MULTIDISCIPLINARY APPROACH TO PELVIC PAIN (MAPP)

TRANS-MAPP CONTROL 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 5.0

Incorporating Protocol Amendment #, **IRB Memo dated November 11, 2009, Protocol Amendments #2, 3, and 4.**

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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

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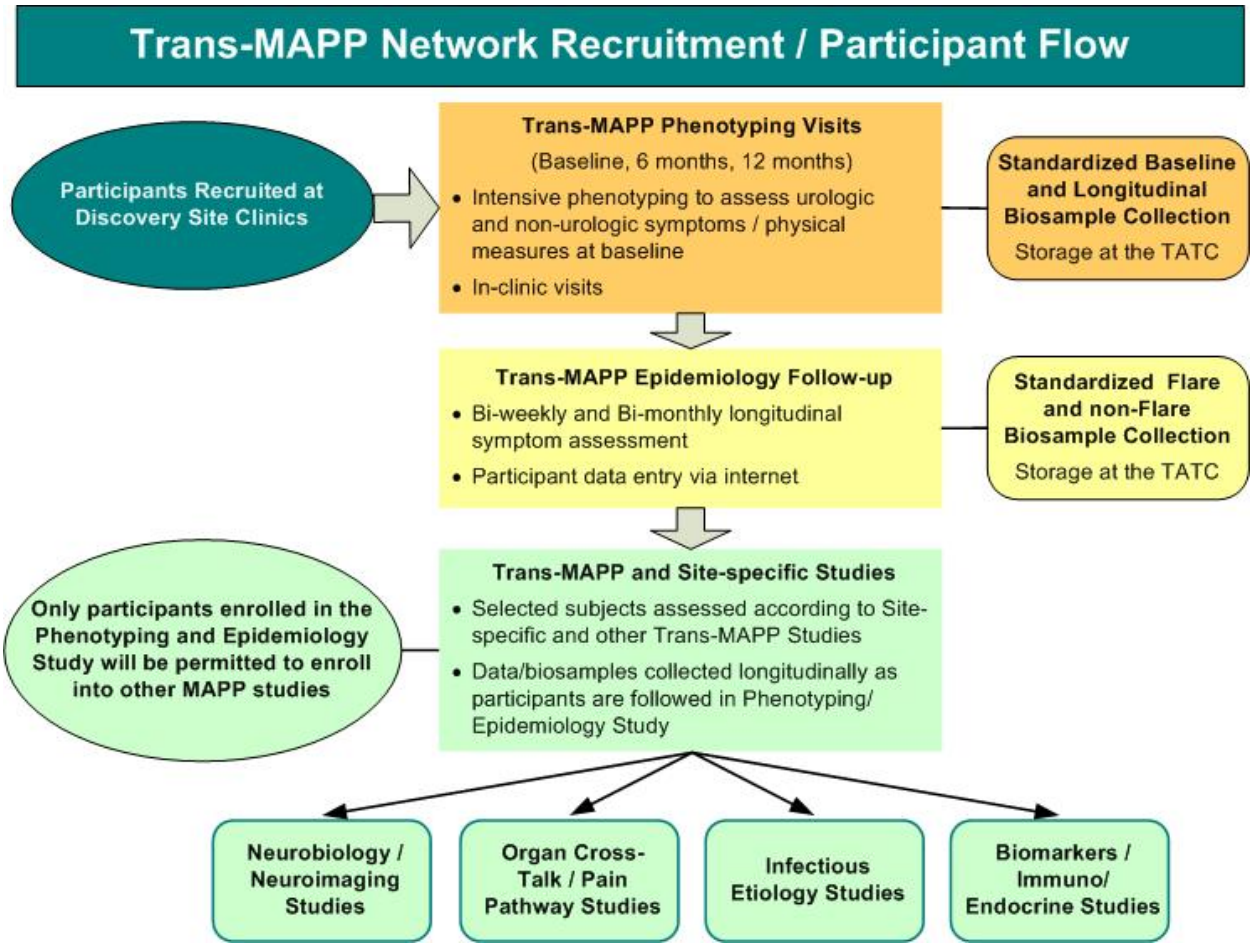
1.5. The Trans-MAPP Epidemiology and Phenotyping (EP) Study: Innovative Studies of the Characteristics of IC/PBS and CP/CPPS and a Source of Study Participants for other Trans-MAPP Research Network Studies

A major focus of the MAPP Research Network is the conduct of the Trans-MAPP Epidemiology and Phenotyping (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



TRANS-MAPP CONTROL PROTOCOL

2. TRANS-MAPP CONTROL PROTOCOL

2.1. Rationale for Trans-MAPP Control Protocol

During the planning phase for the Trans-MAPP Epidemiology and Phenotyping (EP) Study, as well as for multiple other Trans-MAPP and site-specific studies, it became clear that many of the hypotheses being proposed required well-characterized controls. In the context of the Trans-MAPP studies there are two types of controls needed: 1) healthy "normal" controls, and (2) "positive" controls with conditions such as fibromyalgia (FM), irritable bowel syndrome (IBS), or chronic fatigue syndrome (CFS).

Although many operational aspects of this protocol are the same as the Trans-MAPP EP Study, the differences in inclusion criteria, follow-up, and aspects of informed consent are extensive enough to warrant the preparation of this as a separate "companion" protocol.

Because the trans-MAPP studies have been developed since the MAPP awards were issued, sites did not adequately budget for the staff that would be required to recruit and study these controls. Thus, supplemental funding is being requested for each Discovery Site that will be used to provide the capabilities to recruit and then "phenotype" adequate numbers of controls for the Trans-MAPP studies.

2.2. Aims and Hypotheses for theTrans–MAPP Control Protocol

2.2.1. Study Hypotheses

The study will address the following hypotheses:

Hypothesis 1.	Groups of individuals with UCPPS have a higher rate of non-urological somatic and psychological symptoms and syndromes (e.g., FM, IBS, CFS, vulvadynia) than do healthy controls.
Hypothesis 2.	A variety of objective abnormalities (i.e. potential biomarkers) can be identified in UCPPS cohorts versus control cohorts, including differences in rates of genetic polymorphisms and of expression of proteins in serum and urine. Some of these differences will be shown to be specific for subsets of UCPPS patients, and others will be shown to also occur in individuals with other somatic syndromes (FM, IBS, CFS).

2.2.2. Specific Aims

Each of these hypotheses motivates a series of specific aims that will be the focus of the Trans-MAPP Control Protocol and are outlined below:

Aims Related to Hypothesis 1: To recruit and phenotype adequate numbers of both healthy and "positive" controls (FM, IBS, CFS) for the Trans-MAPP studies.

Aims Related to Hypothesis 2: To collect biological samples on these same controls, for comparison with individuals with UCPPS.

3. STUDY DESIGN

3.1. Overview of Trans-MAPP Control Study

The overall design of the Trans-MAPP Control Study includes enrollment of eligible participants during a single baseline screening clinic visit. Each participant will also provide biosamples and extensive ("deep") phenotyping data at the in-clinic baseline visit.

At the initial screening visit, participants meeting diagnostic and eligibility criteria will be enrolled, commencing immediately with an extensive phenotyping battery of baseline measures, biosample collection and a pressure pain threshold procedure.

Discovery Sites will use the same general techniques for recruiting control participants as are used for recruiting other research participants, and may include advertising or using individuals who are seen in clinical settings who fulfill the below eligibility criteria. Sites will be responsible for assuring that their cohorts of control participants are approximately the same age, gender, and ethnic composition as their cohorts of UCPPS patients; this will then ensure that the Trans-MAPP studies that are combining individuals from multiple sites will likewise be matched for these demographic characteristics.

Controls (indicated in the top left box in the figure below) will go through the same "deep" phenotyping battery at baseline as is being performed on all individuals in the Trans-MAPP EPS. This includes a battery of self-report questionnaires, a physical examination, collection of biological samples, and experimental pain testing. However, controls will not be followed longitudinally; thus, they will participate in only one baseline clinic visit.

All of the Discovery Sites for MAPP will participate in the Trans-MAPP Control Protocol. These are:

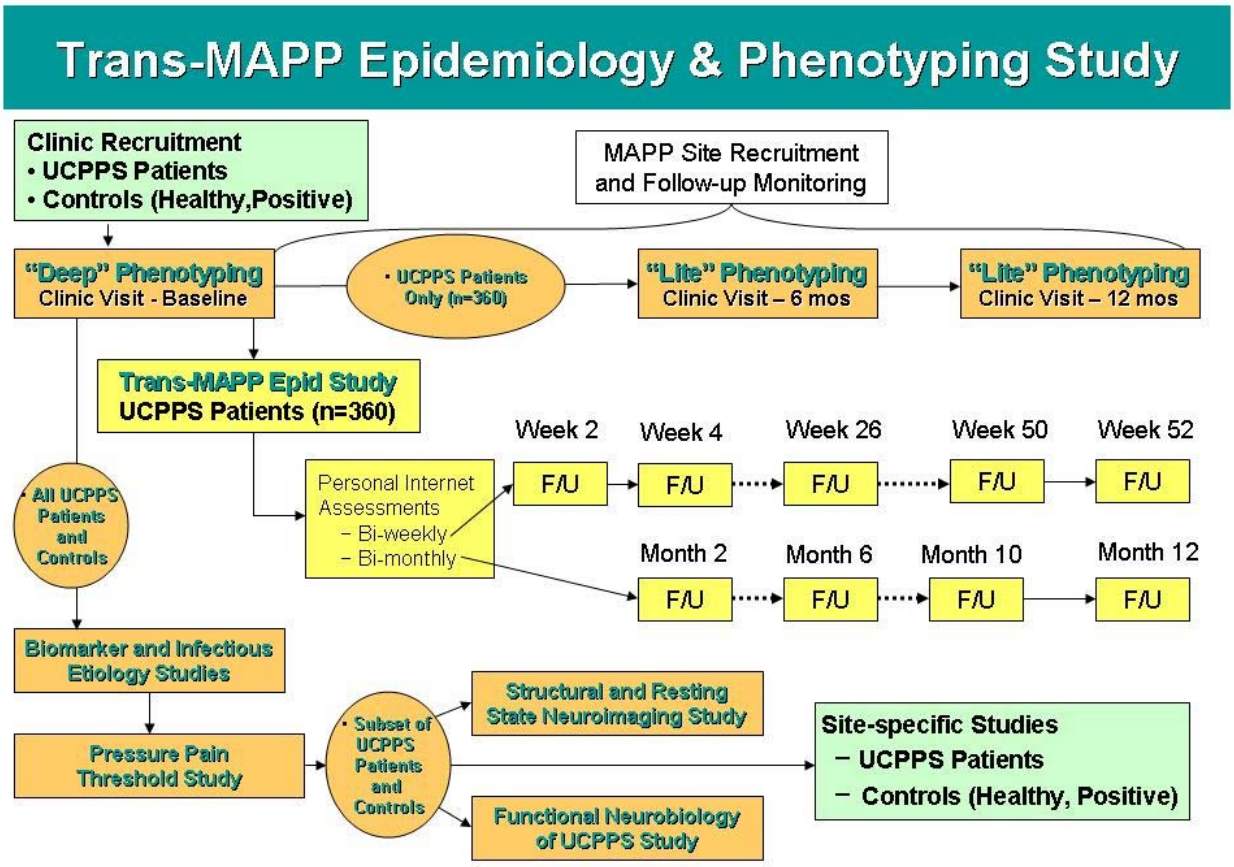
- University of California, Los Angeles (UCLA)
- Northwestern University, Chicago, Illinois
- Washington University, St. Louis, Missouri
- University of Iowa, Iowa City
- University of Washington, Seattle
- University of Michigan, Ann Arbor

In addition to these Discovery Sites, Control participants will also be recruited at

- Stanford University School of Medicine
- University of Miami Medical Center

As detailed previously, participants enrolled 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



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. 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) will be offered the opportunity to receive this pressure pain threshold procedure at a clinic visit. 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 Population and Subgroup Targets

If supplemental funding is awarded to recruit Control participants at 8 sites (6 Discovery Sites, Stanford, University of Miami supporting the recruitment goals of Washington University, St Louis), each site discovery site will be responsible for recruiting 60 healthy controls and 30 positive controls over two years; Stanford will recruit 20 healthy controls and 10 positive controls over two years. Each of these Control Study participants will complete the baseline in-clinic visit of the Trans-MAPP EP Study protocol. Thus, the Trans-MAPP Control Protocol population will include 380 adult healthy controls and 190 adult positive controls with FM, IBS, or CFS. Approximately half of the participants will be male. Consequently, the target distribution of study participants across the Discovery and other recruitment sites will be as summarized in Table 2.

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

Gender	Type of Control		Total
	Healthy	FM, IBS, and/or CFS	
Females	190	95	285
Males	190	95	285
Total	380	190	570

In addition, each site is requested to recruit controls that have an age and race/ethnicity distribution similar to that of the UCPPS subjects in the Trans-MAPP EP Study. The age and race/ethnicity distribution in each protocol will be monitored, and adjustments made if warranted.

No specific targets for positive controls with the co-morbid syndrome conditions are included in this protocol. However, the numbers of subjects recruited in each category, across all discovery sites will also be monitored, and targets created if there are insufficient subjects in a particular group to address overall Trans-MAPP hypotheses.

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

The eligibility criteria for both healthy controls and positive controls are based on the same set of criteria for the UCPPS participants in the Trans-MAPP EP Study, with exception of additional criteria to exclude chronic pelvic pain symptoms and criteria to identify the co-morbid syndromes for the positive controls. All entry criteria are shown below; those specific to either healthy or positive control participants are so indicated.

4.2.1. Inclusion Criteria

Participants are eligible for the Trans-MAPP Control Protocol if they meet the following general and gender-specific criteria listed below:

1. Participant has signed and dated the appropriate Informed Consent document:
    a. Agreed to participate in Trans-MAPP Control 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.

STUDY POPULATION

3. Participant is at least 18 years of age.

Inclusion Criteria for ***Healthy Controls only***

1. Participant reports a response of ***"0" (zero)*** on the pain, pressure or discomfort scale (SYM-Q, Question #1).
2. Participant reports no chronic pain in the pelvic or bladder region, and reports chronic pain in no more than one other body region.
3. Participant reports no urological symptoms that have been evaluated, but are still present.

Inclusion Criteria for ***Positive Controls only***

1. Participant meets the validated criteria for one or more of the following conditions
    a. **Fibromyalgia (FM*):** Requires chronic widespread pain above and below the waist, on the right and left side of the body, and involving the axial skeleton (neck, trunk, back, buttocks) for at least three months and does not have another disorder *that would otherwise explain the pain*. Participant meets FM criteria if responses on the Complex Medical Symtpoms Inventory-Fibromyalgia (CMSI_FM2) CRF are as follows for ***either*** combination listed below:
        1) Widespread Pain Index (WPI), Question #1 on CMSI_FM2 CRF **≥ 7**

            AND

        2) Symptom Severity Score (SS): Question #2 and #3 on CMSI_FM2 CRF **≥ 5**

    - OR -

        3) Widespread Pain Index (WPI), Question #1 on CMSI_FM2 CRF between **3-6**.

            AND

        4) Symptom Severity Score (SS): Question #2 and #3 on CMSI_FM2 CRF **≥ 9**

    * The Tender Point Exam is optional for Fibromyaligia Positive Controls

    b. **Irritable bowel syndrome (IBS):**
        1) Recurrent abdominal pain or discomfort** at least 2-3 days/month in last 3 months with symptom onset at least 6 months prior to diagnosis.
        2) Pain or discomfort at least 2-3 days/month.
        3) For women, this pain occurs not only during menstrual bleeding but also at other times.
        4) Symptom Onset of pain or discomfort 6 months or longer.
        5) ***In addition to fulfilling the above criteria, the participant must also have an association of their pain or discomfort with their bowel habit. They must have at least one Yes response in two of the three criteria below (Criteria #1-#3):***

    Criterion 1:

    Pain or discomfort gets better after BM at least sometimes.

    Criterion 2:

    Onset of pain or discomfort associated with more stools at least sometimes.

    Or

Onset of pain or discomfort associated with fewer stools at least sometimes.

Criterion 3:

Onset of pain or discomfort associated with looser stools at least sometimes.

Or

Onset of pain or discomfort associated with harder stools at least sometimes.

***"Discomfort" means an uncomfortable sensation not described as pain*.

c) **Chronic fatigue syndrome (CFS)**: Requires major fatigue criteria of six months or longer of fatigue severe enough to limit daily activity which is not relieved by rest and is not life-long, as well as four or more ancillary criteria, including: myalgia, arthralgia, headache, sore throat, tender lymph nodes, post-exertional malaise, difficulty with concentration or memory, sleep disturbance. Participant meets CF criteria if responds "Yes" to major fatigue criteria, as well as a "Yes" response to at least 4 of the other 8 qualifying criteria:

1) Major fatigue criteria: Persistent fatigue not relieved with rest that limits activities and is not life-long
2) Impaired memory, concentration or attention (Difficulty with thinking, confusion)
3) Sore throat
4) Muscle pain
5) Multi-joint pain without swelling
6) New headaches
7) Unrefreshing sleep
8) Post-exertion fatigue or exhaustion lasting > 24 hours
9) Tender cervical or axillary lymph nodes

4.2.2. Exclusion Criteria

Any potential control subject meeting any one of the following criteria will not be eligible for enrollment in the Trans-MAPP Control Protocol.

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 or 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, Ulcerative Colitis, Lupus, Rheumatoid Arthritis, or 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, or prostate cryosurgery or laser procedure.

4.2.3. Deferral Criteria

There are several physical conditions for which a control subject will be deferred from further screening for the Trans-MAPP Control Protocol. 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*)

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 those who are post-menopausal and those with a history of hysterectomy.

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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) ($\geq$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)

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 Control Study. These measures can be classified into a number of primary domains as described below.

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, including dose, frequency, and route of administration.

A Quality of Life (QOL) assessment will be performed using the recently revised Rand Short Form-12 (SF-12).[8]

Health care resource utilization data will be collected 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. 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 Male Sexual Function Scale (MSFS)[16,17] will be obtained.

5.1.3. Non-urological Symptom Measures

Data on non-urological pain, utilizing a body map with numbered regions, will be obtained at the baseline clinic visit using the Body Pain Index (BPI)[18] tools. Furthermore, 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. 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

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

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. 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. 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; plasma and urine will be collected during the one visit. Another or replacement cheek swab (for DNA) maybe required if the initial swab was not collected at the baseline clinic visit/s or if the original sample was improperly collected, stored, damaged and/or insufficient sample was obtained. The schedule and volume of these collections is summarized in Table 4.

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

Measure	Approximate Volume	Implementation Schedule
Blood (plasma) specimen	10 ml	Baseline Visit
Spot urine specimen	90 ml	Baseline Visit
VB urine specimen	1 sample - total volume voided ,maximum 50 ml (females); 2 samples - total volume voided, maximum 50 ml per collection(males) *	Baseline Visit
Cheek Swab For DNA	N/A	Once at Baseline Visit (or as needed for missed or replacement specimen)
** the 2nd Male VB3 urine sample following the prostate massage is optional.		

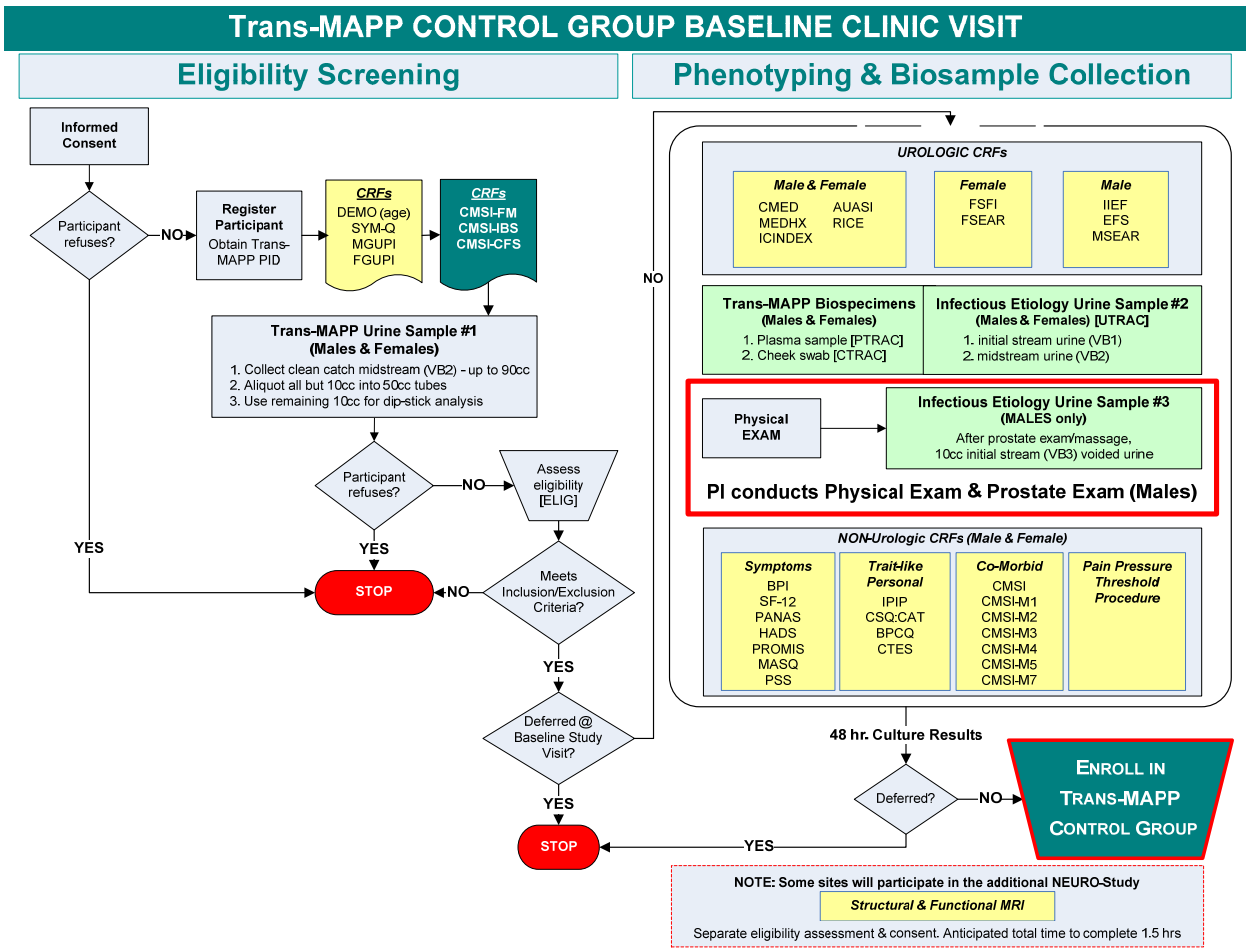
5.2. Contact Schedule and Participant Procedures

Subjects in the Trans-MAPP Control Protocol will receive all procedures and questionnaires outlined for UCPPS subjects; however, control subjects will only complete the baseline visit. In addition, the questionnaires which are done only once at six months in that protocol (to reduce subject burden) will also be given to control participants at this one baseline visit.

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.

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.

Urological Phenotyping CRFs*:

- Concomitant Medications (CMED) – Documentation of current medications
- Medical History (MEDHX)
- Family Medical History Questionnaire (FAMHX)
- 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
- Early in Life Infection History (EIL-INF***)

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)*
    a. Optional for Male Participants only (after prostate exam/massage)**:
        i. Infectious Etiology Urine Specimen #3 (VB3) Tracking (UMIETRAC)
    b. Positive Controls with Fibromyalgia (tenderpoint exam)

* 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.

*** Early in Life Infection History (EIL-INF***) – this form will be administered at baseline; if not completed and/or missed at the baseline visit it should be completed at any visit that the participant returns to the clinic to complete any other study related activities (such as site specific or neuro imaging studies) and is willing to complete this form in addition to the other activities and/or forms.

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)
- 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)
- Co-morbid Diagnostic Syndrome (CMSI) Modules – Fibromyalgia (CMSI_FM2*), Chronic Fatigue Syndrome (CMSI_CFS2), Irritable Bowel Syndrome (CMSI_IBS2), Vulvodynia (CMSI_VDYN2), Migraine (CMSI_MI2), and Temporomandibular Joint Disorder (CMSI_TMD2)

*The Tenderpoint exam is optional for Fibromyalgia Positive Control Participants.

6. STATISTICAL CONSDERATIONS AND ANALYTIC PLAN

A total of 380 UCPPS participants and up to 570 control participants will be recruited from the six participating clinical sites, in addition to the clinics at Stanford and Miami. A detailed statistical analysis plan and sample size and power analysis is included in the Trans-MAPP Epidemiology and Phenotyping (EP) Study protocol, and will not be repeated here. Furthermore, the individual research protocols incorporating these Control participants into their studies include specific statistical analysis plans.

Nevertheless, the general statistical methods to be utilized within these Trans-MAPP studies will be summarized here, for ease of reference within this Control group protocol

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. 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.[39] 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.[40] 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. Sample Size and Power Considerations

6.2.1. Sample Size and Stratification

Each of 6 Discovery Sites (with University of Miami supporting the recruitment goals of Washington University, St Louis), will be responsible for recruiting 60 healthy controls and 30 positive controls over two years; Stanford will recruit 20 healthy controls and 10 positivie controls over two years. . Each of these Control Study participants will complete the baseline in-clinic visit of the Trans-MAPP EP Study protocol. Thus, the Trans-MAPP Control Protocol population will include 380 adult healthy controls and 190 adult positive controls with FM, IBS, or CFS. As outlined in Section 4.1, each site will be expected to recruit equal numbers of males and females.

6.2.2. Interim Analyses and Monitoring

Many of the analyses are contingent upon heterogeneity of somatic and psychological comorbidities in the Trans-MAPP EP Study and the Control Study. 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,[41] the data to support these associations in men with IC/PBS or CP/CPPS are less robust. Furthermore, these Trans-MAPP participants 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 in the Trans-MAPP EP Study may be extended beyond two years and 380 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.

6.2.3. Power Considerations

The power calculations described below, developed for the primary Trans-MAPP EP Study, are repeated here to illustrate 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 6-7.

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

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

The Specific Aims for this protocol focus on the recruitment of control subjects to support the other MAPP Research Network studies. Therefore, details of those analytical considerations are provided in those protocols, and not repeated here. The sample size and power considerations for studies comparing UCPPS subjects to controls are outlined in other Trans-MAPP Research Network studies.

7. HUMAN SUBJECT CONSIDERATIONS

Although many of the Human Subject Considerations for this protocol are identical to that of the Trans-MAPP EP Study, the nature of the subjects (particularly healthy controls) and follow-up are different enough that these issues are repeated here, with adjustments as appropriate.

7.1. Trans-MAPP Control Protocol Participant Recruitment

7.1.1. Participant Recruitment

Control subject recruitment will be conducted through the clinics at each of the designated clinical sites, and/or through local newspaper advertising. Participants may be self-referred or referred through their primary physician (either solicited or unsolicited by the urology/urogynecology clinic). 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 health care 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 baseline visit at which point we will secure written informed consent.

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

There is no participant follow-up for subjects in the Trans-MAPP Control Protocol.

7.1.4. Participant Retention

Since there is only one visit for subjects in the Trans-MAPP Control Protocol, issues of participant retention do not apply.

7.1.5. Participant Withdrawal

Since there is only one visit for subjects in the Trans-MAPP Control Protocol, issues of participant withdrawal do not apply. (Although it is possible a subject may withdraw during the single clinic visit, this is expected to be extremely rare.) However, a participant may withdraw consent for use of his or her data at any time.

7.1.6. Participant Reimbursement

As compensation for their time and effort, participant 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

The subjects in this study will be serving as controls for various studies of the MAPP Research Network. There will not be any direct benefits to the participants, although for some of the positive controls the physical exam and interaction with caring and knowledgeable study staff may be a positive and reinforcing factor. 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 UCPPS symptoms. This study may well lead to the discovery of common risk factors, symptoms, or potential biomarkers related to these complex disorders.

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.

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

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.

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

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 Control Study initiating 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 MAPP 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, together 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.

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: Control 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).