derived subsets of individuals with UCPPS who: (a) have differing underlying pathogenesis resulting in their symptoms, and (b) would likely respond to different treatments. Findings from these translational studies will logically inform the next generation of clinical trials for UCPPS.
2. There are two subsets of UCPPS patients: those with primarily pelvic symptoms, and those who also display many non-urological symptoms and syndromes. These latter individuals have a more systemic condition, characterized by a different natural history than those with isolated UCPPS symptoms, including a higher likelihood of: (a) symptom progression or continuation, (b) symptom variability, and (c) decreased quality of life and increased healthcare seeking behavior than those with primarily pelvic symptoms.
3. Individuals with UCPPS who have been symptomatic for longer periods of time (operationalized as two years or more, for this study) will have greater overall symptoms, decreased quality of life, and greater psychological co-morbidities than individuals with more recent (two years or less) onset of symptoms.
4. IC/PBS in females and CP/CPPS in males represent the same underlying condition. Using common phenotyping protocols in both males and females, the high rate of non-urological symptoms and syndromes noted previously in women with IC/PBS will also be noted in men with CP/CPPS.
5. Just as in other “central pain” conditions, such as FM and IBS, a variety of stressors (dietary, infectious, psychological) will be shown in longitudinal studies to predict worsening of symptoms (flares). Biomarker studies performed during these flares will identify neurohormonal factors in urine and plasma that increase during increased disease activity and decrease during quiescent periods.
6. Groups of individuals with UCPPS exhibit a lower overall pain threshold (i.e., hyperalgesia) compared to asymptomatic controls. This left-shift in stimulus-response function in the entire group of UCPPS patients will be noted, both on experimental pain testing, as well as functional neuroimaging. This finding in the entire group of UCPPS patients will be shown to be driven by the subset of UCPPS patients with the more “systemic” form of the disease noted in Hypothesis 2 above.
7. Specific objective abnormalities (i.e., potential biomarkers) can be identified that are associated with specific risk factors (Hypothesis 5) and to specific pain processing and functional neuroimaging patterns (Hypothesis 6).
8. Disease development in subsets of UCPPS patients results from an underlying pathogenic process, and symptom exacerbations (flares) may be influenced by changes in pathogen type or quantity.
9. Animal models identifying sensitization pathways and differential profiles of organ cross-talk will identify underlying neural mechanisms that can lead to the regional and diffuse hyperalgesia seen in UCPPS patients using experimental pain and imaging studies (Hypothesis 6), as well as biomarkers also noted in Hypothesis 7.

‡Hypotheses related to neuroimaging and animal models developed further in separate site-specific protocols

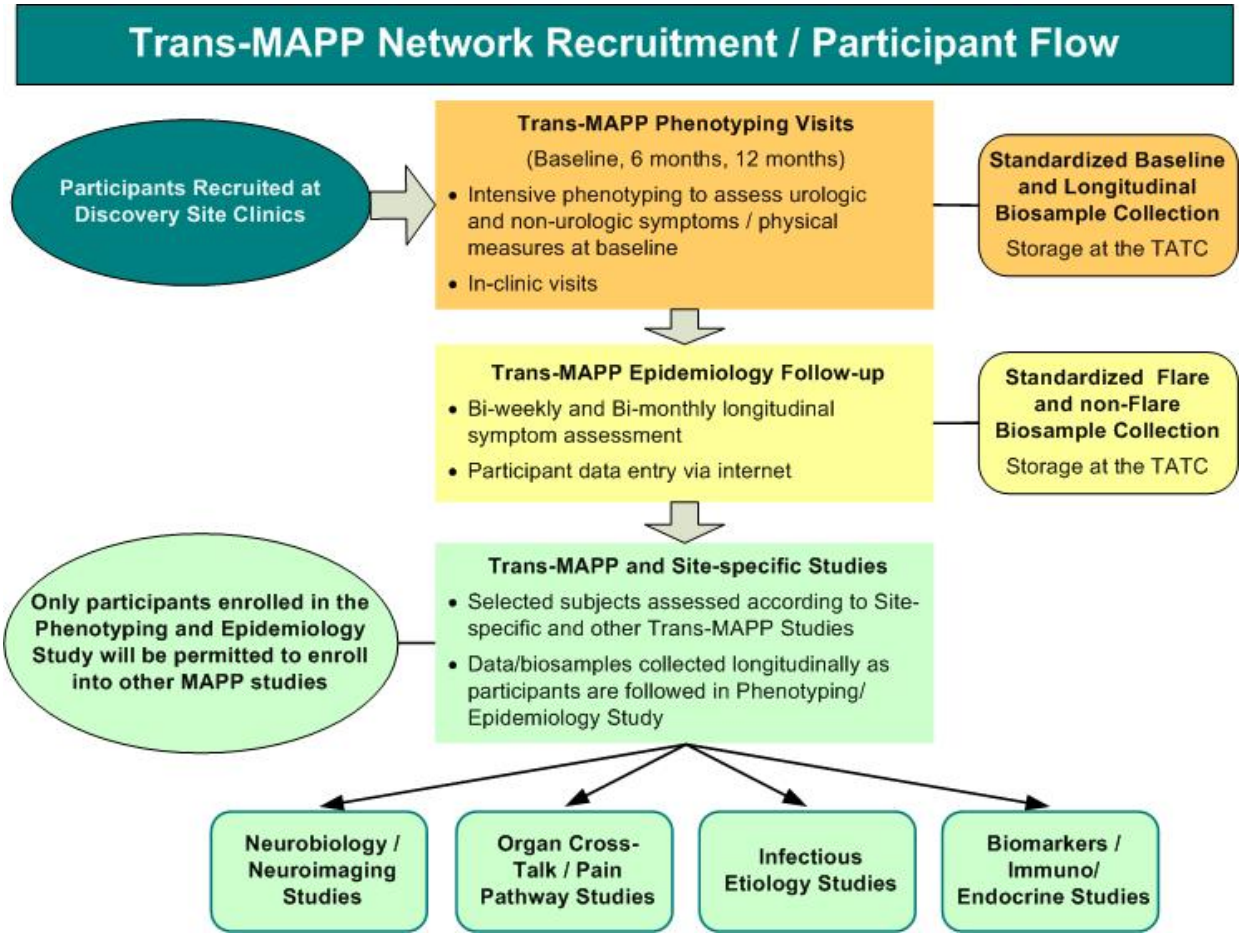
1.5 The Trans-MAPP Epidemiology and Phenotyping (EP) Study: Innovative Studies of the Characteristics of IC/PBS and CP/CPPS and a Source of Study Participants for other Trans-MAPP Research Network Studies

A major focus of the MAPP Research Network is the conduct of the Trans-MAPP Epidemiology and Phenotyping (Trans-MAPP EP) Study. All participating Discovery Sites will recruit participants into this study. As illustrated in Figure 1, the Trans-MAPP EP Study serves a number of purposes, including: (1) the recruitment of study participants for a longitudinal epidemiological study, (2) performance of detailed clinical, epidemiological, and psychological characterization of study participants, (3) collection of biological samples, and (4) providing a source of well-characterized participants for all Trans-MAPP studies conducted across all Discovery Sites and for projects conducted at a single Discovery Site. These latter projects have been classified into 4 broad content domains, as illustrated in Figure 1:

- Neurobiology / Neuroimaging Studies
- Organ Cross-Talk / Pain Pathway Studies
- Infectious Etiology Studies
- Biomarkers / Immunology / Endocrine Studies.

Thus, the Trans-MAPP EP is the foundational component of MAPP Research Network efforts. It represents a collaborative effort of all the individual MAPP Discovery Sites and the Cores.

Figure 1. The Trans-MAPP EP Study: Recruitment Pathway for Study Participants



2 TRANS-MAPP EPIDEMIOLOGY AND PHENOTYPING (EP) STUDY

2.1 Rationale for Trans-MAPP EP Study

In this study, patients with UCPPS will be recruited, examined, and followed longitudinally for a 12-month period in order to evaluate:

- Similarities and differences in symptom presentation, biological factors, and psychosocial issues in men and women with UCPPS;
- Frequency of presentation and types of co-morbid illnesses and conditions, including Chronic Fatigue (CF) syndrome, Fibromyalgia (FM), and Irritable Bowel Syndrome (IBS), and their impact on men and women with UCPPS;
- The role of early-in-life and later-in-life factors that contribute to disease presentation;
- Psychosocial and/or medical factors that contribute to symptom progression or remission and occurrence of symptom flares;
- Factors that contribute to increased healthcare utilization and decreased quality of life.

It is anticipated that the findings from this epidemiological study will provide insight into whether the various UCPPS syndromes in men and women represent a single heterogeneous diagnostic entity, or several separate problems. In addition, this Trans-MAPP EP Study will provide insights about whether psychosocial variables play a significant role in symptom persistence, resolution, or exacerbation, as well as healthcare utilization and whether UCPPS patients can be sub-grouped based on longitudinal symptom patterns. In addition, the careful and comprehensive phenotyping battery used in this study will serve as the core assessment for all participants in MAPP-related studies, including those examining biomarkers, infectious agents, brain imaging and other clinical hypotheses.

2.2 Aims and Hypotheses for Trans-MAPP EP Study

Aim 1: To estimate cross-sectional prevalences and evaluate associations among baseline characteristics of subjects with UCPPS.

Hypothesis 1a: At baseline, a high proportion of UCPPS patients will have other somatic syndromes (CF, FM, or IBS symptoms) and psychological co-morbidities (depression, anxiety symptoms).

Hypothesis 1b: At baseline, somatic syndromes and psychological comorbidities will be more common in those with longer duration of urological symptoms than in those with shorter symptom duration.

Hypothesis 1c: At baseline, both men and women with urologic symptoms will show similar patterns of somatic and psychological co-morbidities.

Hypothesis 1d: At baseline, males diagnosed with IC/PBS or CP/CPPS will show similar profiles of the primary phenotypic variables, including predominant symptoms, psychosocial function, presence of co-morbid non-urologic symptoms, and illness impact, suggesting a common syndrome.

Aim 2: To characterize longitudinal profiles of symptoms and evaluate associations between baseline characteristics and symptom profiles over a one-year period.

Hypothesis 2a: Approximately one-fourth (25%) of individuals will demonstrate symptom progression (worsening) and another one-fourth (25%) will demonstrate symptom regression (improvement) over the 12-month study period.

Hypothesis 2b: Both men and women with urologic symptoms will show similar patterns of symptom progression and improvement.

Hypothesis 2c: The presence of other somatic syndromes and psychological comorbidities at baseline will be associated with a higher likelihood of symptom progression, such as increased urological pain

Aim 3: To characterize the pattern of fluctuations in symptoms and evaluate associations between baseline characteristics and variability in symptoms over a one-year period.

Hypothesis 3a: The presence of other somatic syndromes and psychological comorbidities at baseline will be associated with greater symptom variability over the 12-month study period.

Hypothesis 3b: Predictors of symptom variability over the 12-month study period will be similar in men and women with UCPPS.

Hypothesis 3c: Increases in current life stressors, non-urologic symptoms, and negative mood will be associated with fluctuations in UCPPS symptoms assessed at biweekly and bimonthly intervals.

Aim 4: To identify factors that are predictive of more severe illness impact (including healthcare seeking and decreased quality of life) in individuals with UCPPS.

Hypothesis 4a: Individuals with greater symptom variability over the 12-month study period will demonstrate increased healthcare seeking behaviors and reduced disease-specific and general Health Related Quality of Life (HRQOL), after controlling for UCPPS symptom severity.

Hypothesis 4b: The presence of other somatic syndromes and psychological comorbidities will be associated with greater healthcare seeking behavior and reduced HRQOL, after controlling for UCPPS symptom severity.

Hypothesis 4c: Both men and women with urologic symptoms will show similar levels of healthcare seeking and HRQOL as well as similar associations between these variables and other phenotyping measures.

Hypothesis 4d: Participants with recent onset urological symptoms will have better HRQOL and fewer healthcare seeking behaviors as compared to those with more long-term symptoms.

Aim 5: To identify risk factors for self-reported worsening of symptom (flares) among individuals with UCPPS.

Hypothesis 5a: Consumption of specific foods and beverages will be associated with flares among individuals with UCPPS.

Hypothesis 5b: Specific physical and sexual activities will be associated with flares among individuals with UCPPS.

Hypothesis 5c: Specific self-reported infections will be associated with flares among individuals with UCPPS.

Hypothesis 5d: Stress will be associated with flares among individuals with UCPPS.

3 STUDY DESIGN

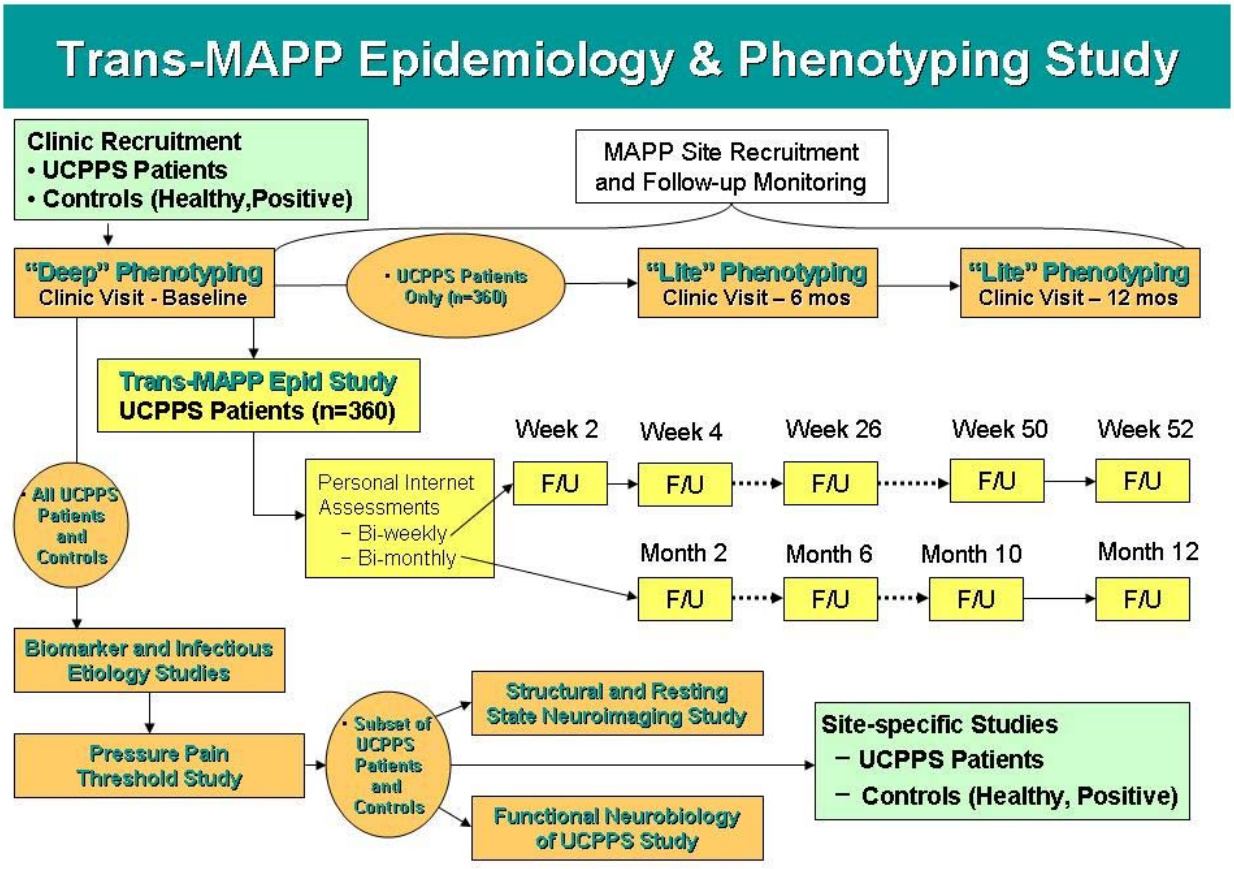
3.1 Overview of Trans-MAPP EP Study

The overall design of the Trans-MAPP EP Study includes enrollment of eligible UCPPS patients during a single baseline screening clinic visit into a cohort of study participants to be followed with internet-based bi-weekly assessments for 12 months. Each participant will also provide extensive ("deep") phenotyping data at the in-clinic baseline visit, and reduced ("lite") phenotyping data obtained at two in-clinic visits at 6 months and at 12 months of follow-up.

At the initial screening visit, participants meeting diagnostic and eligibility criteria will be enrolled directly into the longitudinal cohort study, commencing immediately with an extensive phenotyping battery of baseline measures, biosample collection and a pain pressure threshold procedure. After baseline enrollment and phenotyping, each participant will be followed bi-weekly for 48 weeks, utilizing web-based data collection modules varying in length between biweekly and bimonthly contacts.

As detailed previously, participants enrolled in the Trans-MAPP EP Study will have the option to enroll immediately during the baseline visit into one or more of the other site specific studies, such as the Structural and Resting State Neuroimaging Study and the Functional Neurobiology Study illustrated in Figure 2.

Figure 2. Study Design for Trans-MAPP EP Study



The Trans-MAPP EP Study will also serve to provide a common pool of participants from which all other site-specific network studies can recruit.

3.2 Specimen Collection for Biomarker and Infectious Etiology Studies

In support of Trans-MAPP Biomarker and Infectious Etiology (BIE) Studies, blood, urine and cheek swab biosamples will be collected during the baseline clinic visit and a maximum of 4 urine samples will be collected at home by the participant. In addition, replacement home urine samples may be collected if any of the initial 4 samples are improperly collected, stored, or damaged in shipping. The BIE Studies will compare clinical biomaterial results between UCPPS patients and controls, utilizing both Discovery and Validation efforts to confirm clinically useful biomarkers.

Novel molecular biological methodology will be employed in the Trans-MAPP Infectious Etiology (IE) Studies to explore possible infectious etiology signals in specific patient urine specimens compared to controls, as well as during symptomatic flares and asymptomatic non-flares in patients.

Please see Appendix C (Biomarker / Immunology / Endocrine Studies) for additional information on the Trans-MAPP BIE Studies and Appendix D (Infectious Etiology Studies) for additional information on the Trans-MAPP IE Studies.

3.3 Pressure Pain Threshold Procedure

A Pressure Pain Threshold (PPT) Procedure will be implemented to compare UCPPS patients with controls, using a standardized rubber probe applied to the thumbnail bed of the participant's dominant hand to measure overall central pain threshold. Once the PPT equipment is received and approved for research purposes at the respective recruitment sites, all participants enrolled into the Trans-MAPP EP Study and the Control Groups (Healthy, Positive) at the baseline clinic visit will be offered the opportunity to receive this pressure pain threshold procedure. Participants will also have the option of providing these thumbnail bed pain response measures at follow up clinic visits if not collected at the baseline visit or in addition to the baseline visit assessment.

Please see Appendix E for additional information on the Trans-MAPP Pressure Pain Threshold Procedure.

4 STUDY POPULATION

4.1 Study Participant and Subgroup Targets

The Trans-MAPP EP Study population will include 380 adult patients diagnosed with UCPPS (either IC/PBS or CP/CPPS), at least 18 years of age, recruited from clinical site practices. Approximately half of the participants will be male, and half will have recent onset (within two years) of pelvic pain symptoms and/or limited treatment as determined by self-report. Specifically,

- Each Discovery Site will recruit 60 (30 per year) and Stanford will recruit 20 (10 per year) participants over the first two years of the project with a target at each site of 50% males and 50% females
- Each site will recruit 50% of the male and 50% of the female participants with shorter symptom duration, less than 2 years since symptoms began

Consequently, the target distribution of Study participants across the Discovery Sites will be as summarized in Table 2. Please see Section 6.3.2. for details of interim monitoring.

Table 2. Composition of Trans-MAPP EP Study Participants by Target Factors

Gender	Duration of Pelvic Pain Symptoms		Total
	<2 years	≥2 years	
Females	95	95	190
Males	95	95	190
Total	190	190	380

4.2 Eligibility Criteria (As documented on Eligibility Confirmation - ELIG form)

4.2.1 Inclusion Criteria

Patients are eligible for the Trans-MAPP EP if they meet the following general and gender-specific criteria:

1. Participant has signed and dated the appropriate Informed Consent document.
    a. Agreed to participate in Trans-MAPP EP Study procedures.
    b. Gave permission for use of DNA for genes related to main goals of this study.
2. Gender recorded in Participant Registration module.
3. Participant is at least 18 years of age.
4. Participant reports a response of at least 1 on the pain, pressure or discomfort scale (SYM-Q, Question #1).

For males or females (IC/PBS criteria)

1. Participant reports an unpleasant sensation of ***pain***, ***pressure*** or ***discomfort***, perceived to be related to the bladder and/or pelvic region, associated with lower urinary tract symptoms.
    - These IC/PBS symptoms have been present for the majority of the time during any 3 months in the previous 6 months.
    - These IC/PBS symptoms have been present for the majority of the time during the **most recent 3 months**.

For males only (CP/CPPS criteria)

1. Male participant reports pain or discomfort in any of the 8 domains of the Male Genitourinary Pain Index (MGUPI) (items 1a, 1b, 1c, 1d, 2a, 2b, 2c, 2d).
    - These CP/CPPS symptoms been present for the majority of the time during **any 3 months in the previous 6 months**.

4.2.2 Exclusion Criteria

Any patient meeting any one of the following criteria will not be eligible for enrollment in the Trans-MAPP EP. However, participants who develop any of these exclusion criteria during the follow-up phase of the study will continue to be followed, and included in the cohort study. It will be recorded in the follow-up data if a patient has developed any of the exclusion criteria.

1) Participant has an on-going symptomatic urethral stricture.
2) Participant has an on-going neurological disease or disorder affecting the bladder or bowel fistula.
3) Participant has a history of cystitis caused by tuberculosis, radiation therapy or Cytoxan/cyclophosphamide therapy.
4) Participant has augmentation cystoplasty or cystectomy.
5) Participant has an active autoimmune or infectious disorder (such as Crohn's Disease or Ulcerative Colitis, Lupus, Rheumatoid Arthritis, Multiple Sclerosis, or HIV).
6) Participant has a history of cancer (with the exception of skin cancer).
7) Participant has current major psychiatric disorder or other psychiatric or medical issues that would interfere with study participation (e.g. dementia, psychosis, upcoming major surgery, etc).
8) Participant has severe cardiac, pulmonary, renal, or hepatic disease that in the judgment of the study physician would preclude participation in this study.

Exclusion Criteria for Males Only

1) Male Participant diagnosed with unilateral orchalgia, without pelvic symptoms.
2) Male Participant has a history of transurethral microwave thermotherapy (TUMT), transurethral needle ablation (TUNA), balloon dilation, prostate cryo-surgery, or laser procedure.

4.2.3 Deferral Criteria

There are several physical conditions for which a patient will be deferred from further screening for the Trans-MAPP EP. Once it has been determined that the condition is no longer present, the potential study participant may be re-screened for eligibility. The following list identifies the conditions for deferral, and the criteria that the participant must meet in order to be evaluated further for entry into the study:

Deferral Criteria - Treatment and history

1) If participant has had definitive treatment for acute epidymitis, urethritis, vaginitis, the participant will be deferred for at least 3 months from resolution of symptoms.
2) If participant has history of unevaluated hematuria, this will require the evaluation of a study physician to determine if this has been appropriately evaluated.

Deferral Criterion – Prostate related (Males *ONLY*)

Study Population

3) If male participant has had a prostate biopsy or Transurethral Resection of the Prostate (TURP) within the last three months, he will be deferred for 3 months following prostate biopsy or TURP.

Deferral Criteria - Urine test results*

A clean-catch midstream urine specimen (VB2) will be obtained from all male and female participants during the initial phase of eligibility confirmation, so that a urine dipstick analysis can be done for all participants, and a urine pregnancy test can be conducted for females of child bearing age excluding post-menopausal and those with a history of hysterectomy.

4) If participant has an abnormal dipstick urinalysis indicating abnormal levels of nitrites and/or occult blood, that in the opinion of the Principal Investigator, warrants a deferral, participant will be deferred until normal level of nitrites from dipstick urinalysis is confirmed.

5) If participant has had a positive urine culture in the past 6 weeks, or currently has a midstream urine culture (VB2) (≥100,000 CFU/ml), with a single uropathogen, the participant will be treated and deferred for at least 3 months from the date of positive urine culture result. (Must be documented on Urine Culture Result – UCR form).

* Repeat urine dipstick analysis will be performed at 6 and 12 months for purposes of data collection and not deferral.

Deferral Criterion – Pregnancy Test (Females of childbearing potential *ONLY)*

6) If a female participant has a positive urine pregnancy test she will be deferred until after delivery.

(If a female participant becomes pregnant during the study, she will be withdrawn from the study at the time the pregnancy is identified; data from prior to the pregnancy will be included in the analyses).

5 MEASURES AND FOLLOW-UP

5.1 Risk Factors and Outcome Measures

Extensive data on risk factors and outcomes measures will be collected for the Trans-MAPP EP Study. These measures can be classified into a number of primary domains as described below. Measures are collected on one of four schedules, the contact schedule being described in more detail in the next section:

1) Single point in time: this includes measures that do not change over time, such as demographic information, "trait measures" (e.g., personality), and early life history measures. In general, these measures are collected at the initial in-person clinic visit, although some are collected in the second (6-month) in-person visit to reduce participant burden at baseline;
2) Baseline, 6-month and 12-month phenotyping in-clinic visits;
3) Bi-monthly personal internet-based assessment;
4) Bi-weekly personal internet-based assessment.

5.1.1 General Measures of Sociodemographics, Health, and Quality of Life

Data on age, gender, race/ethnicity, education and income will be collected at the baseline phenotyping visit. A directed medical history will also be obtained. A physical exam will include weight, height, and a brief pelvic evaluation.

Participants will be asked to list all prescription and over-the-counter drugs they are currently taking at each in-clinic phenotyping visit (baseline, 6-, and 12-month), including dose, frequency, and route of administration.

A Quality of Life (QOL) assessment will be performed at each in-clinic visit and bi-monthly contacts using the recently revised Rand Short Form-12 (SF-12).[8]

Health care resource utilization data will be collected at baseline, and at each bi-weekly contact, using two brief questions related to seeking medical care due to urologic or pelvic pain symptoms in the past 2 weeks.

Participants will also be asked about family members' medical history. Family members will include first-degree blood relatives only, these include: parents, grandparents, aunts, uncles, siblings, and children. Data will be collected for family members' history of chronic pain disorders and psychiatric disorders on the Family Medical History Questionnaire (FAMHX).

5.1.2 UCPPS Symptoms Measures

Pain, urgency, and frequency symptom severity measures will be collected at baseline, and at each bi-weekly, bimonthly, and in-clinic contact. Participants will also be queried about flares of their urologic or pelvic pain symptoms.

Standardized urologic measures using the case definition questionnaire from the Rand Interstitial Cystitis Epidemiology (RICE) Study[9], Interstitial Cystitis Symptom Index (ICSI)[10], Interstitial Cystitis Problem Index (ICPI)[10], AUA Symptom Index (AUASI)[11], Female Genitourinary Pain Index (FGUPI)[12], Male Genitourinary Pain Index (MGUPI)[12], Female Self-Esteem and Relationship (FSEAR) Questionnaire[13], Male Self-Esteem and Relationship (MSEAR) Questionnaire[13], Female Sexual Function Index (FSFI)[14], International Index of Erectile Function (IIEF)[15] and the University of Washington Ejaculatory Function Scale (EFS)[16,17] will be obtained at all phenotyping in-clinic visits, as well as at bi-monthly follow-up contacts. The ICSI, ICPI, FGUPI and MGUPI will also be obtained at each bi-weekly contact.

Measures and Follow-up

5.1.3 Non-urological Symptom Measures

Data on non-urological pain, utilizing a body map with numbered regions, will be obtained at each in-clinic visit, and at the bimonthly contacts, using the Body Pain Index (BPI)[18] tools. Furthermore, at this same data collection frequency, mental and physical health data using the Medical Outcomes Health Survey (SF-12)[8], data on anxiety and depression symptoms, using the Hospital Anxiety and Depression Scale (HADS)[19], data on sleep, fatigue and anger using the PROMIS scales[1], and perceived stress using the Perceived Stress Scale (PSS)[20] will be collected. Moreover, at each of the in-clinic phenotyping visits (baseline, 6 and 12 months), mood data using the Feelings and Emotions Questionnaire within the PANAS instrument[21], coping data on catastrophizing, using the Catastrophizing scale (CSQ:CAT)[22], locus of control, using the Beliefs in Pain Control Questionnaire (BPCQ)[23], and cognition using the Multiple Ability Self-Report Questionnaire (MASQ)[24], will be obtained.

A self-reported Complex Medical Symptom Inventory (CMSI)[25] checklist that assesses a broad spectrum of symptoms often found in UCPPS patients will also be administered at the in-person and bimonthly assessments. Furthermore, at the baseline assessment visit, the CMSI Co-morbid Diagnostic Syndrome Modules will also be administered by the evaluating clinician. These modules utilize syndrome-specific diagnostic symptoms to assess for the probable presence of several syndromes commonly found in UCPPS patients, including FM[26], CFS[27], IBS[28], Vulvodynia[29], Migraine[30], and temporomandibular joint disorder (TMJD)[31].

5.1.4 Trait-like Personal Factors

Data on trait-like personality and trauma history factors will be collected once at the in-clinic baseline phenotyping visit using the International Personality Item Pool (IPIP) Measures[32] and the Childhood Traumatic Events Scale (CTES).[33]

5.1.5 Assessment of Risk Factors at Reported UCPPS Symptom Flares

This study will assess putative risk factors for flares of urologic or pelvic pain symptoms, at up to three contacts for participants reporting a flare, as well as for three randomly selected contacts when each participant does not report a flare. In particular, dietary factors, physical activity, stress, sexual activity, and recent infections will be noted. This is discussed further in section 5.2.3.

5.1.6 Biological Specimens

Biologic specimens collected during the course of the Trans-MAPP Study include urine, blood (plasma) and cheek swab for DNA. A cheek swab specimen will be collected at baseline or at any of the follow up in-clinic visits, if it is missed, improperly collected, damaged, or if insufficient sample is obtained during the baseline visit. Plasma and urine will be collected at all three in-clinic visits. In addition, urine will be collected with the home collection kit at the first reported flare, and at one additional randomly selected non-flare time point during the first four months or later in the study if the first collection is missed, improperly collected and/or stored, or damaged in shipping The schedule of these collections is summarized in Table 4.

Table 4. Schedule of Biologic Specimen Collection in Trans-MAPP EP

Measure	Approximate Volume	Implementation Schedule
Blood (plasma) specimen	10 ml	Baseline, 6 , and 12 Month Clinic Visits
Spot urine specimen	90 ml	Baseline, 6 , and 12 Month Clinic Visits
VB urine specimen	1 sample - total volume voided ,maximum 50 ml (females); 2 samples - total volume voided, maximum 50 ml per collection(males) *	Baseline, 6 , and 12 Month Clinic Visits
Cheek Swab For DNA	N/A	Once, at Baseline Visit (or other visit/s, as needed for

[1] PROMIS version 1.0 item banks were used. For further information, please refer to www.nihpromis.org

Measure	Approximate Volume	Implementation Schedule
		missed or replacement specimen)
Flare urine specimen	1 sample 90 ml 1 sample 50 ml	Once, at initial report of flare (specimen collected at home and shipped to TATC); or collected at second or third report of flare, as needed, for missed or replacement samples not collected at the initial prompt.
Non-Flare urine specimen	1 sample 90 ml 1 sample 50 ml	Once, when randomly selected to complete Flare during report of non-flare(specimen collected at home and shipped to TATC); or collected at second or third random selection for report of non-flare, as needed, for missed or replacement samples not collected at the initial prompt.
* the 2nd Male VB3 urine sample following the prostate massage is optional.		

5.2 Contact Schedule and Participant Procedures

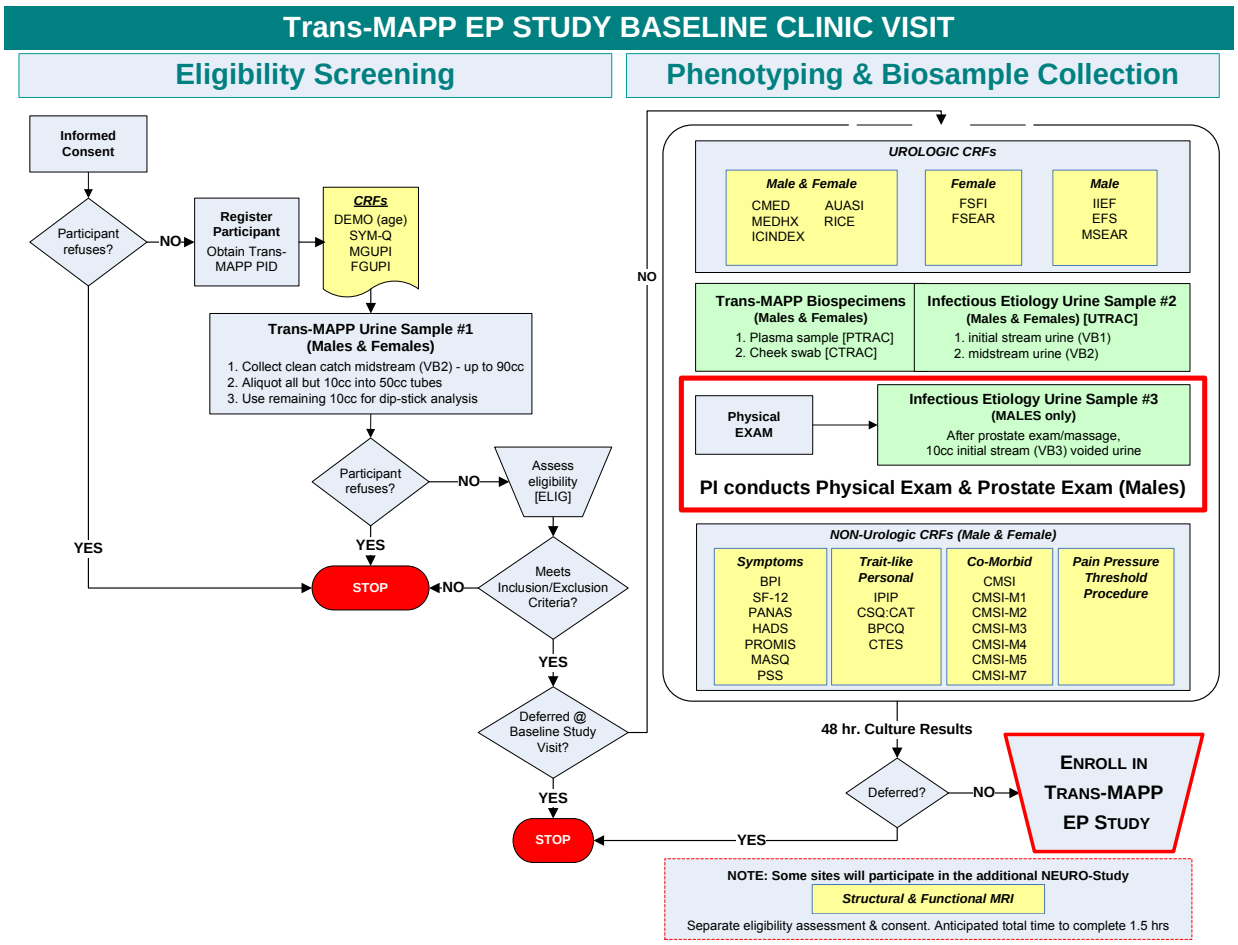
Participants who enroll in the study and complete a baseline clinic visit will be followed up with biweekly and bimonthly internet-based questionnaires, as well as in-clinic visits at 6 and 12 months. A complete listing of data elements to be collected at the follow up visits is provided in Appendix 11.1: Participant Contact Schedule.

5.2.1 Baseline Phenotyping Visit

Potentially eligible participants will be scheduled for an eligibility screening session, followed by an extensive baseline phenotyping session, which together are expected to take approximately 2.5 hours to complete. Participants will be provided with breaks as needed during the clinic visit. As illustrated in Figure 3, the eligibility screening session (left-hand panel) is intended to collect the minimally sufficient data to confirm eligibility, so that the extensive baseline phenotyping session (right-hand panel) is initiated only for participants highly likely to be confirmed after the 48 hour urine culture results are known.

Measures and Follow-up

Figure 3. Sequence of Trans-MAPP EP Study Baseline Data and Biospecimen Collection



At the baseline visit, the following sequence of steps will occur:

- Layered informed consent process; consent obtained for various levels of specimen collection (ICF)
- Contact information provided (Site documentation)
- Demographic information recorded (DEMO) – Documentation of demographic data and history of family member diagnosis of IC/PBS and/or CP/CPPS.
- Symptom assessment via Symptom and Healthcare Utilization Questionnaire (SYM-Q) – including question documenting Flares in the past year.
- Male Genitourinary Pain Index (MGUPI) – to identify male participants with CP/CPPS, and the Female Genitourinary Pain Index (FGUPI) –to assess parallel urological symptoms, although not utilized in determining eligibility for females.
- Eligibility Confirmation form (ELIG) – to be completed (Inclusion, Exclusion, Deferral Criteria) prior to patient-entered questionnaire battery.
- Urine Culture Result (UCR)) – Deferral Criterion for Eligibility Confirmation form completed to document status of urine culture results for participants who have not had a negative urine culture within the preceding 6 weeks,
    - a clean catch midstream urine (VB2) specimen will be obtained for the urine dipstick test and 48 hour urine culture (see further details in Appendix B);
    - a urine dipstick test will be performed for the presence of leukocyte esterase, nitrites, and hematuria;

- if the dipstick is positive for nitrites, the patient will be treated and deferred until urine culture results are available, and for three months from the date of positive urine culture test result.

Assuming that the participant meets all eligibility criteria that can be known prior to the results of the 48 hour urine culture (confirmed on ELIG form), the participant will begin the Phenotyping and Biosample Collection phase (Figure 3, right-hand panel) of the Trans-MAPP EP.

Urological Phenotyping CRFs:

- Interstitial Cystitis Symptom Index (ICSI) and Problem Index (ICPI) form) – (ICINDEX)
- AUA Symptom Index (AUASI)
- Rand Interstitial Cystitis Epidemiology (RICE) Study – IC Case Definition Questionnaire from the RICE study
- Medical History (MEDHX)
- Family Medical History (FAMHX)
- Concomitant Medications (CMED) – Documentation of current medications

Female Participants only:

- Female Sexual Function Index (FSFI)
- Female Self-Esteem and Relationship (FSEAR) Questionnaire

Male Participants only:

- International Index of Erectile Function (IIEF)
- University of Washington Ejaculatory Function Scale (EFS)
- Male Self-Esteem and Relationship (M-SEAR) Questionnaire

As shown in Figure 3 (right-hand panel), all Trans-MAPP EP Study participants will be providing biosamples, including blood (plasma), a cheek swab, and urine samples (VB1, VB2) for infectious etiology studies.

Biosample and Physical Exam CRFs:

- Plasma Specimen Tracking (PTRAC)
- Cheek Swab Specimen Tracking (CTRAC)
- Infectious Etiology Urine Specimen #2 (VB1, VB2) Tracking (UMIETRAC, UFIETRAC)
- Physical Exam (EXAM)*
    - Optional for Male Participants only (after prostate exam/massage**:
        - Infectious Etiology Urine Specimen #3 (VB3) Tracking (UMIETRAC)

* With the participant's consent, physical exam data acquired as part of a clinic exam, up to 14 days prior to the baseline/ screening visit, can be utilized to complete the MAPP study exam data form.

**The prostate exam/massage and the VB3 sample acquired immediately following the prostate massage is optional, male participants can refuse the VB3 and prostate massage and still remain in the study.

Non-Urological Phenotyping CRFs:

Symptoms and Illness Impact

- Brief Pain Inventory (BPI) + revised body map
- Medical Outcomes Health Survey – (SF-12)
- Feelings and Emotions Questionnaire (PANAS)

Measures and Follow-up

- Hospital Anxiety and Depression Scale (HADS)
- Anger, Fatigue, and Sleep Questionnaires (PROMIS)
- Multiple Ability Self-Report Questionnaire (MASQ)
- Perceived Stress Scale (PSS)

Traits and Early Life Experience

- International Personality Item Pool (IPIP) Measures
- Catastrophizing Sub-scale (CSQ:CAT)
- Beliefs in Pain Control Questionnaire (BPCQ)
- Childhood Traumatic Events Scale; Recent Traumatic Events Scale (CTES)

Co-morbid Symptoms

- Complex Medical Symptoms Inventory Questionnaire (CMSI)
- CMSI, Fibromyalgia (CMSI_FM2)
- CMSI, Fibromyalgia – Tender Point Exam (CMSI_FM2-TP)
- CMSI, Chronic Fatigue Syndrome (CMSI_CFS2)
- CMSI, Irritable Bowel Syndrome (CMSI_IBS2)
- CMSI, Migraine (CMSI_MI2)
- CMSI, Vulvodynia (CMSI_VDYN)
- CMSI, Current TMD Symptoms (CMSI_TMD2)

After a 48 hour negative urine culture result is confirmed, the Enrollment Confirmation (ENROLL) form will be completed, confirming that all Eligibility Criteriahave been met.

5.2.2 Biweekly Assessments

Participants will provide self-reported longitudinal symptom data via web-based internet tools. This series of questions is expected to be completed within 5-7 minutes. The following questionnaires will be completed at each biweekly assessment (the Case Report Form, or CRF, names are provided in parentheses):

- Symptom and Health Care Utilization Questionnaire (SYM-Q)
- Interstitial Cystitis Symptom Index and Problem Index (ICINDEX)
- Brief Flare Risk Factor Questionnaire (FLARE): the FLARE questionnaire is completed up to three times if participant reports experiencing a symptom flare, and at three additional random intervals when participant reports NOT experiencing a symptom flare (see Section 5.2.3)

Female Participants only:

- Female Genitourinary Pain Index (FGUPI)

Male Participants only:

- Male Genitourinary Pain Index (MGUPI)

5.2.3 Flare Protocol

A question about current symptom flares is included in all Trans-MAPP EP Study assessment contacts, including the in-person assessments at baseline, 6 months and 12 months, as well as the biweekly and bimonthly internet assessments. At all visits, except the baseline phenotyping visit, if participants answer ‘yes’ to both the current flare question (last question on SYM-Q form) and the question on flares beginning in the previous 2 weeks (first question on FLARE form),

this response combination will trigger an additional brief 'flare risk factor questionnaire' on hypothesized risk factors for flares. This supplemental flare questionnaire will be completed no more than three times by each subject when reporting a symptom flare during the 12-month follow-up period. If a participant reports additional flares (beyond three), the supplemental flare questionnaire will not be triggered. The flare risk factor questionnaire will not be administered to participants reporting flares at the baseline visit, in order to minimize the number of questions being completed at that time.

Participants who report a symptom flare will also be prompted to provide two urine samples, using a home urine collection kit provided to them at the baseline visit, as described in Appendix B. They will be asked to ship the samples to TATC using the relabeled and pre-linked (de-identified) shipping kit provided by TATC. These urine specimens will be provided only once at the time of the first flare. At the time of subsequent symptom flares, the supplemental flare risk factor questions will be answered, but a urine specimen will not be provided. To provide for proper control for urine specimens collected with the home collection kit, each participant will also be asked to send in two non-flare urine samples collected with the home collection kit, on the occasion of their first randomly selected non-flare bi-weekly contact during the first four months. Participants will be notified at the time of data entry if this is the time at which non-flare urine samples will be collected. Participants may be requested to provide replacement home urine samples if any of the initial 4 samples are improperly collected, stored, and/or damaged in shipping. It should be noted that each participant will also provide a urine specimen at the in-person phenotyping visits occurring at baseline, 6 months, and 12 months. These specimens can be analyzed and compared with the flare specimen to investigate urine characteristics that are uniquely present during symptom flares. Although it is possible that a participant will be experiencing a flare at each of these visits, this possibility is unlikely.

In addition, each participant will also complete the supplemental flare risk factor questionnaire at three time points during the 12-month study period when they are not experiencing a symptom flare. These data will serve as control to identify risk factors for symptom flares. The three time points will be randomly selected, using an algorithm within the Data Management System, so that participants who answer 'no' to the flare question will be asked to complete the supplemental flare questions nevertheless. One time point will be randomly selected during each 4-month period within the 12-month study period.

In the flare risk factor questionnaire, exposures will be focused on those occurring within the previous 3-7 days before the flare began (for flare assessments), or 3-7 days before the date of questionnaire completion (for non-flare assessments).

5.2.4 Bi-monthly Assessments

A more extensive set of questionnaires will be administered to each participant every two months during the 12-month study period. The bi-monthly assessment will also be administered via the internet, and the questions are expected to be completed within 10-15 minutes.

This set of questionnaires includes all of the CRFs from the bi-weekly assessments, plus the additional CRFs listed subsequently:

Urological Phenotyping CRFs:

- AUA Symptom Index (AUASI)

Female Participants only:

- Female Sexual Function Index (FSFI)
- Female Self-Esteem and Relationship Questionnaire (FSEAR)

Male Participants only:

- International Index of Erectile Function (IIEF)
- University of Washington Ejaculatory Function Scale (EFS)

Measures and Follow-up

- Male Self-Esteem and Relationship Questionnaire (MSEAR)

Non-Urological Phenotyping CRFs:

- Brief Pain Inventory (BPI) plus Revised Body Map
- Health Survey (SF-12)
- Hospital Anxiety and Depression Scale (HADS)
- Anger, Fatigue, and Sleep Questionnaires (PROMIS)
- Perceived Stress Scale (PSS)
- Complex Medical Symptoms Inventory (CMSI)

5.2.5 Six- and Twelve-Month Clinic Visits

In addition to the CRFs administered at the biweekly and bimonthly assessments, the following CRFs will be completed at the 6- and 12-month clinic visits:

Urological Phenotyping CRFs:

- Early in Life Infection History (EIL-INF*) ***Six Month Visit only***
- Concomitant Medications (CMED) - Documentation of current medications
- Plasma Specimen Tracking (PTRAC)
- Urine Specimen Tracking (UTRAC)*
- Infectious Etiology Urine Specimen #2 (VB1, VB2) Tracking (UMIETRAC, UFIETRAC)Cheek Swab Specimen Tracking (CTRAC)* - *PRN, if insufficient sample, missed or improperly collected at the Baseline visit
- Physical Exam (EXAM)* - *PRN at Principal Investigator's discretion
- Optional for Male Participants only (after prostate exam/massage: Infectious Etiology Urine Specimen #3 (VB3) Tracking (UMIETRAC)
- Study Stop (SSTOP) – Documentation of completion of study or early withdrawal

* Repeat urine dipstick analysis will be performed at 6 and 12 months for purposes of data collection and not deferral.

Non-Urological Phenotyping CRFs:

Symptoms

- Positive and Negative Affect Scale and Emotions Questionnaire (PANAS)
- Multiple Ability Self-Report Questionnaire (MASQ)

Coping and Beliefs

- Catastrophizing Sub-scale (CSQ:CAT)
- Beliefs in Pain Control Questionnaire (BPCQ)

5.2.6 Internet Site Design and Operation

The Trans-MAPP internet site will be the primary data collection tool for longitudinal assessment at the bi-weekly and bi-monthly contacts. A number of steps will be taken to assist in participant tracking and retention:

- The site will be designed to be attractive, engaging, and as user-friendly as possible
- Places to contact, via phone or email, for help for site operation or anything else regarding the study will be clear on every page
- If a patient misses a data collection time-point, the primary enrollment site will be notified by the DCC to follow-up with the participant via email, phone, or mail
- Reminders for upcoming assessments will be emailed from the Discovery Sites to each participant, with easy link to patient's own data collection page. Two weekly follow-up emails will be sent automatically after a missed contact

- Repeated attempts will be made by the Discovery Sites to contact difficult-to-reach participants, and at each time-point, participants will be asked for their most recent phone number, email and physical address

6 STATISTICAL CONSIDERATIONS AND ANALYTIC PLAN

The study is targeted to recruit a minimum of 380 subjects, 60 subjects from each of the six Discovery Sites and 20 subjects from the Stanford site; details of sample sizes and statistical power are provided in Section 6.3. From an analytical point of view, the analyses can be considered as types corresponding to the five specific aims, loosely grouped by the type of outcome measure. The primary predictors and outcomes are shown in the table below; the specific hypotheses are indicated where applicable as well. As noted in Section 6.3.3, the 20 additional participants recruited from the Stanford site will increase the statistical power only slightly above 80% to detect the tabled effect sizes.

Table 5. Summary of Predictors and Outcomes*

Predictors		Outcomes				
		UCPPS Symptoms**			HealthCare	
Factor	When Measured	Baseline	Longitudinal Profiles	Longitudinal Variability	Seeking and HRQOL*	"Flare"
Baseline Demographics	Baseline	✓	✓	✓	✓	
Gender	Baseline	1c	2b	3b	4c	
Duration of Symptoms	Baseline	1b	✓	✓	4d	
Men: Diagnosis of IC/CP	Baseline	1d	✓	✓	✓	
Early Life Experience, Events	Baseline	✓	✓	✓	✓	
Personality Trait	Baseline	✓	✓	✓	✓	
Other Somatic Symptoms	Baseline & Longitudinal	1a, 1b, 1c	2c	3a, 3c	4b	
Psychological Co-morbidities	Baseline & Longitudinal	1a, 1b, 1c	2c	3a, 3c	4b	
Diet, Physical/Sexual activity, Stress	At Flare***					5a,b,c,d
Trans-MAPP Sub-studies						
Biomarkers	Baseline and Longitudinal	✓	✓			✓
Neuro-Pain Pressure Procedure	Baseline and Longitudinal	✓	✓			✓
Infectious Etiology	Baseline and Longitudinal	✓	✓			✓
Genomics	Baseline	✓	✓			

* Some hypotheses may also involve examination among factors listed in the rows of the table. For example, Hypothesis 1b will examine associations between duration of symptoms and both somatic symptoms and psychological co-morbidities; Hypothesis 1d will examine these associations among men only, comparing diagnoses of IC/PBS and CP/CPPS.

** UCPPS symptoms, both baseline and longitudinal, will also be evaluated with respect to healthcare seeking and HRQOL (Hypothesis 4a).

*** This includes randomly selected visits at which "flare" is not reported in order to serve as a control.

6.1 General Statistical Methods

6.1.1 Exploratory and Descriptive Analysis

Before proceeding with statistical analyses to investigate primary research questions, all relevant measures will be fully described, including aspects of data quality. For both predictor variables and outcomes, a summary of each variable, or group of variables, will be produced. Graphical methods including histograms, scatterplots, and boxplots will be used to identify potential outliers and examine assumptions (such as normality) underlying statistical models. Plots of measured variables over time to assess patterns of change will be especially important for the various outcomes to be collected longitudinally; both subject-specific values and group summaries over time will be examined. Means, standard deviations, medians, and ranges will

be computed for measured continuous variables; marginal distributions will be used for categorical factors. The amount and patterns of missing data, if any, will also be characterized at this stage. In addition, several types of data manipulation may be considered. Transformations will be used if needed to produce variables that conform to the distributional assumptions underlying the analytic techniques that will be employed. For instance, some variables may be transformed to log scales, as needed to reduce any marked positive skew. Exploratory analyses and careful collaboration with investigators will be used to guide in the selection and creation of composite variables when required to address study hypotheses.

6.1.2 General Testing and Model-building Strategies

In general, hypothesis tests will be performed using a two-sided significance level (Type I error) of α=0.05, although actual P-values will be reported whenever possible. Multivariable models will be used to (1) control for other covariates, such as potential prognostic or confounding factors, in primary comparisons, (2) identify potential prognostic factors for disease outcomes, and (3) evaluate potentially complex associations among factors. In addition to factors such as gender and diagnosis related to specific hypotheses, other predictors that may be included in multivariable models might include: age, severity or nature of symptoms, results of laboratory tests, and other demographic and disease-specific measures. The actual choice of statistical model for these evaluations will depend on the outcome of interest. For example, to identify prognostic factors that delineate between subjects with or without a particular co-morbid syndrome at baseline, multivariable logistic regression modeling would be used to build a parsimonious model that best discriminates between groups. For continuous measures, such as GUPI scores, linear regression and random effects models for longitudinal data would be used. By necessity, these analyses will be based on parametric models. Therefore, extensive attention will be made to verify model assumptions through examination of graphical displays and summary statistics for raw variables and model residuals. Particular attention will be paid to unusual observations (outliers) that may have undue influence on the analytical results. Standard regression diagnostics, including residual plots and influence statistics, will be used to identify such observations and examine their effect on analyses. These diagnostics will be supplemented with sensitivity analyses when warranted.

To determine whether a variable or set of variables improves prediction within a model, we will consider two issues: (1) how the predictor relates to the outcome variable, conditioned on the other covariates and (2) how much prediction of a model is improved by the addition of predictors, individually or in groups. To examine the relation between a predictor and outcome, we will use regression coefficients, supplemented, where appropriate, by standardized regression coefficients. For examining the predictive ability, we will use c-statistics as measures of the discriminatory ability for logistic regression and R^2 values for linear regression. Longitudinal models will use similar measures such as the Akaike Information Criterion (AIC). In all cases, the incremental value of a predictor or set of predictors will be measured as the incremental change in these criteria.

A stepwise modeling procedure will be used to identify the best parsimonious explanatory model for each outcome and/or hypothesis. Univariable associations will first be examined; predictor factors that appear to be associated with the outcome of interest with a P-value of <0.2 will be considered for inclusion in multivariable regression models to reduce the number of candidate factors. Variables will then be entered in a stepwise fashion into the model, the order based on increments in the c-statistic or R^2 statistics. During this process, residuals will be examined to consider possible departures from linearity through the use of polynomial terms or regression splines.

Although these models will be primarily exploratory and aim to identify important correlations, an issue may arise if these models are also used to generate a predictive model. Specifically, using the same data to build and assess a model can lead to model over-fitting and/or over-optimism about predictive ability. Therefore, if warranted, we will use cross-validation methods, both for

selecting variables for the model and for assessing the predictive ability. In this case, a variable will be added to the model if it improves the cross-validation c-statistic or R^2 statistics.

6.1.3 Additional Considerations for Logistic Regression Models

In addition, for logistic regression models, decision rules derived from logistic modeling can be evaluated as diagnostic tests. For example, the sensitivity of the predictive function is defined as the proportion of subjects with the target condition who have a positive test; the specificity as the proportion of subjects without the target condition who have a negative test. Multiple test cutoff points can be defined using different probabilities of the outcome derived from the logistic regression model. Each of these cutoffs is associated with a true positive rate and a false positive rate based on actual outcome. Optimal cutoffs can then be chosen based on their relative costs and benefits.[34] Analysis of an ROC (receiver-operator-characteristics) curve, in which the sensitivity and 1-specificity of the rule for different cutoff criteria are plotted[35], will be used to graphically describe the relationship between chosen cutoff values of the logistic regression analysis and the associated test characteristics. The ability of the diagnostic tests to discriminate between outcome groups will be reflected in the shape of this curve. The greater the integrated area beneath the curve, the greater the ability of the rule to differentiate individuals with/without the target condition.[36] Furthermore, an ROC curve can be developed and tested using the algorithm of Hanley and McNeil[36] adapted for use on a microcomputer by Centor and Schwartz.[37]

Final models will be evaluated for their calibration and discrimination characteristics. We consider calibration to be the ability of the model to make unbiased estimates of outcome, whereas discrimination is the ability to accurately predict subjects' outcomes. The calibration of the model assesses how well the predictions of the model correspond to the observed outcomes, and will be tested by two complementary statistical approaches. In the first, the observed outcomes in the dataset will be compared to predicted outcomes of the prediction model with percent overall agreement. In the second, the Hosmer-Lemeshow statistics will be calculated, which compares the predicted probability of an outcome to observed outcome proportions. Similarly, the discrimination of the model will also be assessed by two complementary tests. First, the observed outcomes in the data set will be compared to predicted outcomes of the model by calculating sensitivity, specificity, and predictive values. Second, the area under an ROC curve will be estimated.[36]

6.1.4 Cross-sectional Comparisons of Groups

For measured continuous variables, two-group comparisons will generally employ Wilcoxon rank-sum tests to protect against violations of normality assumptions. The Wilcoxon test affords little loss of power, as it is more than 95% efficient with respect to the two-sample *t*-test when normality holds. Similarly, Wilcoxon signed-rank tests will be used for paired data and Kruskal-Wallis tests will be used for *k*-group comparisons. In some instances, *t*-tests and analysis of variance (ANOVA) methods may be used to facilitate group comparisons when the appropriate assumptions are met. Categorical variables, including dichotomous factors, will be summarized by proportions and compared among groups using standard chi-square tests of association and generalized Mantel-Haenszel (MH) methods, as described in Landis *et al.*[38] to accommodate both nominal and ordinal measurement scales. These MH methods are useful for adjusting primary associations for potential confounders and clustering. Whenever possible, exact P-values from Exact Conditional Tests (ECT), such as Fisher's exact test and its multi-degree of freedom extensions, will be produced for these tests.

6.1.5 Evaluation of Longitudinal Profiles Over Time

Studies aimed at characterizing changes over time will utilize methods for longitudinal data analysis. For measured continuous outcomes, the primary models used will be random coefficient growth curve models in which random effects due to subject and/or time are included to account for the correlation among repeated observations on each subject.[39,40] These are

similar to repeated measure ANOVA methods, but are particularly useful for handling staggered timepoints and the presence of non-informative drop-outs. For binary or ordinal outcomes, the methodology of generalized estimating equations (GEE) will be used to evaluate changes over time via logistic models.[41,42]

6.1.6 Evaluation of Variability over Time

Studies aimed at evaluating factors related to the extent of symptom variability over time will be conducted utilizing subject-specific total counts of either improvement, defined as a ≥2-point reduction in the ICSI or a ≥7-point reduction in the GUPI from the previous value, or symptom exacerbation, defined as a >2-point increase in the ICSI or a >7-point increase in the GUPI. For each subject, the number of changes (improvements or exacerbations) over the 12-month time period will be totaled. This value will be analyzed as a Poisson-dependent variable within a blmultivariable model that includes gender, disease status (early vs. chronic), age, and other predictors from the initial phenotyping evaluation such as presence of other chronic pain and/or functional symptoms, psychological variables of mood, personality and cognitions, and patient history variables. The general testing and model building strategies summarized within the previous sections will be followed within the Poisson regression model development framework.

6.1.7 Other Multivariable Methods

Another aspect of disease phenotyping will undoubtedly involve investigating a broad array of highly correlated symptoms based on standardized questionnaire data, for which the goal is to identify subsets of patients based on clusters of symptoms. These extensive symptom data can be approached using a multi-stage application of cluster analysis.[43] At the first stage, participants are grouped based on sets of features in multiple domains, and a separate cluster analysis is conducted for each. A distance-dissimilarity matrix containing the standardized distance between each pair of subjects based on the variables in each domain is created. Clustering of subjects based on these standardized distances is performed using the average linkage method.[44] This algorithm initially assigns each subject to a unique cluster, and then joins pairs of clusters with similar average distances together in a hierarchical manner until all subjects are in one cluster. For each domain, the variables that are contributing most to the differences among the domain-specific clusters can then be identified. A final cluster analysis is then conducted using the most important variables from each of the preliminary individual cluster analyses, through the use of the pseudo T^2 and R^2 statistics.

6.2 Additional Analytical Considerations Specific to the Aims

Aim 1: To estimate cross-sectional prevalences and evaluate associations among baseline characteristics of subjects with UCPPS

The primary analytic approach for Aim 1 will utilize correlation coefficients and measures of association utilizing the statistical methods described in Section 6.1.4.

Aim 2: To characterize longitudinal profiles of symptoms and evaluate associations between baseline characteristics and symptom profiles over a one-year period

Sequential questionnaire data will be analyzed to determine changes in IC/PBS and CP/CPPS symptoms over time. Urologic symptoms will be assessed using both the ICSI and the GUPI as it is possible that each questionnaire may capture different aspects of the symptom experience. Symptom outcomes will be compared between males and females and subgroups determined by early *vs*. chronic symptoms.

Symptom regression will be defined as a ≥2-point reduction in the ICSI or a >7-point reduction in the GUPI from baseline, while symptom progression will be defined as a >2-point increase in the ICSI or a ≥7-point increase in the GUPI from baseline. Score changes of these magnitudes have been shown to be clinically perceptible and meaningful to patients with IC/PBS.[45,46]

These symptom score changes must be stable over the preceding 2 bi-weekly assessments in order to be classified as meeting the symptom "regression" or symptom "progression" criteria at the 6-month or 12-month assessment. Multiple logistic regression will be used to identify predictors of symptom progression or regression. Independent (predictor) variables will include gender, disease status (shorter vs. longer duration), age, and other predictors from the initial phenotyping evaluation such as presence of other chronic pain and/or functional symptoms, psychological variables of mood, personality and cognitions, and patient history variables.

Aim 3: To characterize the pattern of fluctuations in symptoms and evaluate associations between baseline characteristics and variability in symptoms over a one-year period.

Symptom improvement will be defined as a ≥2-point reduction in the ICSI or a ≥7-point reduction in the GUPI from the previous value, while symptom exacerbation will be defined as a >2-point increase in the ICSI or a >7-point increase in the GUPI. For each subject, the number of changes (improvements or exacerbations) over the 12-month period will be totaled. This value will be analyzed as the dependent variable in a multivariable model that includes gender, disease status (early *vs*. chronic), age, and other predictors from the initial phenotyping evaluation such as presence of other chronic pain and/or functional symptoms, psychological variables of mood, personality and cognitions, patient history variables, etc.

These two outcome variables, *viz.*, symptom progression and symptom variability, will also be examined in a moderator and mediator analysis. This analysis will examine the influence of several key proximal mediators of symptom presentation, including non-urological co-morbidity, mood, currently perceived stress, and coping ability on symptom severity and change over time as well as the role of longer term vulnerability factors, including early life trauma and psychological trait variables as moderator variables in determining patterns of symptoms over the 12-month study.

This analysis will apply longitudinal growth curve model (LGCM) to test the hypotheses regarding the impact of vulnerability factors (e.g., early life stress and personality) on the overall severity (mean symptom level), pattern (trajectory of symptoms over time), and impact of IC/CP (QOL and healthcare use). Specifically, for each candidate moderator variable, a general linear mixed model analysis employing sequential sums of squares will be applied to test a completely saturated model that includes the main effects of the candidate moderator variable and time, followed by the main, linear, and quadratic effect of the moderator on symptoms (or impact) over time. Under this framework, a significant interaction involving the moderator variable will indicate that the pattern of symptoms (or impact) depends on the level of the moderator variable. The severity of symptoms (or impact) will be assessed by testing the intercept of the mean-centered outcome trajectories. The interaction of the vulnerability factors (familial modeling, *adverse life events*, genetic factors) will also be tested as a potential moderator of IC/CP presentation. The relationship between the vulnerability factors and co-morbidity, and the relationship between concurrent mediators and UCPPS presentation (e.g., life stress at month 6 and symptom severity at month 6) will be assessed using Pearson correlations.

Mediators of UCPPS. Mediators are intervening variables that occur or change before outcome assessment, and may explain the mechanisms by which a moderator affects outcome.[47,48] In the presence of a significant moderator effect, mediation may depend upon the value of the moderator. Therefore, where significant moderator effects are observed, mediation will be assessed in the context of moderation via mediated-moderator analyses using a structural equation modeling framework.[49-51]

Structural equation modeling will be performed using a full information likelihood estimation mediation analysis to deal with missing data. Specifically, longitudinal cross-lagged

mediation analyses will assess mediation of the relationship between a vulnerability factor and UPPS presentation using current life stress, coping, and symptom anxiety as mediators across Months 2, 4, 6, 8, 10 and 12.[51] Consistent with our hypotheses, we will test a model specifying that the effect of vulnerability on UPPS presentation at Month 4 (or 6, 8,10 or 12) was mediated by changes in the proposed mediators at Month 2 (or 4, 6, 8, or 10, respectively). This model satisfies conditions of temporal precedence and provides a strong test that changes in the proposed mediators leading to changes in UCPPS presentation at the subsequent assessment.[48,51] The effects of baseline status on the mediator variables, functional pain and psychiatric co-morbidity, and the influence of the vulnerability factors on co-morbidity will also be controlled.[51]

Aim 4: To identify factors that are predictive of more severe illness impact (including healthcare seeking and decreased quality of life) in individuals with UCPPS.

Using responses from the MAPP Health Care Utilization questions, a healthcare seeking score will be created for each patient for each 6-month period. The numerator will be the sum of telephone calls + (unscheduled office/ER visits x 2) + medication changes. The denominator will be the number of bi-weekly assessments that are completed by the patient. Both this mean healthcare seeking score and the bi-weekly healthcare seeking data will be used in separate analyses.

Multivariate models will be utilized to identify factors that are associated with greater healthcare seeking scores. These factors will include gender, symptom duration, baseline symptom severity, symptom variability, presence of other somatic symptoms at baseline, and presence of psychological co-morbidities at baseline.

For analyses of predictors of decreased quality of life, condition-specific HRQOL will be assessed using the QOL subscale of GUPI. This subscale includes three questions, with a score range of 0 to 12. General HRQOL will be assessed using the SF12. The GUPI will be administered bi-weekly to yield 26 data points over the 12 months of the study. The SF-12 will be assessed bi-monthly to yield 6 data points. For each questionnaire, mean QOL for the duration of the study will be assessed by summing the questionnaire scores and dividing by the total number of times that it was completed over 6 months. As with healthcare seeking, both the mean and bi-monthly QOL scores will be used in separate analyses. Within each individual, these mean scores will be analyzed using multivariate models as above to identify intra-individual predictors of reduced QOL.

Aim 5: To identify risk factors for self-reported worsening of symptom (flares) among individuals with UCPPS.

To investigate possible associations between recent exposures and flares and to adjust for any potential confounders, we will use conditional logistic regression, including all assessments from each patient in clusters of flare and non-flare assessments. Only patients who have at least one flare and one non-flare assessment will be included in the analysis, as patients with all flare or all non-flare assessments do not contribute information towards predictors of flares. Stratified analyses will be performed by gender to determine whether risk factors for flares are similar by gender.

To test the sensitivity of study findings to flare and non-flare definitions, we will re-analyze the data using flare and non-flare classifications determined by changes in symptom severity as measured by the symptom indices. We will also use these indices to stratify flare/non-flare clusters into larger and smaller changes in symptom severity to investigate whether or not risk factors differ by severity of symptom exacerbation. This analysis can be further stratified by each patient's median symptom score, as a smaller change in symptom severity in a patient with generally higher symptom scores may be different than a smaller change in symptom severity in a patient with generally lower symptom scores, and the same may be true for larger changes in symptom severity. To further test the sensitivity of study findings to flare and non-flare definitions, we will perform sub-analyses restricted to younger

participants and participants with a shorter duration of disease, as studies have observed, at least for CP, that symptom scores tend to improve over time,[52,53] and that older patients or those who have had their condition for a longer period of time appear to be less distressed by their symptoms.[54] These observations suggest that patients may cope better with their disease over time, which could potentially influence how they classify their assessments (i.e., flare or non-flare). For instance, an assessment that a patient might classify as a flare assessment (with correspondingly high symptom score) early in the natural history of their disease might be classified as a non-flare assessment (with correspondingly lower symptom score) later in the natural history of their disease simply because the patient has become less distressed by his/her condition. For similar reasons, we will also stratify participants by their number of flares prior to baseline.

To investigate the possibility that study findings may have been influenced by recall bias, we will restrict each specific analysis to participants who did not report that particular risk factor as the putative cause of their flare. For instance, in the analysis of alcohol consumption and flares, we will conduct a sensitivity analysis excluding participants who reported that they believed that "eating a certain food or drinking a certain beverage" caused their flare to avoid including participants who may have potentially over-reported their alcohol consumption at the time of their flare assessment based on their individual hypotheses.

Finally, to investigate the possible influence of misclassification of exposures due to poor recall, we will perform sub-analyses restricted to flare/non-flare clusters with short durations of time (e.g., <4 days) between the date of onset of flare symptoms and the bi-weekly assessment, as these participants should have better recall of their pre-flare exposures than participants with a longer duration of time between the date of onset of flare symptoms and the bi-weekly assessment.

6.3 Sample Size and Power Considerations

6.3.1 Sample Size and Stratification

The study is targeted to recruit a minimum of 380 subjects, 60 subjects from each of the six Discovery Sites and 20 subjects from the Stanford Site. As outlined in Section 4.1, each site will be expected to recruit equal numbers of males and females, regardless of diagnosis, targeting half of these subjects to be those with symptoms for less than two years. Thus, each site will have a recruitment target of 15 subjects in each of 4 groups defined by sex and duration of symptoms. It is expected that the target of 360 subjects can be met within two years.

6.3.2 Interim Analyses and Monitoring

Many of the analyses are contingent upon heterogeneity of somatic and psychological comorbidities in the MAPP cohort. Although the diagnoses of FM, ISB,CFS, depression and anxiety are known to occur more frequently in female IC/PBS patients than in female controls,[55] the data to support these associations in men with IC/PBS or CP/CPPS are less robust. Furthermore, the MAPP cohort will be assessed for somatic and psychological symptoms rather than physician-assigned diagnoses. It is likely that the occurrence of these symptoms will be greater than the occurrence of specific diagnoses, but, again, there is little data to allow for definitive estimates.

Therefore, an interim analysis will be performed approximately half-way through the study (after 1 year) to evaluate whether changes to the target sample size are required. The distribution of key predictive factors, including somatic and psychological symptoms, will be assessed to ensure that sufficient differences exist. If needed, recruitment may be extended beyond two years and 360 subjects in order to achieve the power needed for all specific aims. In addition, a system of stratification could be instituted, in which these factors are identified prior to study accrual for future subjects. Since this analysis will be used only to refine sample size considerations, and will not involve comparisons of groups or statistical modeling, no formal statistical methods for sequential monitoring will be used.

6.3.3 Power Considerations

The power calculations described below provide the minimal difference that can be detected with the proposed sample size. All calculations assume a two-sided Type I error level of α=0.05 with 80% power; an additional 10% is used as an adjustment factor to compensate for clustering among clinical centers. Drop-outs are also taken into consideration in the calculations for the longitudinal comparisons, as described further below. The sample size and power considerations are based on the original recruitment goal of 360 for the study. Thus, the additional 20 participants to be recruited from the Stanford site will increase the statistical power only minimally above 80% to detect the tabled effect sizes in Tables 6-8.

Cross-sectional Associations

We first consider power considerations for cross-sectional associations. These will generally be among factors measured at baseline, although some may involve measures that do not change but are actually collected at another time point to reduce participant burden.

Consider a comparison of two groups defined by some characteristics such as the presence or absence of a potential risk factor. For binary outcomes, the minimal rate difference that can be detected depends on the prevalence of the risk factor and the rate in those without the risk factor. The table below shows the detectable rate differences and corresponding odds ratios for selected proportions of patients with the risk factor present, and rates within the two groups (based on the chi-squared test). Thus, our sample size of 360 (after adjustment for clustering among clinical centers) provides adequate power to detect absolute differences of 12%-25%. For example, with a risk factor prevalence of 25% and a baseline rate of the outcome of 10% in subjects without the risk factor, we can detect a rate difference of 14%. Also shown in the table are similar results for a sample size of n=180, which would be used for some of the evaluations within groups, particularly by gender. In addition, 95% confidence intervals for rates, such as the proportion of subjects demonstrating symptom progression, will be no wider than ±5.2% with n=360 and ±7.3% with n=180.

Table 6: Detectable Rate Differences and Odds Ratios for a Binary Outcome

Overall Sample Size	Risk Factor Prevalence	Rate in Those with Risk Factor (P1)	Rate in Those Without Risk Factor (P2)	Rate Difference (Delta)	Odds Ratio
n=360	10%	10%	32%	22%	4.2
		25%	50%	25%	3.0
		40%	65%	25%	2.8
	25%	10%	24%	14%	2.8
		25%	42%	17%	2.2
		40%	58%	18%	2.1
	40%	10%	22%	12%	2.5
		25%	40%	15%	2.0
		40%	56%	16%	1.9
n=180	10%	10%	42%	32%	6.6
		25%	60%	35%	4.6
		40%	74%	34%	4.3
	25%	10%	31%	21%	4.0
		25%	50%	25%	3.0
		40%	65%	25%	2.8
	40%	10%	28%	18%	3.5
		25%	47%	22%	2.6
		40%	62%	22%	2.5

Statistical Considerations and Analytic Plan

For continuous outcomes, the minimal effect size that can be detected also depends on the prevalence of the risk factor. As displayed in the table below, the standardized minimal effect size (after adjustment for clustering among clinical centers) that can be detected is between 0.32σ and 0.54σ (based on a two-sample *t*-test). Detectable effect sizes for a total sample size of 180 subjects are also shown.

Table 7: Detectable Effect Sizes for a Continuous Outcome

Overall Sample Size	Risk Factor Prevalence	Effect Size (σ)
n=360	10%	0.54
	25%	0.36
	40%	0.32
n=180	10%	0.78
	25%	0.52
	40%	0.46

Longitudinal Outcomes: Comparing Change Over Time

Sample sizes for this type of analysis can be based on the comparison of slopes between subgroups utilizing random effects regression models, which allow incorporation of both between- and within-subject sources of variability to account for the repeated measures in study design. Power calculations are based on standard formulas that have been extended to allow for drop-outs and random slopes.[56,57] To illustrate, we present three tables showing the minimum detectable differences in slopes over 12 months for continuous outcomes measured bi-weekly, bi-monthly, or only at the three phenotyping in-clinic visits. For bi-weekly measurements, up to 27 repeated observations will be available on each subject. Up to 7 repeated observations will be available for measures obtained from the bi-monthly assessments.

More specifically, consider comparing the longitudinal change in the total MGUPI score between two subgroups, say males with recent onset (<2 y) of UCPPS *vs*. longer-term (≥2 y) onset of UCPPS. Using all patients (n=313 males) randomized to the control arm within each of the four NIDDK-funded CP/CPPS trials, *viz.*, (1) CIPRO/Flomax (n=49); (2) Alfuzosin (n=134), (3) Pregabalin (n=106), and (4) PT pilot trial (n=24), and fitting total CPSI over time in a regression model, yielded a between-subject estimated standard error of 7.95 [sqrt(MSE)]. With 360 subjects, the detectable difference in slopes over 12 months is shown in the table below for various choices of the intra-subject correlation (ρ=0.2, ρ=0.5, ρ=0.8). These effect sizes for detectable differences in slopes have been adjusted for uniform loss-to-follow-up over time of up to 15% by the end of 12 months. Similar calculations are also shown for n=180.

Table 8A: Detectable Differences in Slopes over 12 Months the NIH-CPSI Score.

		Detectable Difference in Slopes		
Overall Sample Size	**Risk Factor Prevalence**	**ρ=0.2**	**ρ=0.5**	**ρ=0.8**
N=360	10%	2.9	2.3	1.5
	25%	1.8	1.5	0.9
	40%	1.5	1.1	0.7
N=180	10%	4.1	3.2	2.1
	25%	2.6	2.1	1.3
	40%	2.1	1.6	1.0

Table 8B: Detectable Differences in Slopes over 12 Months for a Continuous Outcome with Bi-monthly Measurements

	Risk Factor	Detectable Difference in Slopes		
Overall Sample Size	**Prevalence**	**ρ=0.2**	**ρ=0.5**	**ρ=0.8**
N=360	10%	5.1	4.1	2.6
	25%	3.2	2.6	1.6
	40%	2.6	2.0	1.3

N=180	10%	7.2	5.7	3.6
	25%	4.6	3.6	2.3
	40%	3.6	2.9	1.8

Table 8C: Detectable Differences in Slopes over 12 Months for a Continuous Outcome with Repeated Measurements at Phenotyping Visits

Overall Sample Size	Risk Factor Prevalence	Detectable Difference in Slopes ρ=0.2	ρ=0.5	ρ=0.8
N=360	10%	6.4	5.1	3.2
	25%	4.0	3.2	2.0
	40%	3.2	2.5	1.6
N=180	10%	9.0	7.1	4.5
	25%	5.7	4.5	2.9
	40%	4.5	3.6	2.3

Moderator, Mediator Analysis of Symptom Fluctuations

The structural equation modeling (SEM) framework applied for mediation analysis is akin to estimating a series of linear regression equations simultaneously. The sample size is set to provide adequate power to test mediation analyses as this would provide more than adequate power for the moderator and correlation analysis. LGCMs are multi-level analyses comprising with-in individual (level-1) variance on repeated measures and between-individual (level-2) variance. Because there are no specific hypotheses regarding the level-1 variance, and the hypotheses are restricted to explaining between individual variance, the statistical power analysis is conducted based upon multivariate linear regression for a one-level sampling design that yields a simple random sample size required for adequate power to detect specific effect sizes. The effect size for the power analysis is selected based upon our interest in quantifying the specific amount of independent predictive variance, vulnerability factors and mediators accounted for in the outcomes. Estimated effect sizes are drawn from related pilot studies and published papers. Effect sizes for the predictors on outcomes vary: for early life stress, R^2=0.04 to 0.08; for current life stress, R^2=0.07 to 0.21; for symptom anxiety, R^2=0.18 to 0.21; for psychological comorbidity, R^2=0.15 to 0.30 and for coping, R^2=0.21. Using these estimates and G*Power, we can determine the simple random sample size necessary to detect a small but significant and clinically relevant increase (R^2=0.04; effect size r=0.20) in the proportion of variance accounted for after controlling for the other predictors in the LGCM. Results indicated that 200 subjects would provide adequately power (0.8) for the statistical analyses to detect an effect size as small as R^2=0.04 if such an effect exists. So the sample size proposed for this study should be more than adequate.

Case-crossover Design for Flares

Each patient who experiences at least one flare will provide a minimum of one flare assessment and a maximum of three flare assessments as well as three non-flare assessments, resulting in 1:3 up to 3:3 matching. We anticipate that at least 28.5% of the participants will have either all flare or all non-flare assessments, and thus will not be used in the analysis. This percentage was derived by taking the complement of the average reported, lifetime fluctuations (57-86%) in the literature for men with CP/CPPS.[58,59] To account for loss of these patients in the analysis, we inflated our sample size estimates by 40% (28.5/71.5). Sample size calculations also assume 1:3 matching, 80% power, 5% Type I error and a correlation between flare and non-flare assessments of 0.20. As can be seen in the table below, 360 patients will give us at least 80% power to detect a matched odds ratio of 1.75 with a Type I error of 5% assuming a probability of exposure among non-flare assessments of 0.15, and a correlation between flare and non-flare assessments of 0.20.

Table 9: Detectable Matched Odds Ratios for Various Exposure Rates

Probability of	Matched odds ratio

exposure at non-flare assessments	1.50		1.75		2.00		2.25		2.50	
	Inflation Factor		Inflation Factor		Inflation Factor		Inflation Factor		Inflation Factor	
	Before	After	Before	After	Before	After	Before	After	Before	After
0.10	697	976	348	487	160	305	154	216	117	164
0.15	503	704	253	354	132	224	114	160	87	122
0.20	409	573	208	291		185	95	133	73	102
0.25	356	498	183	256	117	164	85	119	66	92
0.30	324	354	168	235	108	151	79	111	61	85

7 HUMAN SUBJECT CONSIDERATIONS

7.1 Trans-MAPP Participant Considerations

7.1.1 Trans-MAPP Participant Recruitment

Participant recruitment will be conducted through the urology/urogynecology clinics at each of the designated clinical sites. In some cases, local newspapers and other media will be used to promote these MAPP research study opportunities. Participants may be self-referred or referred through their primary physician (either solicited or unsolicited by the urology/ urogynecology clinics). Possible participants will be introduced to the protocol by study investigators and/or the research coordinator, and asked whether they are interested in participating in the study.

The process of securing local physician approval and contacting the screening candidate will depend on prevailing guidelines of local IRBs, the requirements of each medical facility and the governmental HIPAA Guidelines which became effective in April 2003. Typically, candidates will first learn of the study from an invitational letter signed by the local principal investigator and/or personal physician. Occasionally, some individuals may learn of the study during a routine encounter with a healthcare provider who has agreed to assist in recruitment. Those individuals who express preliminary interest in the study will have a screening telephone/clinic visit to confirm eligibility. Those who remain interested will be scheduled for the screening/baseline visit, at which point a written informed consent is obtained.

7.1.2 Screening and Enrollment

The screening and enrollment process will require one in-clinic visit. The visit is structured such that essential information required to assess eligibility is acquired prior to the conduct of more intensive and time-consuming procedures required of the baseline visit. [See Appendix A]. Key eligibility criteria will be reviewed and confirmed, baseline measures will be collected, medication data will be collected, a urine sample will be obtained, a blood specimen will be drawn, and a cheek swab will be obtained.

The screening/baseline visit will be conducted as an in-person clinic visit to obtain informed consent for the entire protocol, confirm study eligibility, and provide participants with additional information about the study. Contact information and a questionnaire assessing eligibility will be completed and a urine dip stick and urine culture will be carried out. Those persons who are eligible after the initial screening process will be invited to complete the Trans-MAPP “deep” phenotyping assessments. The completion of the screening/baseline visit, followed by a negative 48 hour urine culture result, defines enrollment in the Trans-MAPP EP Study.

7.1.3 Participant Follow-up

Participants who enroll in the study and complete a screening/baseline visit will be followed up with bi-weekly and bi-monthly internet questionnaires, as well as in-person clinic visits at 6 and 12 months following their initial baseline visit. A complete listing of protocol elements to be collected at the baseline/screening and follow-up visits is provided in Appendix A: Participant Contact Schedule.

During the course of the study, participants will be contacted by the Discovery Site Research Coordinators with email reminders to log on for their bi-weekly and bi-monthly assessments, as well as to facilitate scheduling of the 6- and 12-month follow-up visits. Participants who do not complete their scheduled bi-weekly or bi-monthly contact assessments will be contacted by phone for further prompting or discussion of any issues with study participation.

7.1.4 Participant Retention

Retention of participants is central to internal validity of the study and will be an extraordinarily high priority of the investigators and staff. A key element is a pleasant, attentive and responsive staff that provides a reasonably flexible schedule. Other clinical center features that promote high retention rates include local tracking systems and frequent staff meetings.

7.1.5 Participant Withdrawal

It is anticipated that over the course of the 12-month follow-up period, participants may withdraw from the study. This may occur officially by formal notification from the participants to the investigator, or unofficially when a participant cannot be reached via the usual methods of contact. Every effort will be made to acquire complete data on all participants. However, a participant may withdraw consent for use of his or her data at any time.

Participants who relocate to an area from which it is no longer feasible to travel to the center for the 6- and 12-month in-clinic visits will be asked to continue participation in the study by completing the bi-weekly and bi-monthly online assessments.

7.1.6 Participant Reimbursement

As compensation for their time and effort, subject reimbursement (provided by each site) should be provided. Appropriate amounts and actual schedule of reimbursements should be determined by each site.

7.2 Ethical Issues

7.2.1 Potential Risks to Participants

The potential risks to study participants are minimal as the protocol is predominantly based on questionnaire data. The protocol also includes a single baseline physical examination. Minimal physical risk to participants arises from the physical exam procedures and the collection of blood specimens.

7.2.2 Risk/Benefit Assessment

This is a study to investigate the relationship between UCPPS and other chronic pain conditions to better understand the pathophysiology of these often disabling syndromes. Although there will not be any direct benefits to the participants, the information obtained from this study has considerable potential benefit to future patients and to society as a whole by providing new information about the pathophysiology of these conditions. This study may well lead to the discovery of common risk factors, symptoms, or potential biomarkers related to these complex disorders, and may, therefore, lead to improved management and treatment.

Gender and Minority Inclusion

This is a multi-center study recruiting a clinical population from numerous institutions across the United States. We estimate the racial/ethnic composition of participants to be approximately 85% White/Caucasian, 10% African American, and 5% Latino/Hispanic, Asian/Pacific Islander, and Other. We plan to enroll equal numbers of men and women.

7.2.3 Informed Consent

Interested participants will be asked to sign the informed consent form approved by the local Institutional Review Board (IRB). This form will provide consent for the screening and the follow-up procedures as well as permission to contact them in the future. Potential participants must sign written consent to participate prior to initiating screening/baseline visit data and/or specimen collection.

Each Discovery Site will prepare an informed consent form following the guidelines of their local IRB, and applicable regulations for Informed Consent. The form will, at a minimum, contain a description of the potential risks, benefits, expense to the subject, and alternative treatment. Prior to signing the informed consent, the Research Coordinator will review the details of the consent form orally with the participant, and answer any questions that the participant has concerning participation in the study. The original signed consent form will be kept in the participant study file at the clinical center, while a copy of the signed consent form will be given to the participant. 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 or negative impact on their medical care
- The participant must be informed of the **purpose** of the study and that it involves **research**
- The participant must be informed of any **alternative procedures**, if applicable
- The participant must be informed of any reasonably 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 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 or she decides to enroll
- The participant must be informed **whom to contact** for information about research subjects' rights, information about the research study, and in the event of research-related injury
- The participant must be informed as to whether or not **compensation** is offered for participation in the study and/or in the event of a medical injury
- The participant must be informed that he/she will be notified of any significant **changes** in the protocol that might effect their willingness to continue in the study

The consent process may differ somewhat by clinical center according to local IRB guidelines. The informed consent document will be structured such that it enables potential participants to indicate which aspects of study they may not be willing to engage in. This form will cover all aspects of screening, baseline testing and subsequent follow-up visits.

7.2.4 Consent for Genetic Testing and DNA Storage

A separate section and signature page will be required for consent to collect a cheek swab sample for genetic testing and storage of DNA. In case no cheek swab sample is collected, a blood sample will be used for the genetic testing. In order to proceed with eligibility confirmation, participants must sign consent for use of DNA for genes related to the main goals of this study. However, they may refuse to sign the separate consent for use of DNA for genes unrelated to the main goals of this study without consequence to study eligibility. Specimens will be stored at TATC, and eventually shipped for permanent storage at the NIDDK repository.

Participants will be informed that DNA and other biological samples may be used for many types of genetic and biomarker analyses, but that the confidentiality of this information will be ensured by (1) data security measures, both at the participating sties and DCC, and (2) at the point that their clinical information is combined with biological data (e.g., genetic studies) where these datasets will be de-identified. We will include more specifics about this for the IRB submittals.

7.2.5 HIPAA Authorization

In accordance with the mandated Federal HIPPA regulations, authorizations will be provided to all research participants at the time of presentation of consent that detail all potential risks of disclosure and individuals and organizations who may have access to participant research data.

7.3 Participant Confidentiality

Procedures to assure confidentiality will be strictly observed. All identifiable personal health information data will be (1) kept in confidential locked files; (2) identified by subject number only; and (3) kept separately from identifying information used for subject tracking and follow-up contacts. Identifying information will be kept in separate locked files. No identifying information will be disclosed in reports, publications or presentations.

Protection of participants depends on the joint activities of all Clinical Centers as well as the DCC. Extensive efforts will be made to ensure that participants' confidentiality is maintained. Each participant is assigned a unique study identification number and is never tracked through the study by name, social security number, medical record number, or other personal identifier. A log of the participant names, participant ID numbers, and pertinent registration information (e.g., home address, telephone number, and emergency contact information) is maintained in a locked area at each clinical site. The staff at the DCC does not have access to this log. Only the participant ID number and initials are given to the DCC staff and entered into the study database. Any communication between DCC and clinical sites regarding participant data occurs via the participant ID number. Any forms or documents sent to DCC, IRB or other regulatory authorities will have all personal information removed.

Authorized representatives of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), participating clinical institutions as well as the IRB have access to and may copy both medical records and records from participation in this study consistent with the policy of the NIH Certificate of Confidentiality. Such access is necessary to ensure the accuracy of the findings, the safety and welfare of participants. If any publication or presentation results from this research, participants will not be identified by name or other personal identifier. All research reports, articles, and presentations will report only aggregate findings.

8 STUDY ORGANIZATION AND OVERSIGHT

8.1 Discovery Sites

Six (6) Discovery Sites participating in the Trans-MAPP EP will have primary responsibility for developing the study protocol, recruiting a sufficient number of study participants, maintaining high rates of follow-up and data collection, obtaining data of high quality, and interpreting, presenting, and publishing findings from the study. The 6 Discovery Sites, with Principal Investigators, are as follows:

1. University of California, Los Angeles (UCLA), Los Angeles, CA
   Principal Investigators: Emeran A. Mayer, M.D.
   Professor and Executive Director
   Center for Neurobiology of Stress

   Larissa V. Rodriguez, M.D.
   Associate Professor in Residence
   Department of Urology

2. Northwestern University, Chicago, IL
   Principal Investigators: David J. Klumpp, Ph.D.
   Assistant Professor
   Department of Urology

   Anthony J. Schaeffer, M.D.
   Herman L. Kretschmer Professor & Chairman
   Department of Urology

3. Washington University, St. Louis, St. Louis, MO
   Principal Investigators: Gerald L. Andriole, M.D.
   Professor of Surgery
   Chair, Division of Urologic Surgery
   Director, Prostate Study Center, Barnes-Jewish Hospital

   H. Henry Lai, M.D.
   Assistant Professor of Surgery
   Division of Urologic Surgery

4. University of Iowa, Iowa City, IA
   Principal Investigator: Karl J. Kreder, M.D., M.B.A.
   Professor and Clinical Vice Chair
   Director, Urodynamics and Reconstructive Urology

5. University of Washington, Seattle, WA
   Principal Investigator: Dedra Buchwald, M.D.
   Professor, General Internal Medicine

6. University of Michigan, Ann Arbor, MI
   Principal Investigators: Daniel J. Clauw, M.D.
   Professor of Anesthesiology & Medicine – Rheumatology, Director, Chronic Pain & Fatigue Research Center.

   J. Quentin Clemens, M.D., M.S.C.I.,
   Associate Professor of Urology, Director, Division of Neurology & Pelvic Reconstructive Surgery

Study Organization and Oversight

The Washington University Discovery Site encompasses two additional recruitment/satellite sites:

- Thomas M. Hooton, MD, Professor of Medicine
  Angelo E. Gousse, MD, Professor of Urology
  University of Miami Miller School of Medicine
  Department of Medicine
  Miami, FL 33136

- Timothy J. Ness, MD, PhD, Director, Pain Treatment Research, Professor of Anesthesiology
  Georg Deutsch, PhD, Director, Multidisciplinary Neuroimaging
  Laurence A. Bradley, PhD, Professor of Medicine
  University of Alabama at Birmingham, Birmingham, AL

In addition to the Discovery Sites and Satellite/Recruitment Sites listed above, the following individuals were funded to provide expertise in particular scientific and translational areas related to MAPP goals:

Investigators:	Sean Mackey, M.D., Ph.D. Chief, Pain Management Division, Associate Professor, Stanford University School of Medicine
	Marsha A. Moses, Ph.D. Co-Director (Interim), Vascular Biology Program, Professor, Department of Surgery, Children's Hospital Boston, Harvard Medical School
	J. Curtis Nickel, MD, FRCSC Department of Urology, Queen's University, Kingston, Ontario, Canada
	J. William Costerton PhD, Garth D. Ehrlich PhD Biofilm Research Lab, Allegheny-Singer Research Institute, Microbiology & Immunology and Human Genetics, Drexel University and Center for Genomic Sciences, Pittsburgh, PA

8.2 Data Coordinating Core (DCC)

The Data Coordinating Core (DCC) for the MAPP Research Network is located at the University of Pennsylvania School of Medicine, Philadelphia, PA.

Principal Investigator:	J. Richard Landis, Ph.D., Professor of Biostatistics, University of Pennsylvania
Co-Principal Investigator:	Kathleen J. Propert, Sc.D., Professor of Biostatistics, University of Pennsylvania
Co-Investigator (IC/PBS):	Philip M. Hanno, MD, Professor of Urology in Surgery, University of Pennsylvania
Co-Investigator (CP/CPPS):	Michel Pontari, MD, Vice-Chairperson and Professor, Department of Urology, Temple University

The DCC is responsible for the following:

- Set-up and maintenance of the MAPP longitudinal data collection website for patient-reported outcomes
- Providing biostatistical expertise in research design, outcome measures and analytic strategies for translational and clinical investigations of UCPPS
- Guiding and implementing statistical analyses, interpretation of findings, and supporting presentations and publication of results
- Facilitating the conduct of multi-disciplinary basic and translational research, by providing scientific leadership in the design and implementation of research projects across the MAPP Research Network
- Promoting network-wide quality assurance standards, practices and tools, including a comprehensive, secure www-based data management system (DMS) for collection and centralized storage of all multi-site study data
- Collaborating with the TATC Laboratory on best practices for data collection, specimen tracking and storage, as well as support technical processes between the DCC and TATC
- Providing comprehensive Data Coordinating Core administrative support for the MAPP Research Network, promoting effective communications, coordinating meetings, working groups, document development and management, and distribution of study proceedings
- Supporting the MAPP Research Network Ancillary Projects, assisting in their design, as well as implementing a process for the submission, review, and development of ancillary studies

8.3 Tissue Analysis and Technology Core (TATC)

The Tissue Analysis and Technology Core (TATC) is located at the University of Colorado, Denver School of Medicine, Department of Pathology, Aurora, CO

Principal Investigator:	M. Scott Lucia, M.D., Associate Professor of Pathology, University of Colorado, Denver
Co-Principal Investigator:	Karen Jonscher, Ph.D., Assistant Professor, Director of CNRU Proteomics Core Facility, University of Colorado, Denver
Co-Investigator:	Adrie van Bokhoven, Ph.D., Assistant Professor of Pathology, University of Colorado, Denver
Core Consultant:	Uwe Christians, M.D. Ph.D., Professor, Department of Anesthesiology, University of Colorado, Denver
Core Consultant:	Regina Santella, Ph.D., Professor of Environmental Health Sciences, Columbia University, New York

The TATC will be responsible for the following:

- Providing specimen collection, banking, annotation/blinding, distribution services across the MAPP Research Network
- Providing genomic and proteomic analyses and generate assay platforms for multi-site efforts and individual site efforts as needed
- Coordinating procedures for coding, shipping, processing, receipt and storage of biosamples at the TATC site and future transfer of the biorepository to the NIDDK Biorepository

8.4 NIDDK Program Staff

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) will be responsible for oversight and administration of the scientific conduct of this research. Representatives from the NIDDK will work with the DCC and TATC to develop and implement the study.

Study Organization and Oversight

NIDDK Program Staff:	Christopher Mullins, Ph.D., Director, Basic Cell Biology Programs in Urologic & Kidney Disease John W. Kusek, Ph.D., Director, Kidney & Urological Clinical Trials Leroy M. Nyberg, M.D., Ph.D., Director, Urology Programs

8.5 MAPP Steering Committees and Subcommittees

The primary governing body of the study is the Steering Committee, which is comprised of each of the Directors/Co-Directors at the Discovery Sites, DCC, TATC, and the NIDDK Project Scientists. Dr. Dan Clauw from the University of Michigan is the Chair of the Steering Committee. The Steering Committee develops policies for the study pertaining to access to patient data and specimens, ancillary studies, performance standards, publications and presentations. They develop the study protocols and meet to discuss the progress of the study and resolve problems that arise.

A subset of the Steering Committee membership makes up the Executive Committee. This includes NIDDK MAPP Program staff, together with the Chair (Clauw) and Co-Chairs (Hanno, Pontari) of the Steering Committee, the DCC PI and co-investigators, and the TATC PI. The Executive Committee has frequent (typically weekly) teleconferences and makes the day-to-day decisions of the MAPP, consulting the larger Steering Committee or specific members where necessary.

In addition to the Steering and Executive Committees, subcommittees may be established on such areas as recruitment and quality control, publications, and ancillary studies. Small working groups may be established to prepare manuscripts and presentations. The following subcommittees have been established to address specific study issues:

- Biomarkers Working Group
- Epidemiological Study Working Group
- Neuro-Imaging Working Group
- Organ Crosstalk Working Group
- Phenotyping Working Groups: Urological and Non-urological
- Study Design/Forms Review Subcommittee
- Quality Control Committee
- Publication Committee

8.6 Scientific Advisory Committee (SAC)

A Scientific Advisory Committee (SAC) for the MAPP Research Network was appointed to review protocols and advises the NIDDK Program staff in the overall conduct of the MAPP Research Network. An independent group of experts in areas such as Urology, Rheumatology, Epidemiology, Ethics, Health Economics, and Biostatistics who are not otherwise involved in the study have been recruited by the NIDDK to evaluate the proposed protocol and periodically review the progress of the study.

9 STUDY MANAGEMENT

9.1 Discovery Site Responsibilities

9.1.1 Discovery Site Director and Investigators

Conduct of particular aspects of the study may be delegated to qualified personnel; however, it is the responsibility of each Discovery Site Director to oversee the overall study management. The Discovery Site staff must be trained in all study procedures.

Each Discovery Site is responsible to screen, recruit, enroll and retain a designated number of study participants. It is the responsibility of the Discovery Site study staff to assess their accrual, ensure participant confidentiality, maintain appropriate study documentation, enter and transfer data in a timely manner, and participate in the MAPP study meetings and conference calls.

9.1.2 Institutional Review Board

It is the responsibility of each Discovery Site to conduct the study according to the protocol, and to adhere to all applicable regulatory guidelines, and 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 and TATC, prior to screening or enrolling subjects. The Investigator also maintains the responsibility of initiating protocol re-approval, notification of protocol and/or consent form changes, notification of unanticipated events, and termination of the study according to the appropriate IRB requirements.

9.1.3 Record Retention

Investigators maintain study documents on-site and in an orderly fashion for a minimum of 6 years, and make available to the sponsor or the sponsor's representative: the signed study protocol, amendments, informed consent documents, and approval letters from the IRB, CRFs, all primary source documentation, and all letters of correspondence. The DCC maintains all study records for a period in accordance with their internal SOPs and applicable regulations.

9.2 Data Coordinating Core responsibilities

9.2.1 Quality Assurance

The DCC has developed written standard operating procedures (SOPs) to ensure that all aspects of the study are conducted in a standard and uniform manner. These procedures are organized into a Manual of Procedures (MOP), which complies with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. The DCC will include a comprehensive Quality Assurance (QA) Plan in the MOP that will consist of the following activities:

Personnel Training and Certification: Prior to this Trans-MAPP EP Study initiating patient enrollment, a comprehensive training session will be conducted with all study personnel that will encompass all aspects of the study, including communication, principles of GCP, study implementation and procedures, data entry and verification, test and specimen collection and transfer.

Clinical Protocol, MOP Adherence and Auditing Activities: The DCC will request and verify specific information from clinical centers, to ensure the application of study procedures as they apply to participant safety, required intervals for timely conduct of procedures, appropriate documentation of data and specimens, and compliance with SOPs. This information will take the form of a written report, and may be acquired during clinical site monitoring visits.

Database Auditing: A comparison of a certain percentage of data written on CRFs to that entered into the electronic database provides information that describes and quantifies the

accuracy of the data entry process and use of the data management system by personnel at each Discovery Site. This information will take the form of a written report.

Database Administration and Network Security: The DCC has SOPs established for authorizing and documenting secure access to the study website, study documents and the electronic Data Management System (DMS). These procedures ensure that only authorized personnel are able to view, access and modify study data.

Data Reporting: A set of standard reports will be developed to describe study activities that include accrual, study progress, and data quality. These reports will be developed using Oracle Reports and provided to investigators, NIDDK and designated committees as appropriate.

Preparation and Integrity of Analysis Datasets: The DCC Database Administrator will create a set of standard data access descriptor/view files, which will be used in the generation of SAS analysis datasets. As datasets are extracted from the main study database, they can be utilized separately from direct database processing, thereby, safeguarding the integrity of the data.

Data Management: The DCC provides overall coordination, logistical support, and implementation for all aspects of the study protocol including data collection, data processing, tracking of participant recruitment, tracking of specimens, training, quality assurance, and statistical analysis. The Clinical Research Computing Unit (CRCU), through its clinical data management, project management, and software systems developments, places into the field and maintains a state-of-the-art www-based data system that accommodates all scientific study data, and permits tracking and coordination of all Trans-MAPP Research Network activities within the framework of multidisciplinary project teams.

9.2.2 Website Enhancements

The DCC has developed a MAPP Network website (http://www.mappnetwork.org/) for study-wide communication management, data and document management, and activity management and coordination. The website provides general information to the public, single-point restricted access to tools and information for investigators and clinical center study personnel including study resources, communication tools as well as data entry and management tools. It also provides an additional level of restricted access for DCC study personnel.

During the in-clinic baseline phenotyping visit at the Discovery Site, after eligibility confirmation, each patient will be authenticated by the Research Coordinator (RC) into a specialized module of the data management system (DMS) deployed for patients to enter questionnaire data directly via a web browser.

Using a password-protected identity management module, this DMS will also be accessible to enrolled patients via a web browser for reporting their bi-weekly and bi-monthly contact assessments.

9.2.3 Data Security

The research computing environment for the MAPP DCC is supported by a Biomedical Research Computing (BRC) group within the Clinical Research Computing Unit (CRCU) of the Center for Clinical Epidemiology and Biostatistics (CCEB) at the University of Pennsylvania School of Medicine. The BRC group is responsible to provide an integrated research computing and storage environment in a manner that supports the required confidentiality, integrity, and access of a common set of research data through all stages of its use, operated in a FISMA-compliant/FDA sensitive manner. The MAPP project is maintained within this compliant environment.

The CCEB General System Security Plan (CCEB-GSSP) is available on request to provide a quick read into the security within the CRCU, listing several of the security attributes most requested. Also available on request is a memo from Penn's Chief Scientific Officer affirming Penn's continuing commitment to meeting and maintaining its FISMA compliance. The CCEB/CRCU has performed a security and risk assessment using outside auditors to perform a

gap analysis on its security measures against the FISMA recommended NIST SP800-18 and SP800-53 controls documents. The results of this assessment provided Penn Medicine's Chief Scientific Officer with the confidence to support and write a memo that is the AMC's equivalence of a federal "Authority to Operate (ATO) certification, as required for Federal agencies."

The CRCU database environment for MAPP utilizes Oracle's Advanced Security Option (ASO) with two primary foci: 1.) Strong encryption of the database transmissions to protect data traversing the data networks to and from the CRCU databases; and 2.) Internal database encryption of individual sensitive data elements, thus protecting ePHI data within the database. Both of these features are in use with the MAPP protocols and databases. The CRCU further utilizes a database monitoring tool that maintains an audit of all user session activities that occur against the protected MAPP databases. This tool is able to then recreate requested past user sessions to track all changes that occurred to data in the databases.

9.3 Tissue Analysis and Technology Core Responsibilities

9.3.1 Personnel Training

TATC along with the DCC will conduct a personnel training session and a certification session for staff who will perform clinical procedures before initiation of the protocol. This comprehensive training session includes all aspects of the protocol and MOP implementation such as specimen collection, handling, processing, and shipping. Periodic conference calls and training sessions will be conducted to uphold standard application of procedures.

9.3.2 Specimen Kit Distribution, Banking, Annotation/Blinding

TATC will generate and provide MAPP-specific collection kits for use by Discovery Sites as needed. Requests for kits will be done through an online ordering mechanism located on the MAPP Portal direct from TATC. The collection kits and components are bar-coded and will be linked with the participant at the time of registration of the participant with the DCC. Collected specimens will then be shipped to TATC for inventory into the biorepository.

The collection and handling procedures will follow the guidelines established by the NIH Best Practices Policies for biorepositories (www.biospecimens.cancer.gov). No patient identifiers will be used on the collection tubes and tracking forms. As specimens are received from sites, they will be scanned into the biorepository database, and archived in the appropriate freezer/storage unit until needed. Specimen tracking information will be entered into the database by TATC personnel.

9.3.3 Biorepository Collection, Management and Distribution

The TATC will act as a central repository for all body fluid and tissue specimens generated by the MAPP, its member Discovery Sites and other research entities as approved by the Network. To provide the highest quality non-biased patient samples, uniformly prepared and analyzed and to meet the needs of individual research teams, TATC will provide guidance and personnel training to collection sites on protocol development and specimen collection and handling. The TATC will develop and distribute specialized specimen collection kits, and coordinate specimen collection, processing, annotation, bar-coding, shipping, banking, and distribution. The TATC will identify and implement best information technology architecture for the MAPP research network and provided access to its services through the MAPP Research Network portal hosted by the DCC. The biorepository will meet all NIH standards, and will provide specimens to researchers according to IRB, HIPAA and NIH procedures that protect the confidentiality of all consented patients whose tissue and blood are archived. The TATC will also work with the NIDDK Biorepository to coordinate procedures for collection, coding, storage and eventual transfer as directed by the NIDDK.

Study Management

9.3.4 Specialized Assay Platforms

The TATC will generate and provide specialized assay platforms for specimen analysis such as protein and/or tissue arrays, DNA extractions and purifications as needed for individual Discovery Site efforts or ancillary/pilot projects.

-**Proteomics, Metabolomics, Transcriptomics:** The TATC will provide centralized mass spectrometry services to assist the MAPP Research Network with proper collection and handling of specimens, consultative assistance for proteomics, metabolomics, and transcriptomics studies, and performance of a wide variety of assays, including chromatography-based proteome profiling, protein arrays, cytokine arrays, multiplexed ELISA, mass spectrometry and NMR-based targeted and mass spectrometry analyses (nanoLC ion trap and nanoLC hybrid quadrupole-linear ion trap).

Genomics, Genotyping: The TATC will provide consultative assistance and genomics services to assist the MAPP Research Network with advanced genotyping techniques. Methods for analysis of single nucleotide polymorphisms (SNPs) include single base extension assays with detection of incorporated base by fluorescence polarization, Taqman single SNP assays on 96- or 384-well real-time instruments or Taqman analysis of 32 or 64 SNPs on a nanoscale. Access to Sequenom and Illumina platforms are also available for larger scale studies.

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11 APPENDICES

11.1 Appendix A: Trans-MAPP EP Study Participant Contact Schedule

11.2 Appendix B: Clinic and Home Urine Specimen Collection Protocol

11.3 Appendix C: Trans-MAPP Biomarker / Immunology / Endocrinology (BIE) Studies

11.4 Appendix D: Trans-MAPP Infectious Etiology (IE) Studies

11.5 Appendix E: Trans-MAPP Pressure Pain Threshold (PPT) Procedure

11.6 Appendix F: Case Report Forms (CRFs)

All CRFs used in the Trans-MAPP EP STUDYprotocol will be used for this study. In addition, there will be a single CRF (in development) that indicates that an individual meets the established diagnostic criteria for FM, IBS, CFS, TMD, or vulvadynia (check all that apply).