



Multidisciplinary Approach to Pelvic Pain (MAPP)

TRANS-MAPP EPIDEMIOLOGY & PHENOTYPING (EP) STUDY

MANUAL OF PROCEDURES (MOP)

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)

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1. INTRODUCTION

1.A. MAPP Overview

The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network has been established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) to focus on a broader approach to the study of Interstitial Cystitis (IC)/Painful Bladder Syndrome (PBS) in men and women, and Chronic Prostatitis (CP)/Chronic Pelvic Pain Syndrome (CPPS) in men, than previously undertaken. A wide range of scientific discovery projects, moving beyond the previous traditional bladder- and prostate-focused efforts will be conducted at six Discovery Sites.

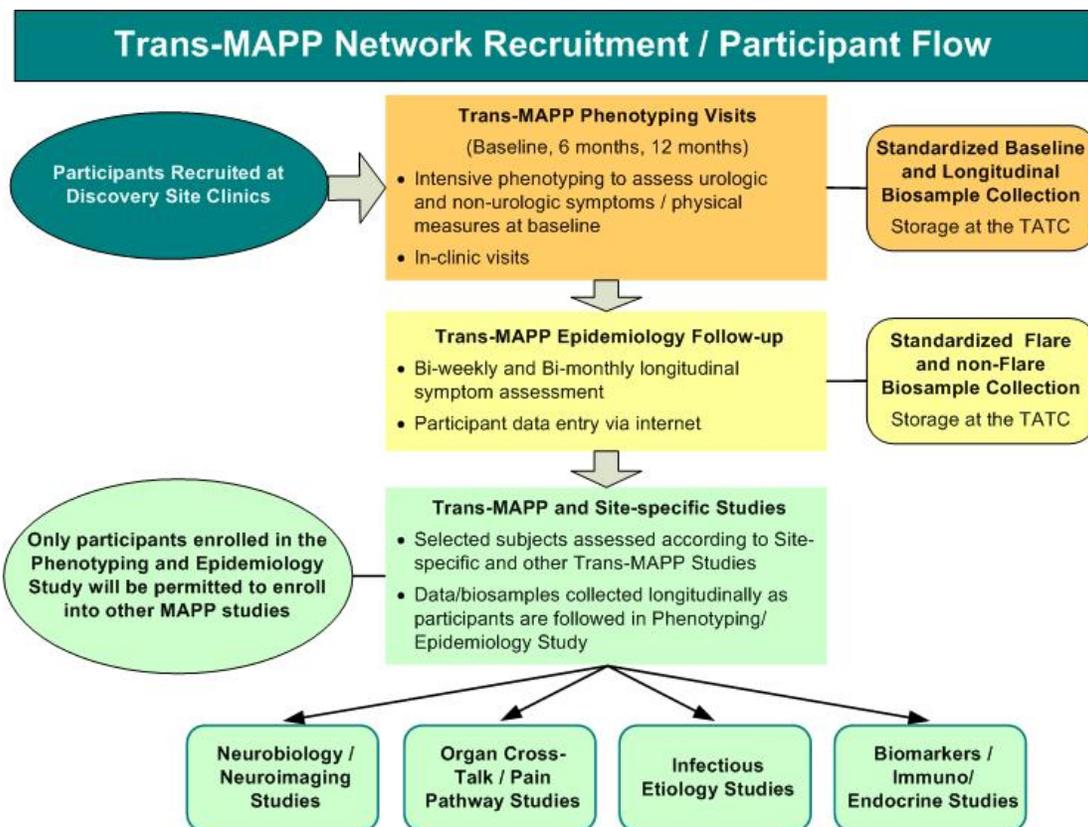
1.A.1. Objectives

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. 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:

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

Thus, the Trans-MAPP EP Study 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



1.A.2. Description

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 participants (30 per year) and Stanford University will recruit 20 participants (10 per year) 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 the below table outlining the composition of the targeted study participants.

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 |

1.B. Study Organization

Participants will be recruited from the following six Discovery Sites and their associated recruitment sites as listed in the table below.

1.B.1. Discovery Sites and Recruitment Centers

| NAME | LOCATION |
|---|-----------------|
| Northwestern University Feinberg School of Medicine | Chicago, IL |
| University of California (UCLA) | Los Angeles, CA |
| University of Iowa | Iowa City, IA |
| University of Michigan | Ann Arbor, MI |
| University of Washington | Seattle, WA |
| Washington University | St. Louis, MO |
| University of Alabama at Birmingham | Birmingham, AL |
| University of Miami Miller School of Medicine | Miami, FL |
| Stanford University | Stanford, CA |

1.B.2. Additional Participating Laboratories and Centers

| CENTER | PRINCIPAL INVESTIGATOR |
|--|---|
| Children’s Hospital Boston, Harvard Medical School, Boston MA | Marsha A. Moses, Ph.D. |
| Data Coordinating Core (DCC), University of Pennsylvania, School of Medicine, Philadelphia, PA | J. Richard Landis, Ph.D. |
| Tissue Analysis and Technology Core (TATC), University of Colorado, Denver School of Medicine, Aurora, CO | M. Scott Lucia, M.D. |
| Department of Urology, Queen’s University, Kingston, Ontario, Canada | J. Curtis Nickel, MD, FRCSC |
| Biofilm Research Lab, Allegheny-Singer Research Institute, Microbiology & Immunology and Human Genetics, Drexel University and Center for Genomic Sciences, Pittsburgh, PA | J. William Costerton PhD, Garth D. Ehrlich PhD |

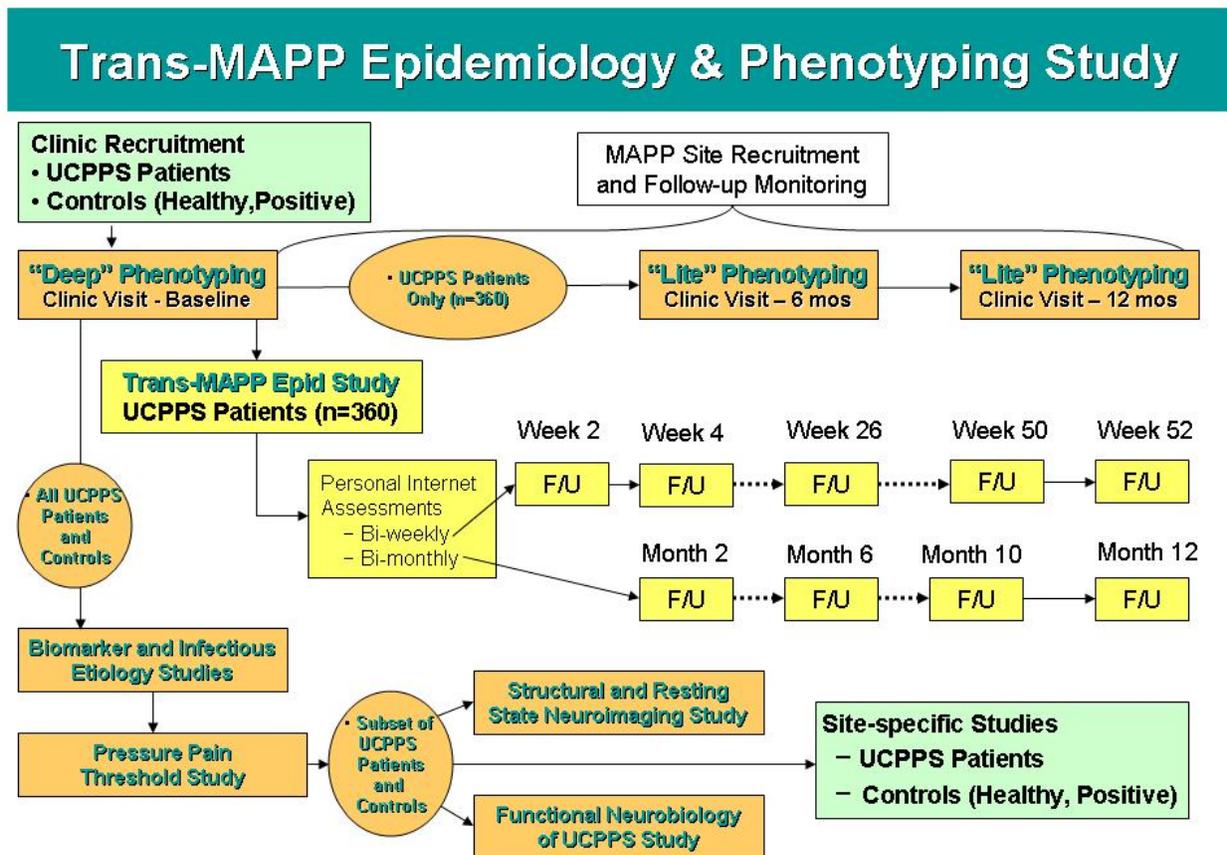
1.B.3. Funding

Funding for the Trans-MAPP EP Study is provided by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), a division of the National Institutes of Health (NIH), Department of Health and Human Services.

1.B.4. Project Cycle

The Trans-MAPP EP project will span five years. The recruitment phase of the study will occur over a 24-month period beginning in December, 2009. The study includes a screening/baseline visit at which official enrollment occurs. Participants will then be followed for 12-months and will be expected to complete a series of biweekly and bimonthly online internet assessments as well as six and twelve month in clinic visits. Participants will be provided a calendar of their biweekly and bimonthly online assessments and when to log on. As such, enrollment and follow-up activities will occur simultaneously as illustrated in the schematic below. The final months of the project will be dedicated to evaluation and data analysis for publication.

Figure 2. Trans-MAPP EP and Control Studies: Recruitment Pathway for Study Participants



1.B.5. Site Specific Studies

Participants enrolled in the Trans-MAPP EP Study will have the option to enroll immediately during the screening/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. Site-specific projects may vary by site; each individual site is responsible to ensure that the appropriate IRB approvals are obtained for any and all site-specific projects prior to enrolling participants.

1.C. General Policy

1.C.1. General Protocol Policy

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

1.C.2. Initiating a Protocol Change

The Executive Committee must review and approve all protocol amendments or revisions. Proposed Protocol changes should be presented in writing to either the Chair of the Executive Committee or to the Data Coordinating Core. The DCC and/or Chair of the Executive Committee will present the proposed amendment to the Executive Committee for review and discussion. If approved MAPP Network Executive Committee approved amendments must be submitted to the IRB for approval and once approved, be incorporated into the protocol. IRB approval must occur prior to the implementation of an amendment. Amendments that include minor changes to the protocol may undergo expedited review if these changes fit into expedited approval criteria. All changes to the informed consent form must also be approved by the IRB.

2. PARTICIPANT ENROLLMENT

2.A. Participant Population and Recruitment

This study will recruit both male and female patients with some form of Interstitial Cystitis (IC)/Painful Bladder Syndrome (PBS) or male patients with Chronic Prostatitis (CP)/Chronic Pelvic Pain Syndrome (CPPS).

Each Discovery site is committed to recruiting 60 participants and Stanford will recruit 20 participants into the Trans-MAPP EP Study. 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 present for less than two years. Thus, each Discovery site will have a recruitment target of 15 subjects and Stanford will have a recruitment goal of 5 subjects in each of 4 groups defined by sex and duration of symptom. Recruitment data will be monitored by the DCC in order to continually assess recruitment rates at each site. Recruitment sources and strategies will vary from center to center, however each clinical center will be responsible for determining how best to recruit participants.

2.B. Identifying Potential Participants

Participant recruitment will be conducted through the urology/urogynecology clinics at most 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.

2.B.1. Contacting Potential Participants

Once a potential participant is identified, he/she will be contacted via telephone or mail to schedule a screening/baseline visit.

- Participant refuses contact: Enter this information into the Pre-Screening CRF as patient refusal with the reason, if provided. No further contact will be made.
- Participant approves contact: Proceed with scheduling the in-clinic screening/ baseline visit as soon as possible.
- Participant does not reply after 3 weeks: Try contacting the participants again by phone or by mail.

Maintain a telephone log of all attempted and actual contact with potential participants by phone, indicating the following information:

- Contact unsuccessful: If a potential participant is unreachable after several attempts at different times during the day, enter this information into the Prescreening CRF as unable to contact patient, with a brief explanation if possible.
- Contact successful: The potential participant has been contacted by phone or mail and is willing to come in for the screening/baseline study visit.

2.B.2. Obstacles to reaching potential participants

- Wrong or Disconnected numbers

If a phone number is wrong or disconnected, try to contact this patient again by mail.

- When to call

If the potential participant cannot be reached, ask if there is a better time to call or another number where they may be reached.

- How many times to call

Make several attempts to contact all participants. Try each number (day, evening, and message) at least twice during each of the following time periods (10:00 am - Noon, Noon - 6:00 pm, 6:00 pm - 8:30 pm, and anytime during the weekend) before leaving a message. If there is still no answer, leave a message such as the following:

Hello, my name is (----). I'm calling on behalf of CENTER NAME about an inquiry (he/she or you) made at our medical center. We would like to speak with (name of potential participant). Would you please call our clinical center at NNN-NNN-NNNN and leave your name, your phone number with area code, and a good time to reach you. Thank you very much.

Do not leave more than one message every couple of days. Do not leave repeated messages. Use your best judgment to ascertain if calls are being avoided or simply bad timing. If the potential participant still cannot be reached, file this information and plan to call again in a few weeks.

2.C. Pre-Screening

The first contact with a potential participant will be considered a pre-screening contact and will include an introduction to the study, a review of the eligibility criteria, a description of tests and procedures involved, and a review of the visit schedule. This should be done to ensure not only the participant's potential eligibility, but also her/his willingness and ability to meet the demands/responsibilities of the study.

Pre-screening may be conducted either over the phone or in the clinic. If the initial contact is by phone, the RC placing the call should identify him/herself and inform the potential participant how she/he was selected. The RC should provide information about the study and answer questions. **The RC should NOT give the potential participant information about study-specific inclusion criteria.**

Data for prescreening activity are recorded on the Prescreening Summary [PRESCR] form on a monthly basis. This form captures efforts of the RC to recruit participants and the flow of potential participants seen at the clinical center. These data are reflected in monthly accrual reports.

2.D. Informed Consent

If the pre-screening contact information indicates that the potential participant is eligible and willing, the RC should schedule a time for the participant to come in to review and complete the informed consent prior to proceeding with the Screening/Baseline Visit #1.

Each Clinical Site is responsible for ensuring that informed consent is obtained from each participant according to the guidelines of its local Institutional Review Board (IRB) and in accordance with the Common Rule (45 CFR Part 46 subpart A, Protection of Human Subjects). The informed consent form must be obtained (signed and dated by the participant) prior to initiation of any study related activity.

The Informed Consent form must provide the following information to each participant:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.

- A disclosure of appropriate alternative procedures or courses of treatment, if any that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

An informed consent *must* be obtained from the participant before study information is collected or study procedures performed.

2.D.1. Obtaining Informed Consent

Potentially eligible participants will be contacted either by phone or in person by the RC to determine their interest and eligibility for the study. Once the participant is contacted he/she will be scheduled for a screening/baseline visit.

- The potential participant should receive a copy of the informed consent, either in person, by mail or by fax.
- The RC should allow the potential participant time to consider the study obligations and discuss the study with his/her family members before signing the consent form.
- The informed consent form must be signed in the presence of the PI or the RC, prior to Visit #1 procedures.
- The RC will request that the potential participant bring, if at all possible, a list of his/her medications, (prescription and over-the-counter) to Visit #1, to facilitate filling out the CMED CRF.

2.D.2. Administration of Informed Consent

Once the person comes into the clinic for the Screening/Baseline Visit #1, he/she must first be administered the study's informed consent.

Administration of Informed Consent

Careful read...

Potential participants will be asked to sign two Informed Consent forms. The first consent form describes the Trans-MAPP EP Study; the second consent describes the Genetic Sample component of the study. Each of the forms contains embedded YES/NO questions and has its own signature requirements. Instruct the participant to read both Informed Consents carefully and to raise any questions or concerns that he/she has and to sign them ONLY after their questions or concerns have been

| | |
|------------------------|---|
| | answered. Participant questions should be answered using lay language. |
| Opt out of ... | While it is expected that all participants will agree to participate in all parts of the study, male participants may decide to participate in the Trans-MAPP EP Study, but opt out of the prostate massage and accompanying VB3 urine sample. |
| Cheek swab... | A separate section and signature page will be required for consent to collect a cheek swab sample for genetic testing and storage of DNA. Participants must be made aware that 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. |
| Consent refusal... | 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. |
| Opt out of... | Male and Female participants may decide to participate in the Trans-MAPP EP Study, but opt out of the parts of the genetic study related to research of other health conditions unrelated to the main goals of this study. |
| Genetic Sampling | Discuss the options and implications of participation in the genetic study, and explain the selections contained in the YES/NO questions about genetic samples. Participants must respond to these YES/NO questions in the Genetic Sampling Informed Consent Form. Responses to the YES/NO questions about provision of genetic samples should be recorded on the ENROLL CRF. |
| Read aloud... | The RC will provide the potential participant with a copy of the Informed Consent Form and ask her/him to read a few sentences out loud to ascertain whether the potential participant needs assistance with the written material. If the participant or their legal representative cannot read the written material, then an impartial witness should be present for the entire consent process. After the participant has had a chance to ask questions and has signed the consent form, the witness would then sign and date the consent, to affirm the process. |
| Comfortable setting... | The informed consent form should be reviewed in a comfortable setting where the participant is able to make a free choice without pressure. Ample time should be given to allow the participant to thoroughly read and process the information. |
| Take home... | If the participant wishes to take the Informed Consent Form home before reaching a decision, then she/he may do so. The RC will need to reschedule the Screening/Baseline Visit and at the subsequent visit, the RC should answer any questions raised by the participant. |
| Continued followup... | The participant should be made aware of her/his responsibilities throughout the Screening and the Follow-up phases of this study. The importance of continued follow-up is stressed. This is balanced with a discussion of the effect of participant withdrawal on the study. |

| | |
|--------------------|---|
| Signed/dated... | The Informed Consent Form must be signed and personally dated by the participant or his/her legal representative, and the person “obtaining consent”. A participant should not be asked to sign the consent statement if he/she has any doubts about enrolling or if the clinic staff believes he/she does not understand what his participation would involve. Under <i>no</i> circumstance is any study information to be collected or study procedures performed for the specific purpose of the study before the participant has signed the informed consent form. |
| Original/copy... | The RC will maintain the <u>original</u> consent document in the participant’s confidential file with other confidential documentation, and provide a copy of the signed and dated informed consent(s) to the participant. A second copy of all informed consent(s) should be made as a back up and stored together in the “study-confidential file”. In addition, a signed/dated progress note must be made in each participant’s file that the informed consent process took place prior to any study procedures. |
| Confidentiality... | To ensure confidentiality, the RC will not send copies of the consent form(s) to the DCC or keep any copies of the Informed Consent Form with the case report forms (CRFs). |
| Sign/date... | <i>Participant must sign and date the informed consent form and accompanying genetic consent form, prior to proceeding with any of the Screening/Baseline procedures.</i> |

2.D.3. Participant Confidentiality

HIPAA

Participants must sign a Health Insurance Portability and Accountability Act (HIPAA) Authorization, in addition to the two Informed Consent Forms. The HIPAA Authorization may or may not be incorporated into the Trans-MAPP EP Study consent, depending on the policy of the Clinical Center. However, if the HIPAA language is incorporated into the Informed Consent Form, the regulation mandates that it be submitted to the IRB for prior approval. This form describes both the kinds of health information collected in this study and also all of the disclosures of health information that will be made. The form must also list parties to whom disclosures of personal health information will be made.

Additional Confidentiality Concerns

- Consent form(s), HIPAA authorizations and source documentation must be securely maintained in a separate location from the CRFs.
- Recruited study participants are assigned a Participant ID number, a unique study identification number.
- The DCC staff has access to the Participant ID number for data management purposes. All communication between the DCC staff and the Clinical Center staff regarding participant data occurs via the Participant ID number only.

2.D.4. Registering Participants to the Trans-MAPP Study

Once consent is obtained, the RC will proceed to register the participant to the Trans-MAPP EP study to obtain a Trans-MAPP EP Study Participant ID.

2.D.5. Assignment of Participant ID and PIN

Participants who appear to be eligible following completion of informed consent process will have their name recorded on the Participant ID Log [PTIDLOG] and will be registered into the Trans-MAPP EP Participant Registration module, and assigned a computer generated participant ID number and PIN provided by the participant registration module at the time of registration. Once a participant ID number and PIN has been assigned, it should never be reassigned for any reason. Participants assigned an ID number and PIN who are ineligible or refuse participation, and who later become eligible or decide to participate, will utilize the same ID number and PIN that they were originally assigned. The **Participant ID Log [PTIDLOG]** should be stored in a secure, locked filing cabinet.

2.D.6. Clinical Centers (CC) and Site Assignments

There are six primary Discovery Sites:

| | |
|----|--------------------------|
| 01 | Northwestern University |
| 02 | University of California |
| 03 | University of Iowa |
| 04 | University of Michigan |
| 05 | University of Washington |
| 06 | Washington University |

Some centers have satellite centers or referral centers that are also participating in the Trans-MAPP Study. Due to funding mechanisms, some centers will be classified under one of the Trans-MAPP Cores (DCC or TATC). These are referred to as ‘sites’ and are listed below:

| CC | SITE | NAME | LOCATION |
|----|------|---|------------------|
| 01 | 01 | Northwestern University Feinberg School of Medicine | Chicago, IL |
| 02 | 01 | University of California (UCLA) | Los Angeles, CA |
| 03 | 01 | University of Iowa | Iowa City, IA |
| 04 | 01 | University of Michigan | Ann Arbor, MI |
| 05 | 01 | University of Washington | Seattle, WA |
| 06 | 01 | Washington University | St. Louis, MO |
| 06 | 02 | University of Alabama at Birmingham | Birmingham, AL |
| 06 | 03 | University of Miami Miller School of Medicine | Miami, FL |
| 07 | 01 | University of Pennsylvania (DCC) | Philadelphia, PA |
| 07 | 02 | Harvard Medical School | Boston, MA |
| 07 | 03 | Queens University | Kingston, ON |
| 07 | 04 | Stanford University | Stanford, CA |
| 08 | 01 | University of Colorado (TATC) | Ann Arbor, MI |

2.E. Study Eligibility Criteria

Determining eligibility is a multiple step process involving the review of information collected on case report forms (CRFs) and the immediate results of a urine dipstick analysis, as well as confirmatory results of a 48-hour culture to test for urine pathogens. Eligibility Criteria (as documented on Eligibility Confirmation - ELIG form) are outlined below.

2.E.1. Inclusion Criteria

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

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

Additional IC/PBS Inclusion Criteria for Males or Females

- 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 the **most recent 3** months.

Additional CP/CPSS Inclusion Criteria for Males Only

- 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/CPSS symptoms been present for the majority of the time during **any 3 months in the previous 6 months**.

2.E.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.

- Participant has an on-going symptomatic urethral stricture.
- Participant has an on-going neurological disease or disorder affecting the bladder.
- Participant has a history of cystitis caused by tuberculosis, radiation therapy or Cytosan/cyclophosphamide therapy.
- Participant has augmentation cystoplasty or cystectomy.
- Participant has an active autoimmune or infectious disorder (such as Crohn's Disease or Ulcerative Colitis, Lupus, Rheumatoid Arthritis, Multiple Sclerosis, or HIV).
- Participant has a history of cancer (with the exception of skin cancer).
- 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).
- Participant has severe cardiac, pulmonary, renal, or hepatic disease that in the judgment of the study physician would preclude participation in this study.

Additional Exclusion Criteria for Males Only

- Male Participant diagnosed with unilateral orchalgia, without pelvic symptoms.

- Male Participant has a history of transurethral microwave thermotherapy (TUMT), transurethral needle ablation (TUNA), balloon dilation, prostate cryo-surgery, or laser procedure.

2.E.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 epididymitis, 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 post-menopausal and those with a history of hysterectomy..

- 4) If participant has an abnormal dipstick urinalysis confirming 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 (Females 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).

2.F. Screening Failures

A participant who does not complete the Screening procedures, for whatever reason, will be considered a screening failure, and will **not** be enrolled into the Trans-MAPP EP Study. All of the completed screening forms, including informed consent form, for participants who are considered screening failures, should be filed at the center in the Source Documentation Binder.

2.G. Participant Withdrawal and Withdrawal Consent

Participants are free to withdraw (or be withdrawn) from the study at any time. There are many reasons a participant may want to do so. They include:

- Unanticipated events unrelated to the study
- Significant concurrent illness
- Protocol noncompliance
- Investigator's discretion
- Withdrawn informed consent
- Relocation
- Dissatisfaction with study
- Loss of interest in the study
- Lost to follow-up
- Reason(s) for withdrawal will be documented on case report forms and entered in the DMS.

The RC will complete the Study Stop [SSTOP] form selecting the most representative reason for withdrawal. Every effort should be made to encourage participants to continue with study visits.

The withdrawal request can be made in person or during a phone contact. Participant data folder is clearly marked to indicate withdrawal and is maintained at the clinical center where the participant was recruited and followed.

2.H. Study and Participant Documents

Study and participant documents must be made available to the Trans-MAPP Network Study Group, NIH, NIDDK, and/or any agents/representatives of these parties. These documents should be organized as outlined in binders or files and stored in accordance with **security and record retention** regulations until further written notice by the sponsor or the DCC. Each clinical center must maintain the following documents:

Clinic Regulatory Binder (1 per clinical center)

This binder contains all essential documents, such as:

- Trans-MAPP EP Study Protocol
- Trans-MAPP EP Study Case Report Form (CRF) Templates
- IRB-Approved Informed Consent Forms
- IRB Documents/Correspondence
- IRB Membership List (current for duration of study)
- Laboratory Certifications/Laboratory Normals (current for duration of study)
- CVs of all clinic personnel

- Medical licensure for study physician
- Signature and Delegation of Responsibilities Log [STAFFLOG]
- Clinic Correspondence – Log and other documentation
- Trans-MAPP EP Study Manual of Procedures (MOP)

Note to file: Documents outlined above may be stored in other/additional binders during the course of the study; however a “Note to File” should be placed in any section where this occurs for a reference and as a reminder to replace documents at time of study termination

Case Report Form Binder

This binder contains all data collection forms and select administrative forms completed during the course of the trial. No participant identifiers other than participant ID number and participant initials should be contained in this binder.

Source Documentation Binder/Folder (1 per study participant)

Contains all documentation collected to support and verify information contained on the data collection forms. This includes the following original source documents: participant signed informed consent, medical records, laboratory results, contact information, administrative forms not contained in Case Report Form Binder, progress notes, and correspondence. In addition, any copies of applicable source documentation should also be stored in this file. Any study documents containing any participant identifiers beyond participant ID number and participant initials should be contained in this file.

Participant Study Binder (1 per clinical center)

This binder contains Participant ID Assignment Log, a copy of all participant signed informed consents and all financial documents related to the study. Any additional study specific confidential documents should be contained in this file. At the completion of the study, the Participant Contact Log should be completed and stored in this file. These files must be stored under secure conditions.

2.1. Extended Follow-Up

2.1.1. Participant Population

The Trans-MAPP Extended Follow-up is a continued effort of the MAPP Research Network to capture additional data in order to better understand symptoms and participant sub-groups as identified by the Trans-MAPP Epidemiology and Phenotyping Study. All Trans-MAPP EP participants who've completed the 12-month initial Trans-MAPP EP study are eligible to participate in the extended follow-up portion of the study. The Trans-MAPP Extended Follow-Up Participant letter (Appendix G) should be provided to potential participants as an introduction to the extended follow up portion of the study.

2.1.2. Informed Consent

Obtaining informed consent for the extended follow up portion of the study is a Site-specific governed activity. Each site is responsible for confirming, prior to administration of any of the follow-up assessments or materials, that informed consent is obtained in accordance with the local IRB sanctioned guidelines for this activity.

3. VISIT SCHEDULE AND ADMINISTRATION

The next section of the manual provides a summary of activities and procedures that occur at each scheduled Trans-MAPP EP Study visit and online computer assessment, once a potential participant is consented. The specific directions for completing each Case Report Form [CRF] are found in the “Directions for Completing Case Report Forms” section of this manual.

The Study Visit Schedule, Appendix A, describes the types of visits and permissible visit intervals (called visit window) used throughout this manual to describe interaction with study participants. The participant study calendar, which is a tool available in the Data Management System (DMS), will be generated based on the date of the Eligibility CRF completed at the Screening/Baseline Clinic Visit [Visit #1]. All contacts and visits will have a permissible window of contact surrounding them that defines the period of time during which a visit is permissible. Online biweekly and bimonthly computer assessments will have a window of 7 days between assessments, 3 days prior and 3 days following the actual target day. The biweekly and bimonthly online assessments are not allowed any other time outside of this 7-day window. If a participant logs into the online participant module at a time that is outside of his/her 7-day visit window, he/she will not be allowed to complete any assessments at that time, but instead will be reminded of the correct date to complete their next online assessment.

The visit window for the 6 month clinic visit is ± 1 week and the visit window for the 12 month clinic visit is 1 week prior to and up to 1 month after the initial target visit date. Participants are expected to complete both the 6 and 12 month online questionnaires at the clinic visit during the same day/visits they provide the 6 and 12 month biospecimens. As such, participants will not have access to the 6 and 12 month online questionnaires until they are in clinic and the survey is initiated by the Research Coordinator. The 6 and/or 12 month participant online survey will require a Research Coordinator to enter his/her Id and password to initiate the survey.

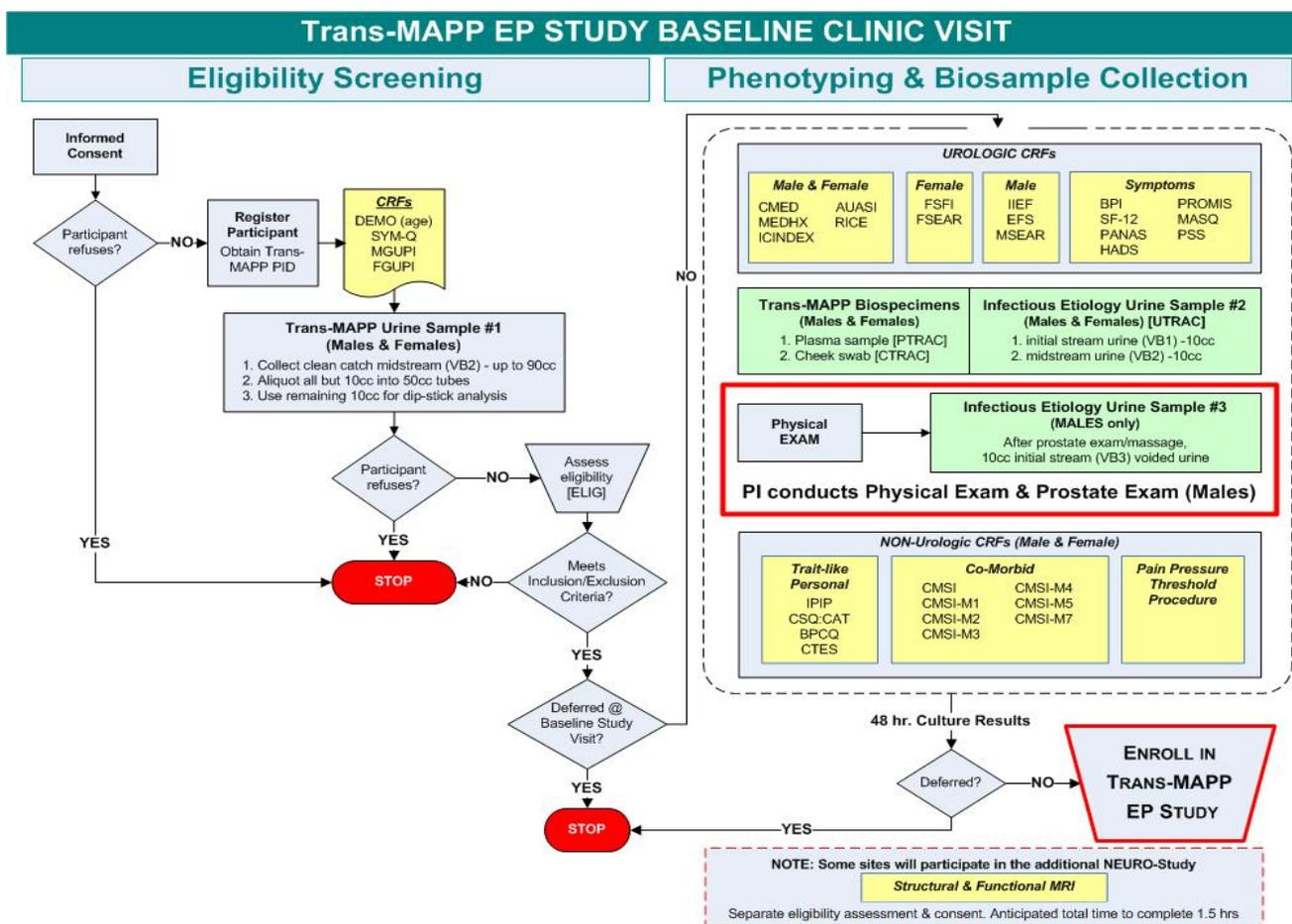
Each Trans-MAPP EP clinic study (baseline, 6, and 12 months) visit has an accompanying checklist/progress note, which lists processes for a particular clinic visit. In addition, the Trans MAPP EP Study schedule is a comprehensive list of the study processes that occur at all visits/online computer assessments.

3.A. Screening/Baseline Visit #1

The screening/baseline process for this study will require one in-person clinic visit to obtain informed consent for the entire protocol, confirm study eligibility, and provide participants with additional information about the study, as well as for eligible participants to proceed with collection of “deep” phenotyping online questionnaires and additional biospecimens.

The baseline visit is structured such that essential information required to assess eligibility is acquired in Part 1 of the visit, prior to the conduct of more intensive and time-consuming phenotyping and biosample collection required of Part 2 of the baseline visit. See Study Visit Schedule in Appendix A. Key eligibility criteria will be reviewed and confirmed in Part 1, prior to proceeding with Part 2, which is the full battery of baseline measures and additional biospecimen collection, as illustrated in the figure below.

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



3.A.1. Screening/Baseline (Part 1) – Eligibility Screening

The following sequence of events will occur during the Screening Baseline Visit-Part 1:

- Layered informed consent process; consent obtained for various levels of specimen collection (ICF)
- Assign Participant a Trans-MAPP Study Participant ID (PID) and PIN
- Register Participant to Trans-MAPP and any other Site Specific Studies
- 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,
 - 1) a clean catch midstream urine (VB2) specimen will be obtained for the urine dipstick test, pregnancy test, and 48-hour urine culture (see further details in the Biospecimen Collection and Processing section of this manual);
 - 2) a urine dipstick test will be performed for the presence of nitrites and/or hematuria;
 - 3) 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.
- Female Participants of child bearing age excluding post-menopausal and those with a history of hysterectomy. – Urine Pregnancy Test

Upon completing Part 1 of Screening/Baseline assessment, the RC should be able to determine if the participant is potentially eligible for the Trans-MAPP EP Study. If necessary, the RC should confer with the PI on questions related to eligibility, and make an overall decision regarding the participant's suitability for participation in the study at that visit, or if the participant should be deferred based on the urine dipstick results.

If the participant does not meet the necessary eligibility criteria, the RC should thank the participants for his/her time and effort, explain to the participants that they did not meet the study eligibility criteria, provide the designated site-specific reimbursement, and discontinue with any additional study measures/visits.

Any candidate failing any of the inclusion or exclusion criteria during the screening/baseline visit will be considered ineligible for the study. If at any time during the screening process the participant is found to be ineligible, they must be informed of this fact as soon as possible. Some participants may have their entry into the study deferred to a later time based on consideration of the deferral criteria. A participant previously **excluded**, based on the exclusion criteria, **cannot** be re-screened.

If the participant meets the eligibility criteria for the study, but also meets one or more deferral criterion, the RC should explain the specifics of the deferral criterion to the participants, as well as the required follow-up and deferral period prior to re-enrollment into the study, and schedule the participants for a new screening/baseline visit prior to providing the participant with the site designated reimbursement for his/her time and effort.

If a participant is deferred, she/he must begin the screening process again, beginning at Visit #1. When returning to repeat the screening/baseline visit the Participant will be issued the same Participant ID and PIN that they were assigned at the their initial screening/baseline visit and will be expected to complete all new screening/baseline CRFs, provide new biospecimen, as well as repeat all other baseline/screening procedures including the online participant questionnaire. In the event that a participant is deferred, do not discard any of the biospecimens collected, please proceed with shipping all biospecimens collected for the deferred participant to the lab (TATC).

To determine the re-screening date for a participant who has been deferred for more than one criterion, the RC will select one date that allows sufficient time for all deferral criteria to have been resolved. Before re-scheduling Visit #1, the RC should contact the participant by telephone close to the ending date of the deferral period to: review the study with the participant, determine whether the condition is absent or has subsided, and ascertain if the participant is still interested in beginning the screening process again. Please see the Deferral section of this manual for additional details on deferral requirements and deferral time frames.

In the rare event that a participant is deferred after he/she previously completed the baseline/screening online questionnaire and biospecimen collection, it is the Research Coordinator's responsibility to contact the DCC to inform them that this participant was deferred and to archive the baseline/screening participant survey. Please proceed with sending all biospecimens collected, even for deferred participants to the lab (TATC).

If the participant meets all necessary eligibility criteria, , the RC should proceed with the completion of the "deep" phenotyping baseline visit assessments and the collection of the additional baseline biospecimens.

NOTE: The Eligibility CRF must be data entered into the Oracle Clinical Module prior to proceeding with the study visit and is absolutely necessary to enter in order to log the

participant into the online system to complete the baseline Participant Survey as well as to generate the participant follow up calendar.

3.A.2. Screening/Baseline Visit (Part 2) – Phenotyping and Biospecimen Collection (Eligible Participants Only)

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 Biospecimen Collection phase (right-hand panel of Figure 3, above) of the visit. Part 2 of the Screening/Baseline visit commences with extensive online phenotyping battery of baseline measures, biosample collection and a pressure pain threshold (PPT) procedure. The completion of the screening/baseline visit, followed by a negative 48-hour urine culture result, defines enrollment in the Trans-MAPP EP Study.

The RC will demonstrate and provide each participant with instructions on how to log onto and complete the online participant questionnaires, as well as answer any questions the participant may have. The RC should then escort eligible participants to a quiet comfortable location where he/she can complete the online “deep” phenotyping baseline assessments.

During Part 2 of the Screening/Baseline Visit the following sequence of steps will occur:

Participants will complete the online 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 Male Sexual Function Scale (MSFS)
- Male Self-Esteem and Relationship (M-SEAR) Questionnaire

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)

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 and will be given a physical example. Once Participants complete the Symptoms and Illness Impact Questions module of the online assessment, the survey will prompt the participants to contact the Research Coordinator. At this point in the survey participants will be given a break in the online questionnaire to provide the remaining necessary baseline biospecimens, outlined below. For detailed instructions on biospecimen collection see (Appendix D), Biospecimen Collection Manual.

Biospecimens and Physical Exam Components:

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

*Please note that the male prostate massage and VB3 sample is optional and is not required to participate in the study.

Once Participants completes the biospecimen collection and physical exam procedures, he/she should then be escorted back to the computer room at which time the RC will need to assist the participant with logging back into the online system to complete the remainder of the online questionnaires. Once the Participant is logged back into the online questionnaire the RC will need to hit the “continue” button to have the computer advance to the remaining modules of the baseline questionnaires. The remaining questionnaires are:

Non-Urological Phenotyping CRFs:

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 (CMSI)*
- *Please note, the CMSI questionnaire (which is the final questionnaire of the Baseline Participant Survey) directs which of the following CMSI diagnostic modules will be completed following completion of the Participant Survey:
- Fibromyalgia (CMSI_FM2)
 - Chronic Fatigue Syndrome (CMSI_CFS2)
 - Irritable Bowel Syndrome (CMSI_IBS2)
 - Vulvodynia (CMSI_VDYN2)
 - Migraine (CMSI_MI2)
 - Temporomandibular Joint Disorder (CMSI_TMD)

Neuroimaging study CRFs*:

- Eligibility Confirmation, Neuroimaging Study (ELIG_SCAN)
- Magnetic Resonance Environment Screening (MR_SCREEN) - Administrative

****Neuroimaging study CRFs Completed ONLY if the Participant is participating in the Trans-MAPP Neuroimaging Study.**

3.A.3. Completing the Screening/Baseline Visit

After Participant completes the Screening/Baseline procedures and online questionnaires:

- Run Participant CMSI Report from the RC Data Management Tools screen.
- Review the Completeness Report – stress to participant the importance of completing the entire survey/questionnaires. If participant did not complete the entire survey, as indicated on the report, confirm with him/her that they intended to not complete the form, if not, assist participant in logging back onto the system to complete the survey, however please remember that it is not mandatory that he/she completes the session.
- Administer the applicable CMSI modules Administer the applicable CMSI modules (Fibromyalgia (CMSI_FM2)*, Chronic Fatigue (CMSI_CFS2), Irritable Bowel Syndrome (CMSI_IBS2), Migraine (CMSI_MI2), Vulvodynia (CMSI_VDYN2), Temporomandibular Joint Disorder (CMSI_TMD2)) as indicated on the participant report.
*Please note, the CMSI, Fibromyalgia Tender Point (CMSI_FM2-TP) procedures are optional.
- Conduct Pressure Pain Threshold (PPT) Procedure
- If eligible, schedule participant for Trans-MAPP Neuro Imaging Study (See Trans-MAPP Neuro Protocol for details)

Prior to Participant leaving clinic, provide him/her with:

- Two assembled at home collection kits with completed the header information on the linking form (UTRAC_Home_Linking).
RC must pre-record the header information into the DMS prior to providing the kits to the patients. Only Participants PID # and PIN should be recorded on the forms in the places as indicated and no other identifying information. Please see Appendix D, Biospecimen Collection Manual, for detail instructions on assembling and distributing kits.
- Instruction sheet for accessing and completing the online Participant questionnaire
- A reminder of their study PID# and PIN (this can be included on the Contact Completion Calendar or separate site specific format)
- The date for next in-clinic (6-month) visit
- Site specific reimbursement for their time and effort
- Copy of signed informed consent
- Site Contact if they have questions
- Introduce and schedule participant for any site specific studies that he/she may participate

Once Participant leaves, RC will need to:

- Ship the collected Plasma Specimen and the Home Collection Linking Form to the TATC and enter shipping details into the DMS
- Properly store the other biospecimens at the required temperature as indicated in the lab section of the manual of procedures.
- Send urine aliquot for 48hr urine culture to local lab/clinic.

3.A.4. Confirming Eligibility

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

It is expected that the ENROLL CRF as well as all other Screening/Baseline CRFs be data entered in the DMS within 3 days of the study visit.

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.

3.B. 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)

3.C. Extended Follow-Up

Extended follow-up assessments will resume at Visit #26 (Month 16), 4 months following the completion of the initial 12 month Trans-MAPP EP study. These assessments will be the same online Bi-monthly surveys as completed during 12 month follow-up phase. Participants are to be contacted using tools for the Trans-MAPP Extended Follow-up which have been added to the MAPP Portal page. As shown below, two new links have been added to the live study version of the Portal page. These new tools are:

1. **The Extended Follow-up Participant Follow-up Schedule:** This schedule plots all of the scheduled survey contacts for each Participant who enrolls in the Extended Follow-up.
2. **The Extended Follow-up Pending Surveys Report:** This report displays all Participants with upcoming Extended Follow-up survey contacts over the course of the **4 months** following generation of the report. This report can be used to identify potential Participants for recruitment into the Extended Follow-up.



Calendar Directory **DMS** Network Meetings Publications Phase 2 Concepts Edit Calendar

Training/Certification Version

- Research Coordinator - Participant Registration Tools
- Trans-MAPP Data Management System
- Research Coordinator - CMSI Report
- Research Coordinator - Generate Visit Schedule

Live Study Version

- Research Coordinator - Participant Registration Tools
- Trans-MAPP Data Management System
- Research Coordinator - CMSI Report
- Research Coordinator - Generate Visit Schedule
- Extended Follow-up Study - Generate Visit Schedule**
- Research Coordinator - Pending Surveys Report
- Extended Follow-up Study - Pending Surveys Report**
- Research Coordinator - Participant Home Collection Report

Trans-MAPP EP Study Manual of Operations

Below is an example screen shot displaying Participants with upcoming survey contacts in the 4 months following November 5th, 2013:



Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain
Extended Follow-up: Pending Participant Survey Report 05-Nov-2013

Participants within a current visit window that have not yet completed their survey:

| PID | Site | Visit | Target Date | Earliest Date | Latest Date | Visit Type | Extended Follow-up Enrollment Date |
|--------|--------------|-------|-------------|---------------|-------------|----------------|------------------------------------|
| XXXXXX | MAPP XXXX | 28 | 30-Dec-13 | 23-Dec-13 | 6-Jan-14 | Ext. Follow-up | |
| XXXXXX | MAPP XXXX | 31 | 9-Dec-13 | 2-Dec-13 | 16-Dec-13 | Ext. Follow-up | |
| XXXXXX | MAPP XXXX | 33 | 9-Jan-14 | 2-Jan-14 | 16-Jan-14 | Ext. Follow-up | |
| XXXXXX | MAPP XXXX | 34 | 27-Dec-13 | 20-Dec-13 | 3-Jan-14 | Ext. Follow-up | |
| XXXXXX | MAPP XXXX | 34 | 27-Dec-13 | 20-Dec-13 | 3-Jan-14 | Ext. Follow-up | |

The list of Participants generated by the Pending Visits report as shown above may be used to contact Participants with survey contacts within the next 4 months and obtain their consent and proceed with confirming their enrollment in the Extended Follow-up Study.

Please note, once Participants enroll in the Extended Follow-up, the date of their Enrollment form will be filled-in under the header of the “Extended Follow-up Enrollment Date” column.

Trans-MAPP EP Study Manual of Operations

Once a Participant has consented to enrolling in the Extended Follow-up, please email, fax, mail, or provide by the best means possible a visit schedule as shown below. The visit schedule displays the dates in 4-month intervals for each survey contact in the Extended Follow-up phase.

Please note, many Participants will have been finished with the first 12-month portion of the Trans-MAPP Epidemiology and Phenotyping Study when they are re-contacted and will not be starting with the Extended Follow-up at V.#26 (the first survey contact for the Extended Follow-up). Please confirm to each Participant the Visit Number/Month and range of dates for the first Extended Follow-up survey contact.



Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain
Participant 102202 - M75C.

Extended Follow-up Participant Visit Schedule:

| Visit Number | Month | Target Date | Earliest Date | Latest Date | Visit Type | Actual Date |
|--------------|-------|-------------|---------------|-------------|------------------------------------|-------------|
| 26 | 16 | 29-OCT-2013 | 22-OCT-2013 | 05-NOV-2013 | Extended Follow-up | 22-OCT-2013 |
| 27 | 20 | 18-FEB-2014 | 11-FEB-2014 | 25-FEB-2014 | Extended Follow-up | |
| 28 | 24 | 10-JUN-2014 | 03-JUN-2014 | 17-JUN-2014 | Extended Follow-up | |
| 29 | 28 | 30-SEP-2014 | 23-SEP-2014 | 07-OCT-2014 | Extended Follow-up | |
| 30 | 32 | 20-JAN-2015 | 13-JAN-2015 | 27-JAN-2015 | Extended Follow-up | |
| 31 | 36 | 12-MAY-2015 | 05-MAY-2015 | 19-MAY-2015 | Extended Follow-up | |
| 32 | 40 | 01-SEP-2015 | 25-AUG-2015 | 08-SEP-2015 | Extended Follow-up | |
| 33 | 44 | 22-DEC-2015 | 15-DEC-2015 | 29-DEC-2015 | Extended Follow-up | |
| 34 | 48 | 12-APR-2016 | 05-APR-2016 | 19-APR-2016 | Extended Follow-up | |
| 35 | 52 | 02-AUG-2016 | 26-JUL-2016 | 09-AUG-2016 | Extended Follow-up | |
| 36 | 56 | 22-NOV-2016 | 15-NOV-2016 | 29-NOV-2016 | Extended Follow-up | |
| 37 | 60 | 14-MAR-2017 | 07-MAR-2017 | 21-MAR-2017 | Extended Follow-up Study Close-out | |

Once a Participant has enrolled in the Extended Follow-up, please confirm via the Extended Follow-up Enrollment (ENROLLX) form at V.#60 as shown below.

Trans-MAPP EP Study Manual of Operations

Please also note that the Enrollment form also captures information in case a Participant chooses **not** to enroll in the study. Please also be sure to enter an Enrollment form for each Participant who declines to participate in the Extended Follow-up.

Patient Casebooks

Search : 1 Patients Selected From Home Page

Casebook Spreadsheet

Set Visit Focus: Patient: Casebook: Visit:

Patients: 1-1 of 1

CRFs: 1-2 of 2

Select Patients and...

| Select | Patient | Enrollx | Sstopx | VISIT 60 | | | | | | | | | | | |
|--------------------------|---------|--------------------------|--------------------------|----------|--|--|--|--|--|--|--|--|--|--|--|
| <input type="checkbox"/> | Number | <input type="checkbox"/> | <input type="checkbox"/> | | | | | | | | | | | | |
| <input type="checkbox"/> | 102201 | <input type="checkbox"/> | <input type="checkbox"/> | | | | | | | | | | | | |

| | | |
|---|---|---|
|  | Participant ID: <input type="text" value="102201"/> | Pin # <input type="text" value="D74C"/> |
| | CRF Date: <input type="text"/> | Visit # <input type="text" value="60"/> |
| | Clinical Center: <input type="text" value="MAPP 0401"/> | |

Enrollment Confirmation

Research Coordinator completes following contact of Participant regarding Extended Follow-up Study.

1. Was the Participant successfully contacted and informed of the Trans-MAPP Yes No Epidemiology and Phenotyping Extended Follow-up Study?
2. Did the Participant consent to participate in the Extended Follow-up study? Yes No

If question 2 is YES, please complete question 2a.

If question 2 is NO, please skip to question 3.

- a. Please record the date of the Participant provided consent to participate in NA the Extended Follow-up Study: MM/DD/YYYY
- b. Please record the date of the first scheduled Extended Follow-up Study NA contact: MM/DD/YYYY

3. Please select the primary reason the participant did not successfully enroll in the Extended Follow-up Study:
 - Participant not interested in participating/following protocol.
 - Participant does not consider this study beneficial
 - Participant has concerns about the research processes
 - Participant prefers additional compensation
 - Participant has concerns about data privacy / protection of personal medical information
 - Participant not bothered enough by the symptoms to justify participation
 - Participant lost to follow-up/no contact information available.

4. Research Coordinator ID (4-digit ID)

As shown above for the Enrollment form at V.#60, an Extended Follow-up Stop (SSTOPX) form is also included at V.#60. V.#60 is the only data entry visit in Oracle Clinical for the Extended Follow-up. When a Participant completes the final Extended Follow-up visit at

Trans-MAPP EP Study Manual of Operations

V.#37 or in case of a withdrawal, please complete an Extended Follow-up Stop form as shown below at V.#60.

| | | |
|---|-------------------------------|-----------------------------------|
|  | Participant ID: <u>102201</u> | Pin # <u>D74C</u> |
| | | Clinical Center: <u>MAPP 0401</u> |
| | CRF Date: _____ | Visit # <u>60</u> |
| | | |

Study Stop Point, Extended Follow-up Study

Research Coordinator completes at 60-month contact or at final contact if Participant withdraws from the Extended Follow-up Study study early.

1. Has the Participant successfully completed the 60-month on-line survey for Yes No the Trans-MAPP Epidemiology Phenotyping Extended Follow-up Study?

If No, indicate reason for withdrawal:

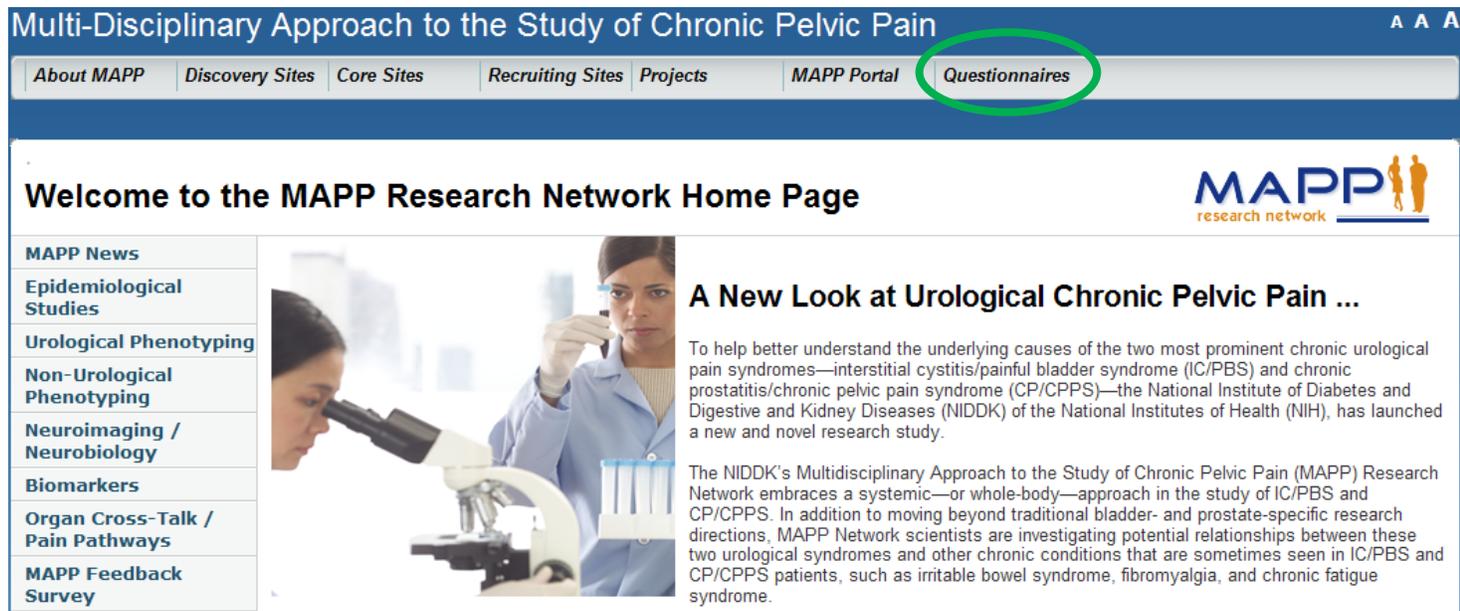
- a. No longer willing to follow the protocol/interested in participating Yes No
- b. Lost to follow-up Yes No
- c. Participant has personal constraints Yes No
- d. Medical condition/event Yes No
- e. Physician's Discretion Yes No
- f. **Administrative Stop per Protocol *** Yes No
 (* Select this reason only if Extended Follow-up Study is discontinued by Steering Committee/Study Sponsor)
- g. Other Yes No
 Specify: _____

Female Participants only:

- h. Female Participant is pregnant? Yes No NA
- h1. If Yes, Date of most recent menstrual period:
(MM/DD/YYYY)
- 2. Visit Number of Participant's last Contact:
- 3. Date of the Participant's last completed survey:
(MM/DD/YYYY)

Once a Participant has enrolled in the Extended Follow-up and has received the Visit Schedule detailing survey contacts, the Participant will be able to connect to the online Participant surveys via the same “Questionnaires” link used for the original 12-month at-home and in-clinic visits as circled in green below on the MAPP homepage:

www.mappnetwork.org



Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain

[About MAPP](#) | [Discovery Sites](#) | [Core Sites](#) | [Recruiting Sites](#) | [Projects](#) | [MAPP Portal](#) | **[Questionnaires](#)**

Welcome to the MAPP Research Network Home Page

MAPP News

- Epidemiological Studies
- Urological Phenotyping**
- Non-Urological Phenotyping
- Neuroimaging / Neurobiology
- Biomarkers
- Organ Cross-Talk / Pain Pathways
- MAPP Feedback Survey



A New Look at Urological Chronic Pelvic Pain ...

To help better understand the underlying causes of the two most prominent chronic urological pain syndromes—interstitial cystitis/painful bladder syndrome (IC/PBS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)—the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), has launched a new and novel research study.

The NIDDK’s Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network embraces a systemic—or whole-body—approach in the study of IC/PBS and CP/CPPS. In addition to moving beyond traditional bladder- and prostate-specific research directions, MAPP Network scientists are investigating potential relationships between these two urological syndromes and other chronic conditions that are sometimes seen in IC/PBS and CP/CPPS patients, such as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome.

3.D. 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 a urine sample, using a home urine collection kit provided to them at the baseline visit, as described in Appendix B. They will be asked to ship this sample to TATC using the relabeled and pre-linked (de-identified) shipping kit provided by TATC. This urine specimen 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 a non-flare urine sample 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 a non-flare urine sample will be collected. 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).

In the event that a specimen collection error or shipment problem occurs for any at-home specimens and the specimens are damaged, destroyed, or otherwise unusable, please contact both the TATC and DCC with all details about the issue. After contacting both the TATC and the DCC, please complete and enter in the Oracle Clinical DMS a Replacement Home Specimen Collection (REPLACE) form. Following the documentation of the specimen(s) which must be replaced, the FLARE or NON-FLARE questionnaire will be queued in the

DMS to appear at the appropriate time in order to collect the replacement data and specimen(s).

3.D.1. Flare/Non-Flare Prompt at 6 or 12 Month Clinic Visit

In the rare event that collection of a flare or non-flare urine sample is prompted via the online participant questionnaire at the 6 or 12 month clinic visit no additional urine samples are required. The already scheduled urine collection for the 6 and 12 month in clinic visits will satisfy the flare urine collection, so no additional urine sample is needed. Please do inform the participant that he/she will not need to collect and ship to the TATC the flare/or non-flare urine sample for the flare/non-flare event that was prompted by the online questionnaire at the 6 or 12 month clinic visit.

3.E. 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 Male Sexual Function Scale (MSFS)
- 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)

3.F. Six- and Twelve-Month Clinic Visits

In addition to the CRFs administered at the biweekly and bimonthly assessments, the following CRFs and procedures 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

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)

Biospecimens and Physical Exam Components

- Plasma Specimen Tracking (PTRAC)
- Urine Specimen Tracking (UTRAC)
- Cheek Swab Specimen Tracking (CTRAC)* - *PRN, if not collected at the Baseline visit
- Physical Exam (EXAM)* - *PRN at Principal Investigator's discretion
- Pressure Pain Threshold (PPT) Procedure
- At the 12 month visit, as well as any applicable visit, the Study Stop (SSTOP) form is available to document completion of study (12 month clinic visit) or early withdrawal (any visit other than 12 month visit).

3.G. Extended Follow-Up Assessments

At the completion of the initial 12 months of follow-up participants will have the opportunity to continue for an extended follow-up period of up to 60 months (5 years) from the baseline visit. During this extended follow-up period, participants will be expected to log into the secure portal every 4 months to complete a series of questionnaires. The questionnaires to be completed during the extended follow-up period are the same questionnaires as outlined above (see Sec. 3.D) as completed at the Trans-MAPP EPS bimonthly internet assessments.

Internet Site Design and Operation

The Trans-MAPP internet site (<http://www.mappnetwork.org>) will provide 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

4. CASE REPORT FORMS (CRFS) AND CRF-RELATED PROCEDURES

4.A. Acquisition of Forms from the DCC

The CRFs are provided to the Clinical Centers in electronic format as Adobe portable document format (PDF) files. The RCs at the Clinical Centers are responsible for printing all RC-completed data collection forms and administrative forms for the visits which they conduct. To streamline the printing process, the RC-completed forms necessary for each visit are grouped together in one packet, and are presented in the order they should be completed. For some visits, instructions on the CRFs or Visit Checklists specify when particular CRFs should be completed. For example, at the baseline visit, forms collecting eligibility criteria and symptom questionnaires should be completed prior to the administration of physical exams or other study procedures.

Each CRF has a code name located in **bold** at the bottom right of the page. Each form is dated at the bottom left corner to identify the version of the CRF. This is important should a form be revised at a later date. Please refer to the Data Entry Form and Administrative Form version logs to ensure that you are using the correct form versions.

4.B. General Instructions for the Completion of CRFs

The following guidelines are applicable to all CRFs being completed for this study:

***PLEASE NOTE:** It is imperative that all header information of ALL PAGES of ALL CRFs be completed, even if a particular page (or pages) of a CRF is blank.

Two types of forms are used in this study: Data Forms and Administrative Forms:

- Data Forms contain participant data that are entered into the database.
- Administrative Forms are used for processing Data Forms, tracking data flow and in scheduling study procedures and appointments. Administrative Form data are not entered into the database.

The RC and PT should always verify the forms in a packet against the corresponding Visit Checklist and the Visit Schedule (**SCHEDULE**) to confirm that all forms are available before the participant arrives for a clinic visit. Individual CRFs not included in a visit packet can be printed from the Adobe .PDF files available via the study website prior to the visit. As CRF amendments occur, the DCC will notify the clinical centers and make updated versions available within the application files.

All CRFs should be completed in **black** ink. Do not use pencil or blue or red ink. Always use participant's initials, not full name. **Print** legibly and clearly. All questions must be answered (all fields completed), as specified on the CRF. Be concise, however, avoid using abbreviations and symbols. **UNK** should be written in any space left unanswered. When the participant is not sure of an answer, they should use a "**best estimate**" rather than not answer the question. It is important that the RC complete *ALL INFORMATION ON ALL PAGES* of the CRF Master Heading **before** continuing with the form to ensure easy identification in case of separated pages. Master headings are at the top of each CRF page. The Master Heading elements include: **the Participant ID (PID), a Participant Identification Number (PIN), the Discovery Site number, Clinical Center number, CRF Date, and Visit Number. The Personnel Identification number ("RC ID") of the study staff member completing the form is located at the bottom of all applicable forms which the RC completes.** The RC ID

number should be completed following form review. Do not write comments in the margins or on the reverse side of the forms. A legible source document **must** exist for all data recorded on the CRF.

Errors should be corrected on the CRFs by crossing out the error with a single line and entering the correct information. *Always* initial and date the change. Circle the correct answer for clarification, if necessary. **Never** use correction fluid.

The RC is responsible for reviewing all of the completed forms at the respective visits when they each record data. All personal identifying information must be removed from lab or procedure reports prior to forwarding copies to the DCC/TATC, if it is applicable/necessary for this to be done. All source documentation sent to the DCC must have all personal identifying information obliterated (“blacked out”) and the study identifying information (Participant ID and Participant Initials) should be recorded. Making a photocopy after blacking out the name assures complete confidentiality.

4.B.1. Forms Completion

In general, the RC completes all CRFs, unless otherwise specified on the form (Participants are also directed to complete some forms, as specified in the form’s instructions). Upon completion and review of the RC-completed forms, the RC ID will be recorded at the bottom of each CRF. The RC should review all forms for legibility, accuracy, and completeness *before* they are entered into the database or sent to the TATC. The Visit Checklists will assist in documenting the review, entry, and verification process. If the RC identifies an error while reviewing the forms, the error should be corrected on the current form by crossing out the error with a single line in black ink, entering the correct information and initialing and dating the change. The RC should circle the correct answer for clarification, if necessary.

4.B.2. Personnel Identification Numbers (PI ID / RC ID)

Each Principal Investigator (PI) and Clinical Center staff member (Research Coordinators [RCs]), involved in data collection, review, and/or CRF data entry will be assigned a 4-digit ID (“**RC ID**”). This number is entered in the last question on select RC-completed forms, and refers to the staff member conducting the visit and completing the form.

4.B.3. Participant Completed Forms

For those forms completed by the participant, the RC will instruct the participant in form use and completion. The RC should be readily available to assist the participant with any questions. If the RC believes that the participant may have difficulty reading the forms, the RC may interview the participant to complete the forms. Since the participant may find some of the information on the forms to be sensitive, whenever possible, the participant should be encouraged to complete the forms alone.

The RC should review the Participant-completed forms for completeness and legibility before the Participant leaves the clinic, in case additional information or clarification is required.

4.B.4. Participant Interview Completed Forms

For those forms completed by the RC through Participant Interview, the RC will collect and record information obtained from direct interview.

In completing the forms, the RC clarifies any participant answer that is unclear or incomplete. The interviewer should have the participant elaborate or reconsider an incomplete or

inappropriate answer without leading the participant or influencing the content of the answer; thereby, creating a possibly biased answer.

Some questions addressed in the CRFs are personal and may be considered very sensitive by the participant. When a participant shows reluctance in answering a question, the interviewer should reassure the participant regarding the confidentiality of the response and explain the importance of the question.

4.B.5. Header Information on CRF:

Participant ID (PID): This is determined by the RC and logged in the PTLOG at each Clinical Center. It is a six-digit number that is unique to the Clinical Center and the Participant. Once assigned, a Participant’s ID is not deleted or transferred to another study participant. **Participant Initials:** The first letter from the first, middle and last name of the participant is noted in the space provided for the initials. If a participant does not have or use a middle initial, the first letter of her first and last name is used.

Participant Identification Number (PIN): The Participant Identification Number (PIN) is a secondary identifier used to confirm the Participant for which data corresponds. The Participant ID (PID) and Participant Identification Number (PIN) must correspond on all CRFs for a Participant.

Discovery Site Number: Each Discovery Site will be assigned a unique two-digit Discovery Site Number that permanently identifies it for the duration of the study.

Clinical Center: Each sub-site of a Discovery Site will be assigned a 2-digit number Clinical Center number so that it may be identified in conjunction with the Discovery Site number as a secondary unique identifier of the origin of the data recorded on each CRF.

Visit Number: Visit numbers have been identified in the protocol when specific events happen during the course of the study. Visit numbers range from 01-25

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

RC and PI ID: Each Research Coordinator and Principal Investigator must have a unique 4-digit identifier. The DCC uses the unique ID to link specific data to a particular person in times when data clarification is needed..

4.C. Specific Instructions for Completing Data Entry CRFs

This section provides specific instructions on how to complete each Data Entry CRF. **Please note the forms are listed in the order of CRFs completed by the RC and CRFs completed by the Participant.** If, after consulting this section, you are still unsure of how to complete a form, please contact Clinical Data Management at the DCC.

| Case Report Forms – Data Entry Forms (in alphabetical order by Form Name) | |
|--|-----------------|
| Form Name | Form Code |
| CRFs completed by Research Coordinator: | |
| Pre-screening – Epidemiology and Phenotyping Study Pt.s | PRESCR-EPS |
| Prescreening – Healthy Controls | PRESCR-HEALTHY |
| Prescreening – Positive Controls | PRESCR-POSITIVE |
| Screening/Eligibility forms: | |
| Demographics | DEMO |
| Symptom Assessment Questionnaire - Baseline | SYM-Q_Baseline |
| Female Genitourinary Pain Index - Baseline | FGUPI-Baseline |
| Male Genitourinary Pain Index – Baseline | MGUPI-Baseline |
| Eligibility – Epidemiology and Phenotyping Study Pt.s | ELIG |
| Eligibility – Control Participants | ELIG-Controls |

Trans-MAPP EP Study Manual of Operations

| Case Report Forms – Data Entry Forms (in alphabetical order by Form Name) | |
|---|----------------------|
| Form Name | Form Code |
| Urine Culture Result | UCR |
| Enrollment | ENROLL |
| Medical History, Treatment, and Physical Exam: | |
| Medical History | MEDHX |
| Family Medical History | FAMHX |
| Concomitant Medications | CMED |
| Physical Exam | EXAM |
| Co-morbid Diagnostic Modules completed per answers given on Complex Medical Symptom Inventory: | |
| Fibromyalgia | CMSI-FM2 |
| Fibromyalgia – Tender Point Exam | CMSI-FM2-TP |
| Chronic Fatigue | CMSI-CFS2 |
| Irritable Bowel Syndrome | CMSI-IBS2 |
| Vulvodynia | CMSI-VDYN2 |
| Migraine | CMSI-MI2 |
| Temporomandibular Joint Disorder (TMJD) | CMSI-TMD2 |
| Specimen Tracking CRFs: | |
| Plasma Specimen Tracking | PTRAC |
| Cheek Swab Specimen Tracking | CTRAC |
| Urine Specimen Tracking | UTRAC |
| Urine Specimen Tracking - Infectious Etiology (Male/Female) | UTRAC-IE-M/F |
| Urine Specimen Tracking - Infectious Etiology (Male/Female) | UMIETRAC UFIETRAC |
| Urine Specimen Tracking - Home Collection Kits Linking Form | UTRAC_Home_Linking |
| Urine Specimen Tracking – FLARE-First Home Collection Kit | UH1FTRAC |
| Urine Specimen Tracking – FLARE-Second Home Collection Kit | UH2FTRAC |
| Urine Specimen Tracking – NON-FLARE-First Home Collection Kit | UH1NFTRAC |
| Urine Specimen Tracking – NON-FLARE-Second Home Collection Kit | UH2NFTRAC |
| Pain/Pressure Procedure | PPT |

| Case Report Forms – Data Entry Forms (in alphabetical order by Form Name) | |
|--|-----------|
| Form Name | Form Name |
| PRN forms (filled out as-needed): | |
| Study Stop | SSTOP |
| Consent Withdrawal | CONWITHDR |
| Replacement Home Specimen Collection | REPLACE |
| Procedural or Unanticipated Problems | PUP |
| CRFs completed by Participant via online survey: | |
| Symptom Assessment Questionnaire (for Follow-up Contacts) | SYM-Q |
| Brief Flare Risk Factor Questionnaire | FLARE |
| Interstitial Cystitis Symptom Index | ICINDEX |
| Interstitial Cystitis Problem Index | |
| AUA Symptom Index | AUASI |
| RICE Case Definition Questionnaire | RICE |
| Early In Life Infection History | EIL-INF |
| Female CRFs | |
| Female Genitourinary Pain Index (for Follow-up Contacts) | FGUPI |
| Female Sexual Function Index | FSFI |
| Female Self-Esteem and Relationship Questionnaire | FSEAR |
| Male CRFs | |
| Male Genitourinary Pain Index (for Follow-up Contacts) | MGUPI |
| International Index of Erectile Function | IIEF |
| University of Washington Ejaculatory Function Scale | EFS |
| Male Self-Esteem and Relationship Questionnaire | MSEAR |
| Non-urologic CRFs | |
| BPI (Intensity, Body map, Interference) | BPI |

Trans-MAPP EP Study Manual of Operations

| Case Report Forms – Data Entry Forms (in alphabetical order by Form Name) | |
|--|-----------|
| Form Name | Form Name |
| SF-12 | SF-12 |
| PANAS | PANAS |
| Hospital Anxiety and Depression Scale | HADS |
| PROMIS - Anger - Short Form | ANGER |
| Multiple Ability Self-Report Questionnaire | MASQ |
| PROMIS - Fatigue - Short Form | FATIGUE |
| PROMIS - Sleep - Short Form | SLEEP |
| Perceived Stress Scale | PSS |
| IPIP | IPIP |
| Thoughts About Symptoms | CSQ |
| Beliefs in Pain Control Questionnaire | BPCQ |
| Childhood/Recent Traumatic Events Scale | CTES |
| Complex Medical Symptoms Inventory | CMSI |
| Neuroimaging Study CRFs | |
| Eligibility Confirmation, Neuroimaging Study | ELIG_SCAN |
| Magnetic Resonance Environment Screening (Administrative) | MR_SCREEN |

4.D. CRFs completed by Research Coordinator:

PRE-SCREENING – EPIDEMIOLOGY AND PHENOTYPING STUDY Pt.s [PRESCR-EPS]

Pre-screening – Healthy Controls [PRESCR-HEALTHY]

Pre-screening – Positive Controls [PRESCR-POSITIVE]

Purpose: To collect information regarding the prescreening process for each of the three types of subjects to be recruited:

- Epidemiology and Phenotyping Study subjects
- Healthy Controls
- Positive Controls

This data will be used to generate monthly accrual reports. In particular, the total reported for Question #2 must be a sum of the values recorded for Question #s 3, 4, 5, and 6 for reporting purposes. Please refer to the instructions on the forms regarding how to be sure the totals for Question #s 3, 4, 5, and 6 reflect the total reported in Question #2 each month. Special consideration must be taken for subjects whose decision to participate is pending from one month to the next. Please see the instructions in the margin next to Question #s 3, 4, 5, and 6 on the forms about how to account for subjects whose decision is “pending”.

Who: Research Coordinator completes

When: Once a month (This form should be entered in the DMS no later than the 5th of every month for reporting purposes.)

4.E. Screening/Eligibility forms:

[DEMO] DEMOGRAPHICS

Purpose: To collect demographic data on a participant, as well as family history of PBS/IC and/or CPPS/CP.

Who: Research Coordinator completes

When: Baseline Visit

General Directions

Question #7 Annual family income is to be recorded in US dollars.

Question #11 A partner can be someone of the same sex.

[SYM-Q BASELINE] SYMPTOM ASSESSMENT QUESTIONNAIRE – BASELINE

Purpose: To collect eligibility information at Visit #1 and information regarding the participant’s assessment of symptom changes, specifically pain, urgency and frequency. To capture the Participant’s mood, single most bothersome symptom, and health care utilization. For female Participants the most recent menstrual period is documented. This form also collects information about current flares and flares in the past year.

Who: Participant completes **SYM-Q Baseline** and RC enters in the DMS at the baseline visit.

When: Baseline Visit

[FGUPI-BASELINE] FEMALE GENITOURINARY PAIN INDEX

Purpose: To collect information regarding the female participant’s assessment of pain and urinary symptoms. Four domains are evaluated: pain/discomfort, urination, impact of symptoms, and quality of life.

Who: Female Participant

When: Baseline Visit

[MGUPI-BASELINE] MALE GENITOURINARY PAIN INDEX

Purpose: To collect eligibility information at the baseline visit and information regarding the male participant’s assessment of pain and urinary symptoms. Four domains are evaluated: pain/discomfort, urination, impact of symptoms, and quality of life.

Who: Male Participant

When: Baseline Visit

[ELIG] ELIGIBILITY CONFIRMATION – EPIDEMIOLOGY AND PHENOTYPING STUDY PARTICIPANTS

Purpose: To determine and ensure the participant’s eligibility for entry into the study for *Epidemiology and Phenotyping Study Participants*. All Inclusion Criteria responses must be “Yes” to be eligible for enrollment*. All exclusion/deferral responses must be “No” for the participant to be eligible for enrollment.

* Male Participants may still be eligible for the study if the answer to question #6b. is “0-No”. Please see instructions on the CRF for question #6b.

Who: Research Coordinator

When: Baseline Visit

General Directions:

Please note: Participants must consent to provide DNA specimens (blood and cheek swab) as detailed on the Eligibility form in order to be eligible for the study. Participants must also consent to provide urine specimens for biomarker studies in order to be eligible.

Deferral criteria require that a urine specimen be collected for dipstick, urinalysis, and (for female Participants) pregnancy test. Results of the urine culture must be documented on the Urine Culture Result – Deferral Criterion for Eligibility Confirmation [UCR] form.

Data entry instructions:

For ALL Epidemiology and Phenotyping Study Participants, the **ELIG** form must be the first form entered in the DMS. If a Participant must be *deferred* please enter **ONLY** the ELIG form and no other baseline visit CRFs. If a Participant is found to be *ineligible* also please enter **ONLY** the ELIG form and no other baseline visit CRFs.

[ELIG-CONTROLS] ELIGIBILITY CONFIRMATION – CONTROL PARTICIPANTS

Purpose: To determine and ensure the participant’s eligibility for entry into the study for **Control Participants**. All Inclusion Criteria responses must be “Yes” to be eligible for enrollment. All exclusion/deferral responses must be “No” for the participant to be eligible for enrollment.

Who: Research Coordinator

When: Baseline Visit

General Directions:

Please note: Participants must consent to provide DNA specimens (blood and cheek swab) as detailed on the Eligibility form in order to be eligible for the study. Participants must also consent to provide urine specimens for biomarker studies in order to be eligible.

During eligibility assessment, confirm the type of Control for which each Participant is being screened and document on the ELIG-Controls form accordingly.

For Positive Controls, the following Complex Medical Symptoms Index (CMSI) Modules **must** be completed*:

- Fibromyalgia (CMSI_FM2)
- Irritable bowel syndrome (CMSI_IBS2)
- Chronic fatigue syndrome (CMSI_CFS2)

* See also the segments detailing the CMSI modules following the CMSI questionnaire in the Non-urologic CRFs section of the MOP.

Deferral criteria require that a urine specimen be collected for dipstick, urinalysis, and (for female Participants) pregnancy test. Results of the urine culture must be documented on the Urine Culture Result – Deferral Criterion for Eligibility Confirmation [UCR] form.

Data entry instructions:

For ALL Control Participants, the **ELIG-Controls** form must be the first form entered in the DMS. If a Participant must be *deferred* please enter **ONLY** the ELIG-Controls form and no other baseline visit CRFs. If a Participant is found to be *ineligible* also please enter **ONLY** the ELIG-Controls form and no other baseline visit CRFs.

[UCR] URINE CULTURE RESULT – DEFERRAL CRITERION FOR ELIGIBILITY CONFIRMATION

Purpose: To confirm that the Participant does not have a midstream urine culture $\geq 100,000$ CFU/ml, with a single uropathogen, per urine culture test results. If a Participant does have a midstream urine culture $\geq 100,000$ CFU/ml, with a single uropathogen, then the Participant must be treated and deferred.

Who: Research Coordinator

When: Baseline Visit

[ENROLL] ENROLLMENT CONFIRMATION

- Purpose:** To confirm that a Participant has successfully enrolled in the study, or to document why a Participant has not enrolled following eligibility screening.
- Who:** Research Coordinator
- When:** Baseline Visit

General Directions:

Data on this form will be used for monthly accrual reports and for visit scheduling purposes, so all applicable fields must be completed for all Participants.

4.F. Medical History, Treatment, and Physical Exam:

[MEDHX] MEDICAL HISTORY

- Purpose:** To obtain information about the participant's history of Interstitial Cystitis (IC)/Painful Bladder Syndrome (PBS) and/or Chronic Pelvic Pain Syndrome (CPPS)/Chronic Prostatitis (CP) as well as general medical history.
- Who:** RC completes form with information obtained from participant interview
- When:** Baseline Visit

General Directions

- Q #1: This refers to when the participant's symptoms *first appeared*. This scenario is not necessarily the same as when the participant's symptoms were *first diagnosed* by a physician.
- Q. #s 1a, 2a, and 3a: If the participant does not recall the exact age, ask the participant to make a best guess.

Responses on MEDHX will be verified with participant's medical records at the Clinical Center or another treatment facility.

Please also note that if a participant has been diagnosed with any of the conditions/disorders in questions 9 - 17 and/or has had any of the procedures listed in questions 18 - 20, by answering "1-Yes" to any of those questions all checkboxes for the corresponding sub-sets of conditions/disorders/procedures specified must be answered "1-Yes, 0-No, or 88-Unknown". Please do not leave any sub-sets of checkboxes blank if any of the answers for questions 9 - 17 and/or 18 - 20 are "1-Yes".

[FAMHX] FAMILY MEDICAL HISTORY

- Purpose:** To obtain information about the participant's first degree blood relatives' history of common chronic pain and common psychiatric disorders.
- Who:** Participant-completed
- When:** Baseline Visit (or at Six-month or Twelve-month Visit, as needed)

General Directions

Please be sure the Participant understands that first-degree blood relatives include only the following: parents, grandparents, aunts, uncles, siblings, children.

If the answer to Q.#1 is "No" or "Don't know" please leave the rest of the form blank.

If the answer to Q.#1 is "Yes", please be sure the Participant completes, to the best of his or her ability, the table on page 2 of the FAMHX form.

[CMED] CONCOMITANT MEDICATIONS

- Purpose:** To collect information from the Participant in order to record all concomitant medications/supplements/vitamins/herbal remedies currently taken by the participant, while in the study.
- To monitor the use of medications that are for urologic or pelvic pain symptoms.
- Who:** RC Completed.
- When:** Visit #s: Baseline, 6-month, and 12-month Visits.

General Directions:

Medications refer to prescription or non-prescription drugs, over-the-counter drugs, vitamins, nutritional supplements or herbal remedies. RC's should document names, doses and frequency of use.

The information for this CRF is obtained from the Participant's report of the most recent dose(s) of over-the-counter medications and/or prescriptions.

****The Participant should bring to each clinic contact all containers for medications currently being taken.***

Question #1: This is reported as 0 (No), if the Participant ***does not*** report use of any over-the-counter medications and/or prescriptions.

If the Participant ***does*** report use of any over-the-counter medications and/or prescriptions, this question is answered as 1 (Yes) and the number of records to be reported is completed.

Line #: This is a 3-digit sequential number which begins with "001", "002", "003", etc.

Drug Code #: This is the code that is been obtained from the ***Medication Reference*** tool in the Data Management System application.

Drug Name: This is the generic name for the medication/treatment, generated from the ***Medication Reference*** tool.

Date of Last Dose: The most recent date the Participant reports taking the medication to be recorded.

Total Daily Dose (TDD): This information is obtained from the Participant and as documented on any medication containers the Participant brings to the clinic visit. The RC must multiply the *Strength of the dose* (the individual dose amount) by the *Total Number of Doses per 24 Hours*.

Frequency: Please use the Concomitant Medications Legend to select the ***most specific*** response possible.

Unit: Please use the Concomitant Medications Legend to select the ***most specific*** response possible.

Route: Please use the Concomitant Medications Legend to select the ***most specific*** response possible.

For Urologic or Pelvic Pain Symptoms:

Confirm with the Participant if each medication was taken due to any urologic or pelvic pain symptoms. These symptoms may be associated with any of the conditions (IC/PBS or CP/CPSS) related to this study. Please clarify in the space provided in the comments section at the bottom of the CMED form any reason a medication is taken for urologic or pelvic pain

symptoms which are not related to the conditions associated with this study (for example, if a medication is being taken to treat symptoms associated with a kidney stone).

Additional CMED pages, without Question #1, have been provided if multiple pages are needed to record multiple concomitant medications for a visit.

If a drug code for a concomitant medication that the participant has recorded is unavailable in the Medication Reference Tool on the web application, the RC should call the Clinical Data Manager at the DCC. If the Clinical Data Manager is unable to locate the information for the RC, the medication and other relevant data will be recorded on a log maintained at the DCC and the Clinical Data Manager will develop a code and enter the data in CMED at the DCC.

[EXAM] PHYSICAL EXAM

- Purpose:** To obtain information about the participant's study specific health status through a physical examination of abdominal and genitourinary systems.
- Who:** Investigator completed or his/her approved designee. Upon completion, the RC should review this form for completeness.
- When:** Baseline Visit

General Directions

Questions #1 and #2: It is *preferable* that height and weight be measured without shoes.

Question #11 (Males only): Collection of the VB3 specimen is encouraged of all male Participants, but, as with any study procedures, this procedure may be skipped at the Participant's request. Please record an answer of "0-No" if a male Participant declines to give a VB3 specimen.

4.G. Specimen Tracking CRFs:

[PTRAC] PLASMA SPECIMEN TRACKING

- Purpose:** To document collection and shipping details regarding the plasma specimens to be sent to the TATC. Please see the CRF for further instructions.
- Who:** Research Coordinator
- When:** Baseline, 6-month, and 12-month Visits

[CTRAC] CHEEK SWAB SPECIMEN TRACKING

- Purpose:** To document collection and shipping details regarding the cheek swab DNA specimens to be sent to the TATC. Please see the CRF for further instructions.
- Who:** Research Coordinator
- When:** Baseline Visit (6-month/12-month Visit PRN if not collected at Baseline)

[UTRAC] URINE SPECIMEN TRACKING

- Purpose:** To document collection and shipping details regarding the urine specimens to be sent to the TATC. Please see the CRF for further instructions.
- Who:** Research Coordinator
- When:** Baseline, 6-month, and 12-month Visits

**[UMIETRAC, UFIETRAC] URINE SPECIMEN TRACKING - INFECTIOUS ETIOLOGY
(MALE/FEMALE)**

- Purpose:** To document collection and shipping details regarding the urine specimens from male and female Participants, respectively, for the Infectious Etiology studies to be sent to the TATC. Please see the CRF for further instructions. Also, please see the detailed instructions sheet included in the specimen collection kit, provided by the TATC, which is to be given to the Participant to ensure the most sterile and accurate specimen collection methods. Please contact the TATC to re-order these kits well in advance of any Participants' baseline or 6/12-month contacts if supply of these kits runs low.
- Who:** Research Coordinator
- When:** Baseline, 6-month, and 12-month Visits
-

**[UTRAC_HOME_LINKING] URINE SPECIMEN TRACKING - HOME COLLECTION KITS
LINKING FORM**

- Purpose:** To confirm specimen collection, documentation, and tracking details of the home collection FLARE and NON-FLARE urine specimens for each Participant for the records maintained at the Tissue and Technology Core (TATC).
- Who:** Participant
- When:** PRN per the report by the Participant of when the first symptom flare occurs and at a designated random interval when the Participant does not report experiencing a symptom flare.
-

[UH1FTRAC] URINE SPECIMEN TRACKING – FLARE-FIRST HOME COLLECTION KIT

- Purpose:** To document collection and shipping details regarding the **FIRST** home collection urine specimen for each Participant that is to be sent to the TATC following the first reported symptom flare. The kit to be used for this home collection specimen is in the **RED** FLARE bag and is marked with a **BLUE** dot. Please see the **UH1FTRAC** CRF for further instructions.
- Who:** Participant
- When:** PRN per the first reported symptom flare.
-

[UH2FTRAC] URINE SPECIMEN TRACKING – FLARE-SECOND HOME COLLECTION KIT

- Purpose:** To document collection and shipping details regarding the **SECOND** home collection urine specimen for each Participant that is to be sent to the TATC following the first reported symptom flare. The kit to be used for this home collection specimen is in the **RED** FLARE bag and is marked with an **ORANGE** dot. Please see the **UH2FTRAC** CRF for further instructions.
- Who:** Participant
- When:** PRN per the reported symptom flare that triggers the first FLARE questionnaire.
-

[UH1NFTRAC] URINE SPECIMEN TRACKING – NON-FLARE-FIRST HOME COLLECTION KIT

- Purpose:** To document collection and shipping details regarding the **FIRST** home collection urine specimen for each Participant that is to be sent to the TATC at the **randomly assigned interval** when the Participant **DOES NOT** report experiencing a symptom flare. The kit to be used for this home collection specimen is in the **GREEN** NON-FLARE bag and is marked with a **BLUE** dot. Please see the **UH1NFTRAC** CRF for further instructions.
- Who:** Participant

When: PRN per the **randomly assigned interval** when the Participant ***DOES NOT*** report experiencing a symptom flare.

[UH2NFTRAC] URINE SPECIMEN TRACKING – NON-FLARE-SECOND HOME COLLECTION KIT

Purpose: To document collection and shipping details regarding the ***SECOND*** home collection urine specimen for each Participant that is to be sent to the TATC at the **randomly assigned interval** when the Participant ***DOES NOT*** report experiencing a symptom flare. The kit to be used for this home collection specimen is in the ***GREEN*** NON-FLARE bag and is marked with an ***ORANGE*** dot. Please see the UH2NFTRAC CRF for further instructions.

Who: Participant

When: PRN per the **randomly assigned interval** when the Participant ***DOES NOT*** report experiencing a symptom flare.

[PPT] PRESSURE/PAIN PROCEDURE

Purpose: To record the results of the Pressure/Pain Threshold Procedure results obtained from the Pressure/Pain Threshold device.

Who: Research Coordinator

When: Baseline, 6-month, and 12-month Visits

General Directions:

The Pressure/Pain Threshold Procedure entails three runs using the Pressure/Pain Threshold device. Please be sure to document the results of each of the three runs in the spaces provided on the form.

4.H. PRN CRFs

[SSTOP] STUDY STOP POINT

Purpose: To record the date the participant completed the trial or the date and the primary reason for a participant's termination from the follow-up phase of the study.

Who: Research Coordinator and Principal Investigator

When: 12-month visit, or at time of early study withdrawal.

General Directions

The Study Stop Point [SSTOP] form is completed at the time of withdrawal, if a participant opts to withdraw from the study early. Otherwise, the form is completed at the end of the 12-Month Visit (Visit #25), the last study contact. If the participant withdraws in between visits, please use the visit number of the most recent visit for which the participant was seen. For example, if the participant wishes to no longer participate between visits 2 and 3, please use Visit #2 when completing the SSTOP form.

Qx #1: Indicate if the participant has successfully completed the trial. If the answer is “No”, the reason for not successfully completing the trial must be indicated. ***Only one most applicable and appropriate reason must be checked.*** Reasons include, but are not limited to:

- ◆ No longer willing to follow the protocol/interested in participating
- ◆ Lost to follow-up
- ◆ Participant has personal constraints
- ◆ Medical Condition/Event

- ◆ Physician's discretion
 - ◆ Other
- Female Participants only:
- ◆ Female Participant is pregnant

Qx #s 5 and 6: The PI and the RC *must* sign and date the Study Stop Point [SSTOP] form.

[CONWITHDR] CONSENT WITHDRAWAL

- Purpose:** To document the withdrawal of consent for a Participant's DNA specimen(s) to be used for the purposes of this study and/or other studies. The DNA specimens include cheek swab and blood specimens.
- Who:** Research Coordinator
- When:** Visit at which the Participant informs the study staff of the wish to withdraw consent of the use of DNA specimen(s).

General Directions:

If a Participant wishes to withdraw consent for the use of DNA specimens, all fields on this CRF must be completed as appropriate, the DNA specimens must be destroyed, and documentation detailing when the specimens were destroyed must be kept with the Participant's study records.

[REPLACE] REPLACEMENT HOME SPECIMEN COLLECTION

- Purpose:** To document and track additional home FLARE and/or Non-FLARE specimen collection in the event that an error in collection and/or shipment requires that a home urine specimen be collected again.
- Who:** Research Coordinator
- When:** PRN in the event of any errors in home urine specimen collection and/or shipment.

[PUP] PROCEDURAL OR UNANTICIPATED PROBLEMS

- Purpose:** To collect information concerning any Procedural or Unanticipated Problems (PUPs) that the participant experiences during the course of the trial. PUPs may occur at clinic contacts and in relation to study procedures (such as blood draw, for example), or in the intervals between clinic contacts while the Participant is enrolled in the study.
- Who:** RC and/or PI completes. The RC and/or PI determines the study-relatedness and grades the severity of the PUP using the codes provided on the form.
- When:** **The PUP form is completed on an as-needed basis in the event of an procedural or unanticipated problems that occur, whether they are related to the study or not. Please note that Procedural or Unanticipated Problems may be related to a Protocol Deviation and/or Violation. Please note the codes in the legend to record a PUP as a Protocol Deviation and/or Violation.**

General Directions

The following items are listed in the order in which they appear on the form. When completing the form, please refer to the PUP codes at the bottom of the form.

Visit Number: The Visit Number in the header will be the current visit number, if the PUP is being reported during a scheduled visit window. If a participant contacts the RC between

scheduled visits, the *next* visit number is entered (i.e., if the CRF is completed between Visit #03 and Visit #04, the Visit Number would be 04).

- CRF Date:** CRF Date will be entered in the database as the date of the visit number to which it corresponds even if the PUP(s) may have been recorded between visits. Contacts made with the participant may be recorded on the Comments Sheet (**COMM**), identifying the PUP(s) and the date of contact when the participant reported the PUP(s).
- Question #1:** Any PUP(s) reported by the participant are recorded for the current visit and this question is checked as “Yes”. Question 1a. must confirm the total number of PUPs being recorded and the details of each must be recorded in the space(s) provided in the panel(s) on the form. A second page is available if more than two PUPs are reported at one visit.
- Problem #:** This is a 3-digit sequential number starting with ‘001’, ‘002’, ‘003’, etc. This number repeats during the study **only** if documentation of a continuation of the event being recorded is necessary at a subsequent visit. Each newly reported PUP is recorded with the next, new, sequential number.
- PUP Code:** The PUP Code consists of three letters and two numbers, as listed in the PUP Code panel on the form. The three letters are abbreviations for PUPs as follows: SPC-Specimen collection-related; PRO-Procedure-related; MIS-Miscellaneous, and PDV-Protocol Deviation and/or Violation.
- Date of Onset:** Record the date of onset of the symptoms that the participant experienced that resulted in the PUP, even if the date lasted one day or less. If the PUP is continued from a previous visit and considered a follow-up, re-record the date of onset and be sure to use the original Problem # for the PUP.
- Treatment for PUP:** The RC will code whether the participant received any form of *treatment from a physician or other health care provider* for the PUP. Only physician/health care provider prescribed/recommended treatment is recorded.
- Comments:** Describe the PUP(s) based on the information provided by the participant. Anything transcribed directly from the participant should be set apart by quotation marks. Treatments, if prescribed by the physician, should also be described in this space. Attempts should be made by the RC to include all pertinent information, for monitoring and reporting purposes at the DCC.

* Also, any supporting documentation of the PUP should be maintained in the Participant’s Source Documentation.

- PI ID:** This must be completed on all PUP forms. It is a **4 digit number chosen by the** Principal Investigator (PI) or PI’s designee.

All PUP forms are signed and dated by the PI. When recording a new PUP, complete the entire PUP record in each panel. If the PUP is not yet resolved, follow-up should continue at each visit until the event is resolved. Because of this, the RC should review all previously reported PUPs at every visit.

Additional PUP pages, without Question #1 and including additional PUP panels, have been provided if multiple pages are needed to record multiple PUPs for a visit.

4.1. CRFs completed by Participant via online survey:

[SYM-Q] SYMPTOM ASSESSMENT QUESTIONNAIRE (FOR FOLLOW-UP CONTACTS)

- Purpose:** To collect information regarding the participant's assessment of symptom changes, specifically pain, urgency and frequency. To capture the Participant's mood, single most bothersome symptom, and health care utilization. For female Participants the most recent menstrual period is documented. This form also collects information about current flares and triggers the FLARE Questionnaire, when applicable.
- Who:** Participant
- When:** All Follow-up Visits
-

[FLARE] BRIEF FLARE RISK FACTOR QUESTIONNAIRE

- Purpose:** To capture details about a current symptom flare. The FLARE questionnaire also aims to document potential contributing factors to a symptom flare, such as food/drinks consumed, behaviors, and infections.
- Who:** Participant
- When:** The first three Follow-up Visits when a Participant reports experiencing a symptom flare.
An algorithm in the DMS will also designate three random intervals when the FLARE questionnaire will be administered, but when the Participant reports *NOT* experiencing a symptom flare. At each of the first flare and non-flare data collection points, respectively, a flare and non-flare urine specimen will also be collected. Please see instructions from the TATC.
-

[ICINDEX] IC SYMPTOM & PROBLEM INDEX

- Purpose:** To collect information on the participant's assessment of IC/PBS symptoms and problems related to these symptoms.
- Who:** Participant
- When:** All Visits
-

[AUASI] AUA SYMPTOM INDEX

- Purpose:** To capture details about the severity of urinary symptoms in the previous month from the visit at which the form is administered.
- Who:** Participant
- When:** Baseline, Bi-monthly, 6-month, and 12-month Visits
-

[RICE] RICE CASE DEFINITION QUESTIONNAIRE

- Purpose:** To capture information about symptoms related to pelvic pain, urgency, and frequency in the 3 months prior to the visit at which the form is administered. The RICE form is a companion CRF in the MAPP network to forms and data being collected for the RICE (RAND Interstitial Cystitis Epidemiology) study.
- Who:** Participant
- When:** Baseline, Bi-monthly, 6-month, and 12-month Visits
-

[EIL-INF] EARLY IN LIFE INFECTION HISTORY

- Purpose:** To record data about bladder infection history, kidney infection history, and family history of urinary tract infections.
- Who:** Participant

When: 6-month Visit

4.J. CRFs for Female Participants ONLY

[FGUPI] FEMALE GENITOURINARY PAIN INDEX

Purpose: To collect information regarding the female participant's assessment of pain and urinary symptoms. Four domains are evaluated: pain/discomfort, urination, impact of symptoms, and quality of life.

Who: Female Participant

When: All Follow-up Visits

[FSFI] FEMALE SEXUAL FUNCTION INDEX©

Purpose: To collect information regarding the participant's changes in domains of female sexual functioning during the study.

Who: Female Participant

When: Baseline, Bi-monthly, 6-month, and 12-month Visits

[FSEAR] FEMALE SELF-ESTEEM AND RELATIONSHIP QUESTIONNAIRE

Purpose: To collect information about the female Participant's perspectives of sexual function and partner relationship.

Who: Female Participant

When: Baseline, Bi-monthly, 6-month, and 12-month Visits

4.K. CRFs for Male Participants ONLY

[MGUPI] MALE GENITOURINARY PAIN INDEX (FOR FOLLOW-UP CONTACTS)

Purpose: To collect information regarding the male participant's assessment of pain and urinary symptoms. Four domains are evaluated: pain/discomfort, urination, impact of symptoms, and quality of life.

Who: Male Participant

When: All Follow-up Visits

[IIEF] INTERNATIONAL INDEX OF ERECTILE FUNCTION

Purpose: To capture data about male sexual function.

Who: Male Participant

When: Baseline, Bi-monthly, 6-month, and 12-month Visits

General Directions:

[EFS] UNIVERSITY OF WASHINGTON EJACULATORY FUNCTION SCALE

Purpose: To capture data about the severity of the male Participant's symptoms related to ejaculation.

Who: Male Participant

When: Baseline, Bi-monthly, 6-month, and 12-month Visits

[MSEAR] MALE SELF-ESTEEM AND RELATIONSHIP QUESTIONNAIRE

Purpose: To collect information about the male Participant’s perspectives of sexual function and partner relationship.
Who: Male Participant
When: Baseline, Bi-monthly, 6-month, and 12-month Visits

4.L. Non-urologic CRFs

[BPI-MALE/FEMALE] BRIEF PAIN INVENTORY

Purpose: To utilize the body map in order to capture areas the Participant feels pain. The BPI form also captures data regarding the intensity of pain and interference of pain in the Participant’s quality of life.
Who: Participant
When: Baseline, Bi-monthly, 6-month, and 12-month Visits

[SF12] HEALTH STATUS QUESTIONNAIRE ®

Purpose: To collect information regarding the participant’s assessment of their general quality of life as related to their health, and as measured by various types of activities and emotional concerns.
Who: Participant
When: Baseline, Bi-monthly, 6-month, and 12-month Visits

[PANAS] PANAS

Purpose: To capture data about various feelings and emotions the Participant has felt over the past week.
Who: Participant
When: Baseline, Bi-monthly, 6-month, and 12-month Visits

[HADS] HOSPITAL ANXIETY AND DEPRESSION SCALE

Purpose: To collect information regarding the participant’s changes in the emotional component of their illness during the study.
Who: Participant
When: Baseline, Bi-monthly, 6-month, and 12-month Visits

[ANGER] PROMIS - ANGER - SHORT FORM

Purpose: To capture data about the Participant’s feelings of anger in the 7 days prior to the visit at which the form is administered.
Who: Participant
When: Baseline, Bi-monthly, 6-month, and 12-month Visits

[FATIGUE] PROMIS - FATIGUE - SHORT FORM

Purpose: To capture data about the Participant’s feelings of fatigue in the 7 days prior to the visit at which the form is administered.
Who: Participant
When: Baseline, Bi-monthly, 6-month, and 12-month Visits

[SLEEP] PROMIS - SLEEP - SHORT FORM

Purpose: To capture data about the Participant's patterns and quality of sleep in the 7 days prior to the visit at which the form is administered.

Who: Participant

When: Baseline, Bi-monthly, 6-month, and 12-month Visits

[MASQ] MULTIPLE ABILITY SELF-REPORT QUESTIONNAIRE

Purpose: For the Participant to rate the ability/difficulty to perform every-day types of activities that might be affected by symptoms.

Who: Participant

When: Baseline, 6-month, and 12-month Visits

[PSS] PERCEIVED STRESS SCALE

Purpose: For the Participant to indicate feelings and thoughts during the past month.

Who: Participant

When: Baseline, Bi-monthly, 6-month, and 12-month Visits

[IPIP] IPIP

Purpose: For the Participant to rate personal behaviors per the scale provided.

Who: Participant

When: Baseline

[CSQ] THOUGHTS ABOUT SYMPTOMS

Purpose: To capture data about mechanisms the Participant uses to cope or deal with symptoms.

Who: Participant

When: Baseline, 6-month, and 12-month Visits

[BPCQ] BELIEFS IN PAIN CONTROL QUESTIONNAIRE

Purpose: For the Participant to rate opinions about pain symptoms.

Who: Participant

When: Baseline, 6-month, and 12-month Visits

[CTES] CHILDHOOD/RECENT TRAUMATIC EVENTS SCALE

Purpose: To capture data about traumatic events in the Participant's past.

Who: Participant

When: Baseline

[CMSI] COMPLEX MEDICAL SYMPTOMS INVENTORY QUESTIONNAIRE

Purpose: For the Participant to report the occurrence of symptoms related to Fibromyalgia, Chronic Fatigue Syndrome, Irritable Bowel Syndrome Temporomandibular Joint Disorder, Migraine, and (if applicable for female Participants) Vulvodynia. Data related to other symptoms and disorders are also captured on this form.

Who: Participant

When: Baseline, 6-month, and 12-month Visits

[CMSI_FM2] COMPLEX MEDICAL SYMPTOMS INVENTORY - FIBROMYALGIA

Purpose: To capture data about the Participant’s symptoms related to Fibromyalgia, if reported per the CMSI Questionnaire

Who: Research Coordinator

When: Baseline

[CMSI_FM2-TP] COMPLEX MEDICAL SYMPTOMS INVENTORY – FIBROMYALGIA, TENDER POINT EXAM

Purpose: To capture data about the Participant’s symptoms related to Fibromyalgia via a Tender Point exam, if reported per the CMSI Questionnaire. *Please note that this form is optional.

Who: Research Coordinator

When: Baseline

[CMSI_CFS2] COMPLEX MEDICAL SYMPTOMS INVENTORY – CFS

Purpose: To capture data about the Participant’s symptoms related to Chronic Fatigue Syndrome, if reported per the CMSI Questionnaire

Who: Research Coordinator

When: Baseline

[CMSI_IBS2] COMPLEX MEDICAL SYMPTOMS INVENTORY – IBS

Purpose: To capture data about the Participant’s symptoms related to Irritable Bowel Syndrome, if reported per the CMSI Questionnaire

Who: Research Coordinator

When: Baseline

[CMSI_VDYN2] COMPLEX MEDICAL SYMPTOMS INVENTORY - VULVODYNIA

Purpose: To capture data about the Participant’s symptoms related to Vulvodynia, if reported per the CMSI Questionnaire

Who: Research Coordinator

When: Baseline

[CMSI_MI2] COMPLEX MEDICAL SYMPTOMS INVENTORY - MIGRAINE

Purpose: To capture data about the Participant’s symptoms related to Migraine, if reported per the CMSI Questionnaire

Who: Research Coordinator

When: Baseline

[CMSI_TMD2] COMPLEX MEDICAL SYMPTOMS INVENTORY - TMJ

Purpose: To capture data about the Participant’s symptoms related to Temporomandibular Joint Disorder, if reported per the CMSI Questionnaire

Who: Research Coordinator

When: Baseline

[ELIG_SCAN] ELIGIBILITY CONFIRMATION, NEUROIMAGING STUDY*

- Purpose:** To confirm that a potential Participant for the Trans-MAPP Neuroimaging study is eligible to be scanned and to participate in the Neuroimaging study.
- Who:** Research Coordinator
- When:** Baseline
- *Please note: This CRF is Completed ONLY if Pt. is participating in Trans-MAPP Neuroimaging Study.*

4.M. Specific Instructions for Completing Administrative CRFs

This section provides specific instructions on how to complete each Administrative CRF. Please note the forms are listed alphabetically by Form Name. If, after consulting this section, you are still unsure of how to complete a form, please contact Clinical Data Management at the DCC.

| Case Report Forms – Administrative Forms (in alphabetical order by Form Name) | |
|---|------------------|
| Form Name | Form Code |
| Clinical Center Staff “Signature and Delegation of Responsibilities” Log | STAFFLOG |
| Clinic Correspondence Log | CCORRESP |
| Comments Sheet | COMM |
| Participant Contact Information | PTCONT |
| Participant Correspondence Log | PCORRESP |
| Participant ID Assignment Log | PTLOG |
| Progress Notes | PROGRESS |
| Visit #1 - 25 Checklists | VISIT1 - 25 |

CLINICAL CENTER STAFF “SIGNATURE AND DELEGATION OF RESPONSIBILITIES” LOG [STAFFLOG]

Binder: Clinic Regulatory Binder

All personnel working on the TRANS-MAPP EPIDEMIOLOGY AND PHENOTYPING STUDY must sign the Clinical Center Staff “Signature and Delegation of Responsibilities” Log [STAFFLOG].

The PI should indicate delegation of study responsibilities by initialing in the column associated with the task he or she is delegating and signing and dating each row. This form should be updated regularly as new staff are added or removed.

CLINIC CORRESPONDENCE LOG [CCORRESP]

Binder: Source Documentation Binder

All correspondence between the clinic and the DCC should be recorded on the Clinic Correspondence Log. Refer to the Correspondence Type codes listed at the bottom of each page for the type. “From” and “To” should indicate the names of the persons involved in the correspondence. Refer to the Status Codes listed at the bottom of each page for the status, and update the status as appropriate.

Trans-MAPP EP Study Manual of Operations

PARTICIPANT CONTACT INFORMATION [PTCONT]

Binder: Source Documentation Binder

The Participant Contact Information [PTCONT] form should be completed by the participant at Visit #1 and is strictly confidential. This form should never be forwarded to the DCC. If a participant's information changes throughout the course of the study, she should complete a new form.

PARTICIPANT CORRESPONDENCE LOG [PCORRESP]

Binder: Source Documentation Binder

All correspondence between the clinic and the participant *must* be tracked on the Participant Correspondence Log [PCORRESP] form. Any communication, no matter how insignificant it may seem, should be recorded on this log.

COMMENTS SHEET (COMM)

Purpose: This CRF records any relevant information for a visit or a CRF. It can be attached to the CRF or an alternative used to record "Progress Notes" for a visit.

Who: RC and/or PI completed.

When: This CRF is completed on an as needed basis.

PARTICIPANT ID ASSIGNMENT LOG [PTLOG]

Binder: Part of the Clinic Regulatory Binder, but stored separately

The Participant ID Assignment Log [PTLOG] contains a list of all of the participant ID's and identifies the name and initials of the participant assigned to each ID. This log is strictly confidential and must be kept in a secure location.

PROGRESS NOTES [PROGRESS]

Binder: Source Documentation Binder

The Progress Notes [PROGRESS] form should be used to track the participant's clinic visits, and as source documentation for the study data. Any notes made by the RC or PI must be signed by the person writing the note.

VISIT #1 – VISIT #25 CHECKLISTS (VISIT1 – VISIT 25)

Purpose: The Visit #1 – Visit #25 Checklists (VISIT1 – VISIT25) forms list all the forms and outline general administrative procedures to be completed for each visit (**please refer to the Visit Scheduling and Administration section of the MOP for more details**). These forms *must* be completed for every participant, and filed in the participant's study binder. The checklists *must* also be included in any transmission of CRFs by the Physical Therapist to *either* the clinical center *or* the DCC.

Any forms marked "No" for an item must have an explanation provided in the comment section.

The review and data entry sections *must* be initialed and dated. At Visit 1, the Eligibility Confirmation section must also be initialed and dated.

Who: RC completed.

When: These CRFs are completed when data collection is complete for each visit.

MAGNETIC RESONANCE ENVIRONMENT SCREENING [MRSCREEN]*

Purpose: This CRF is completed as a follow-up check to the ELIG_SCAN form in order to confirm that a Participant is a suitable candidate for the Trans-MAPP Neuroimaging study, and to provide the Participant with some guidelines about what to expect during the day of the Neuroimaging study MRI scan.

Who: RC completed.

When: Baseline, following completion of the ELIG_SCAN form.

** Please note: This CRF is Completed ONLY if Pt. is participating in Trans-MAPP Neuroimaging Study.*

5. MAPP WEB PORTAL ([WWW.MAPPNETWORK.ORG](http://www.mappnetwork.org))

The study's official website is <http://www.mappnetwork.org>. The website consists of public and private sections.

Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain

[About MAPP](#) [Discovery Sites](#) [Core Sites](#) [Projects](#) [Resources](#) [MAPP Portal](#)

Welcome to the MAPP Research Network Home Page

MAPP News

- Epidemiological Studies
- Urological Phenotyping
- Non-Urological Phenotyping
- Neuroimaging / Neurobiology
- Biomarkers
- Organ Cross-Talk / Pain Pathways

Sponsor Links

- Department of Health & Human Services (HHS)
- National Institutes of Health (NIH)
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- USA Gov

A New Look at Urologic Chronic Pelvic Pain ...

To help better understand the underlying causes of the two most prominent chronic urologic pain syndromes, interstitial cystitis/painful bladder syndrome (IC/PBS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), has launched a new and novel research study.

The NIDDK's Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network embraces a systemic—or whole-body—approach in the study of IC/PBS and CP/CPPS. In addition to moving beyond traditional bladder- and prostate-specific research directions, MAPP Network scientists are investigating potential relationships between these two urologic syndromes and other chronic conditions that are sometimes seen in IC/PBS and CP/CPPS patients, such as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome.

The multidisciplinary (i.e., scientists employing a variety of research approaches) MAPP Network includes researchers with clinical, epidemiological, and basic research expertise all working collaboratively:

- Clinical researchers bring experience treating patients
- Epidemiological investigators study the occurrence of and identify risk factors for IC/PBS and CP/CPPS
- Basic research scientists examine what's happening on a cellular level

The MAPP Network includes multiple key focus areas:

- Epidemiological Studies
- Urological Phenotyping
- Non-Urological Phenotyping
- Neuroimaging / Neurobiology
- Biomarkers
- Organ Cross-Talk / Pain Pathways

The MAPP Research Network is comprised of six Discovery Sites that conduct the research studies and two Core Sites that coordinate data collection, analyze tissue samples, and provide technical support.

The MAPP Network also challenges all of the investigators to bring new perspectives to their studies. By pushing the scientists to adopt novel and innovative research approaches, the MAPP Network aims to discover new and clinically relevant insights that may lead to improved treatment options and better patient care.

How Can You Participate?

- **Public Domain Contents**

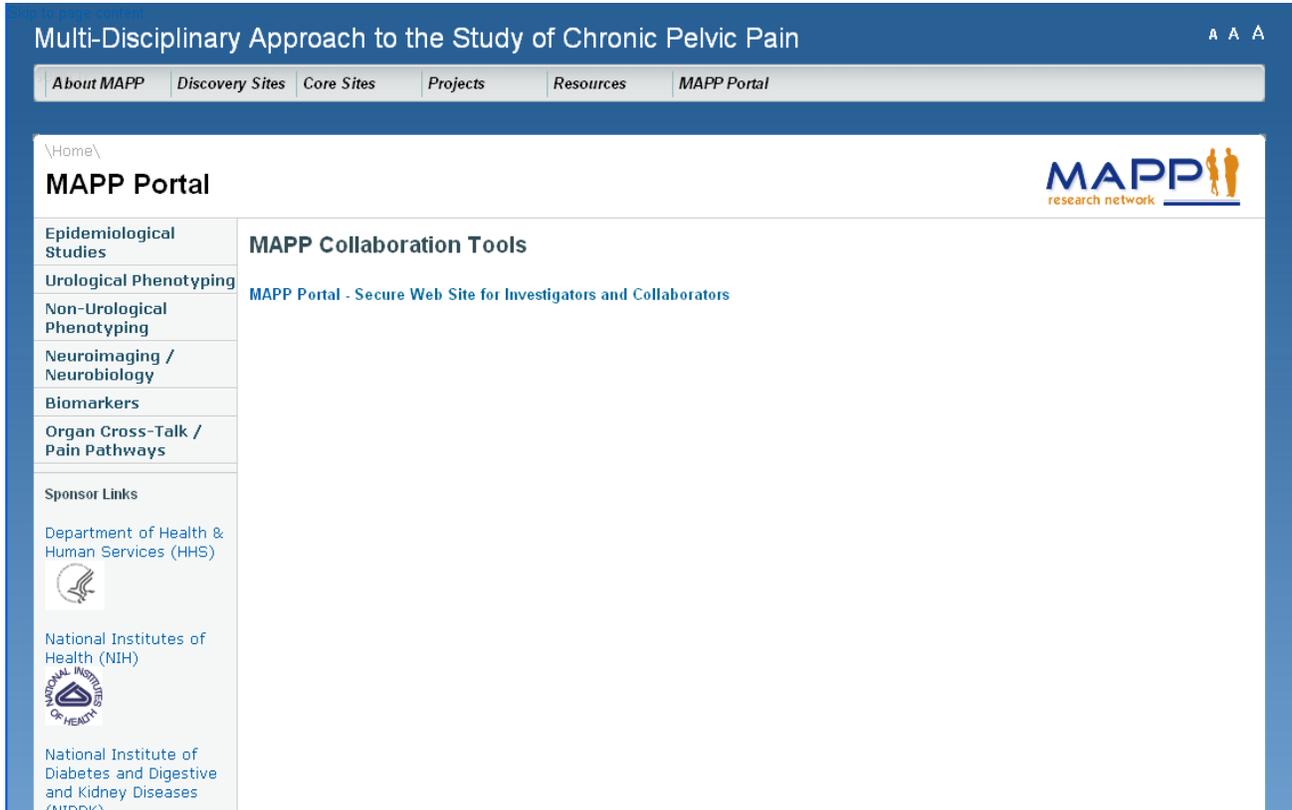
- ❖ MAPP Network and Study Specific public information
- ❖ General Participant Information
- ❖ Recruitment Site Contacts
- ❖ Link to Participant Survey

- **Private Domain Contents**

- ❖ Data Management System
- ❖ Research Coordinator Data Entry tools

Trans-MAPP EP Study Manual of Operations

- ❖ Study Case Report Forms
- ❖ Study documents
- ❖ Participant Web Survey Module



Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain

About MAPP | Discovery Sites | Core Sites | Projects | Resources | MAPP Portal

\Home\
MAPP Portal

MAPP Collaboration Tools
MAPP Portal - Secure Web Site for Investigators and Collaborators

Sponsor Links

Department of Health & Human Services (HHS)

National Institutes of Health (NIH)

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

A MAPP web account is necessary to access the private areas of the website. Access is limited to MAPP Study PIs, Investigators, RCs and other MAPP study staff. To inquire about obtaining a MAPP website account, please contact the MAPP Project Coordinator, Theresa Creighton (theressa@mail.med.upenn.edu).

6. DATA MANAGEMENT SYSTEM USER GUIDE

6.A. Accessing MAPP Data Management System (DMS) Tools

The MAPP Data Management System (DMS) tools are accessible via the private/secure domain of the study's website, www.MAPPNETWORK.org. You will need to log into the private domain of the study's website utilizing your MAPP web account to access the study tools and click on the MAPP Portal DMS tab.

*Please note, as show below, there are two versions of the MAPP data management systems:

1. The Training/Certification Version – Please use this version of the MAPP DMS when completing RC training and certification procedures.
2. The Live Study Version – This version of the DMS may only be used once all RC training and DMS certification procedures have been successfully completed. Please use this version of the MAPP DMS for registering participants and performing data entry.



In general, there are 4 main domains for the MAPP Study tools:

- Research Coordinator – Participant Registration Tools
 - 1) MAPP Participant Registration

- 2) MAPP Participant/Study Assignment
 - 3) Specimen Collection/Shipment
 - 4) Kit Requests
 - 5) CMED Drug Dictionary
- Trans-MAPP Data Management System
 - 1) Oracle Clinical Module – for data entry of RC completed forms (CRFs)
 - Research Coordinator – CMSI Report
 - 1) CMSI and participant survey completeness report
 - Research Coordinator – Generate Visit Schedule
 - 1) Participant visit schedule report
 - Research Coordinator – Pending Surveys Report
 - 1) Displays pending Participant Surveys once the visit window for a follow-up contact has opened.

The various MAPP study tools will be described in this section except for the Oracle Clinical module, which is described in the Oracle Clinical MOP, Appendix E.

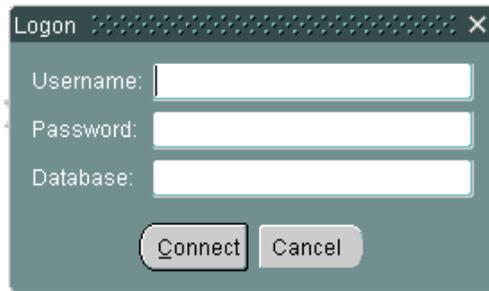
6.B. Research Coordinator – Participant Registration Tools

To access the MAPP Research Coordinator – Participant Registration Tools, log into the private domain of the study’s website with your MAPP web portal account and click the “DMS” tab, then click the “Research Coordinator – Participant Registration Tools” link.

The screenshot shows the MAPP Portal interface. At the top, it reads "Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain". Below this is the "MAPP Portal" header with the MAPP research network logo. A navigation menu includes "Public Home", "Project Leader", "Research Coordinators", "Trans-MAPP Studies", "Tissue Analysis & Technology Core", "Working Groups", "Site Specific Studies", and "Ancillary Committees". A secondary menu has "News", "Calendar", "Directory", "DMS", and "Network Meetings". The "DMS" tab is selected, and a dropdown menu is visible with the following items: "Research Coordinator - Participant Registration Tools" (circled in red), "Trans-MAPP Data Management System", "Research Coordinator - CMSI Report", and "Research Coordinator - Generate Visit Schedule". At the bottom, there is a "DMS Manual of Procedure" link and a PDF file named "Trans-MAPP EpiPhenotyping OCDMS MOP" with a size of 5786 KB.

Access to the Research Coordinator – Participant Registration Tools requires a MAPP Research Coordinator DMS user account. Access to this module is limited to MAPP Research Coordinators **ONLY!** To log into the Research Coordinator module, enter your username, password, and the name of the database (OCTRIALP). Note that the username/password you are to use is not the same as the username/password you used to log into the portal.

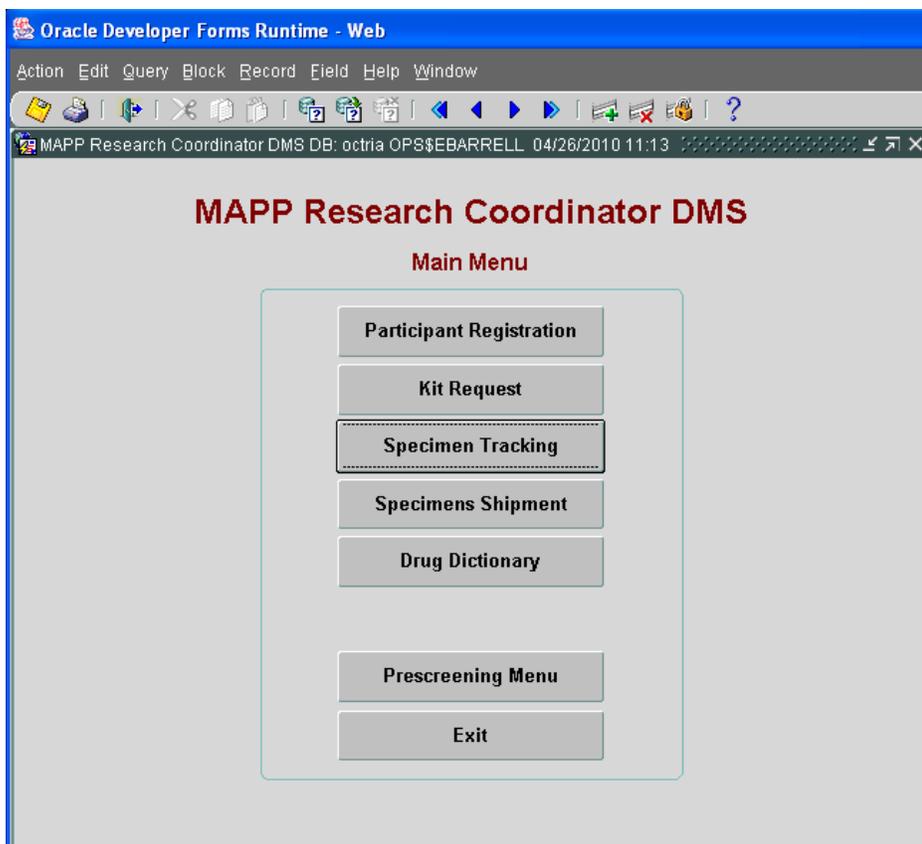
To inquire about obtaining a MAPP Research Coordinator DMS account, please contact the MAPP Project Coordinator, Theresa Creighton (theressa@mail.med.upenn.edu).



6.B.1. MAPP Research Coordinator DMS Main Menu

After logging into the database, the MAPP Research Coordinator DMS Main Menu will appear. The main menu consists of buttons that provide access to the various modules within the Research Coordinator – Participant Registration Tools module. Those modules include:

- Participant Registration
- Kit Request
- Specimen Tracking
- Specimens Shipment
- Drug Dictionary
- Pre-screening



6.B.2. Participant Registration Module

To proceed with registering a participant, press the “Participant Registration” button on the MAPP Research Coordinator DMS Main Menu. The Participant Registration Module serves two purposes. First, to assign participants a MAPP Network PID and PIN that will be used for all MAPP Network associated projects. Secondly, to register participants to the Trans MAPP and associated MAPP Site Specific studies.

6.B.3. Assigning Participant PID and PIN

To register a new MAPP Network participant, choose your site by clicking on the button next to the “site” field. Then enter the participant’s initials, and press the “tab” key. You will then be prompted to re-enter the initials, and notified if your second entry does not match the first. Then choose the participant’s gender by clicking on the circle next to “M” for male, or “F” for female. Next, enter the participant’s year of birth in the field labeled “Year of Birth”. Press the “tab” key and you will be prompted to re-enter the year of birth, and notified if your second entry does not match the first. The initials and year of birth are double entered because those two fields are used to create the participant’s pin. Therefore it is very important that these two items are entered accurately. After entering the year of birth twice, press the “save” button located on the upper portion of the data entry screen. This will generate the participants 6 digit participant ID and the participant’s pin.

The 6 digit participant ID is an automatically generated number that is assigned at the time of registration. The accompanying PIN will consist of the participant's first initial, followed by the last two digits of the participant's birth year, followed by the participant's last initial.

Example: PID: 100001
PIN: A72B

Record all numbers, including leading zeroes, when you record this number on CRFs.

The screenshot shows a web-based application interface. At the top, there is a menu bar with options: Action, Edit, Query, Block, Record, Field, Help, Window. Below the menu is a toolbar with various icons for file operations and navigation. The status bar at the top of the application window displays: MAPP DB: octrialp FORM: PARTICIPANT OPS\$GUEST2 12/10/2009 15:53.

The main content area is titled "Participants" in red. It contains several input fields: ID, PIN, Site, Initials, Gender (with radio buttons for M and F), and Year Of Birth. Below these fields is a row of navigation buttons: First, Last, Previo..., Next, New, Save, Query, and Remove.

A horizontal line separates the "Participants" section from the "Projects" section. The "Projects" section has two columns: "Available" and "Selected". Each column contains a list box with a blue header bar. Between the list boxes are two buttons: a right-pointing arrow (>) and a left-pointing arrow (<).

At the bottom of the application window, there are two large buttons: "Save" and "Exit".

6.B.4. Registering Participants to Trans-MAPP EP Study

After a participant has been registered and a PID/PIN combination has been created, the participant must be assigned to a MAPP Network project or projects.

To register a participant to the Trans-MAPP Epi study or any other available study, please select the study name from the available studies listed in the left box and move it to the box on the right, as shown below. After assigning the participant to a project or projects, press the “save” button at the bottom of the screen.

The screenshot shows a software window titled "MAPP DB: octrilp FORM: PARTICIPANT" with a timestamp of "12/10/2009 15:59". The main heading is "Participants". Below this, there are input fields for "ID" (100786), "PIN" (S72B), "Site" (MAPP 0101), "Initials" (SEB), "Gender" (radio buttons for M and F, with M selected), and "Year Of Birth" (1972). A row of buttons includes "First", "Last", "Previo...", "Next", "New", "Save", "Query", and "Remove".

The "Projects" section is divided into two columns: "Available" and "Selected". The "Available" list contains "TME-TRANSMAPP-EPI", "MMM-Study 5", "MRIS-MRI Study", and "TMC-TRANSMAPP-Control". The "Selected" list is currently empty. Navigation arrows (> and <) are positioned between the two lists. At the bottom of the window, there are two large buttons: "Save" and "Exit".

6.C. Kit Request

To access the kit request module, press the “Kit Request” button on the Main Menu. Pressing the “kit request” button will open the screen below. To request kits, choose the site from the list of sites, then choose the username of the person requesting the kit from the CCCID field and enter the current date in the Request Date field. After that, indicate the number of each type of kit being requested. If additional kits of a particular type are not needed, enter a “0” next to that kit type. In order to submit a kit request, each kit type must have a value entered next to it. Once you’ve indicated the number of each kit type being requested, press the “save” button. This will save the request and generate a kit request ID that will be referenced by the central lab.

The screenshot shows a web browser window with the following details:

- Menu: Action Edit Query Block Record Field Help Window
- Address Bar: MAPP DB: octrialp FORM: DCCKITREQUESTS OPS\$GUEST1 12/10/2009 16:02
- Form Title: **DCC Kit Requests**
- Fields: Kit ID, Clinical Site (dropdown), CCCID, Name, Request Date
- Kit Selections: Plasma Specimen Kit, Male IE Urine Kit, Home Collection Kit, Cheek Swab Kit, Female IE Urine Kit, Urine Dip Sticks, Biomarker Urine Kit
- Navigation: First, Last, Previous, Next, New
- Buttons: Exit, Save

6.D. Specimen Tracking

To access the specimen tracking module, press the “specimen tracking” button on the main menu. This will open up the specimen tracking module. To create a set of specimen records for a participant, enter the participant’s ID press the “tab” key, and then enter the PIN. If the ID and pin match, the site will be auto-populated. If they do not match, a warning message will appear and you will need to either correct the participant ID or the PIN. After the site field is auto-populated enter the Visit Date in the format MM/DD/YYYY, then select the visit number from the list (Baseline, 6 month, 12 Month). Once all of the fields have been entered, press the “proceed” button, and the screen will auto-populate with all of the possible specimens that can be collected at the given visit. For each specimen type, you should then either enter or scan the barcode for each kit, in the appropriate row. Then enter the CRF date, the RCID of the person who filled out the appropriate specimen form, whether or not the specimen was collected, and the date the specimen was collected. The “shipped” and “shippeddt” fields will be auto-populated after the specimens are indicated as shipped via the specimen shipping module. After entering the appropriate data for each specimen type, press the “save” button.

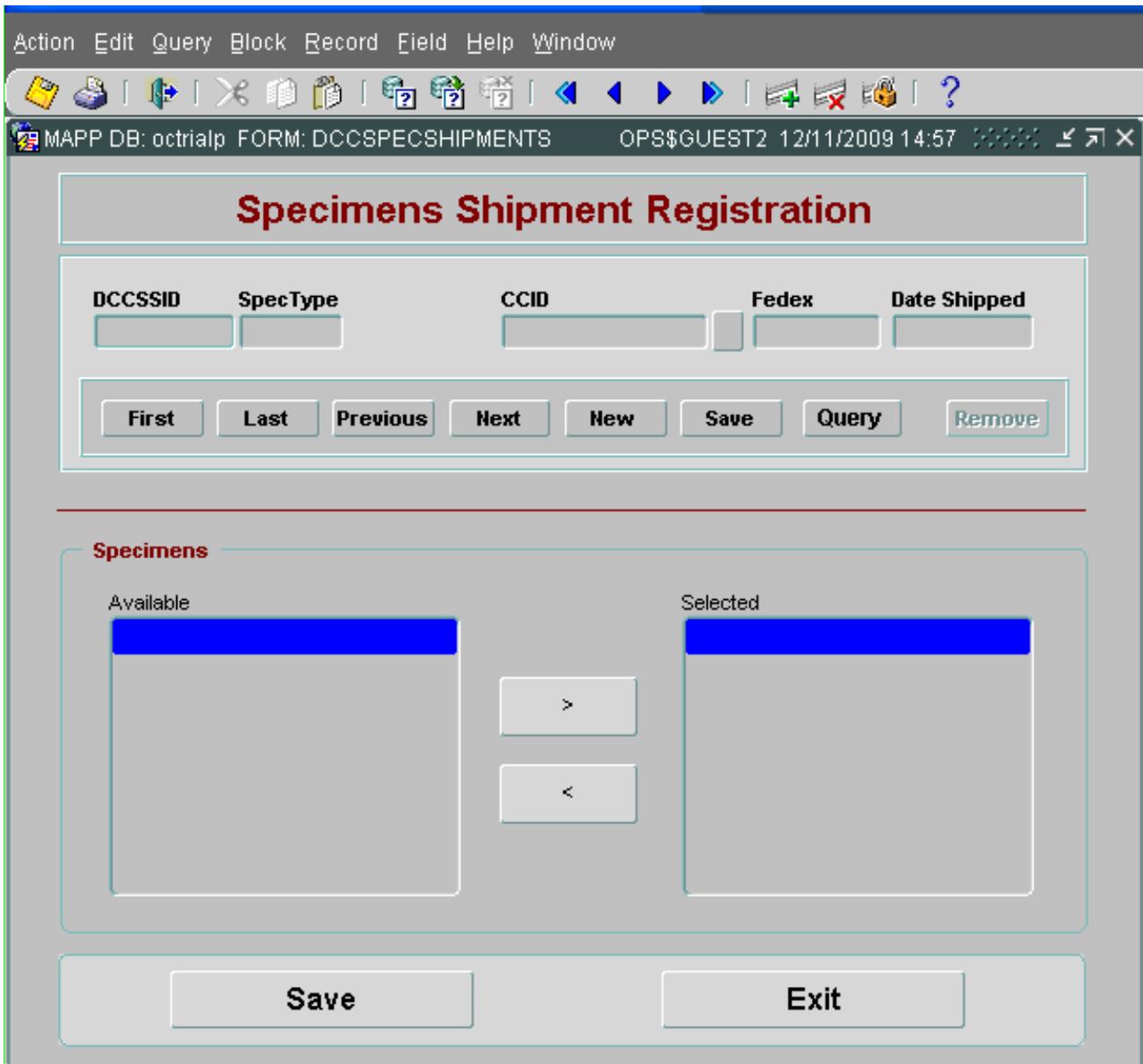
| | | | |
|-----------------|----------------------|---------------|----------------------|
| Participant ID: | <input type="text"/> | Pin: | <input type="text"/> |
| Site: | <input type="text"/> | | |
| Visit Date: | <input type="text"/> | Visit Number: | <input type="text"/> |

Proceed
Cancel / Exit
SAVE

| Barcode | Spec Type | Crf Date | Rcid | Collected | Collectdt | Shipped | Shippeddt |
|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| <input type="text"/> |
| <input type="text"/> |
| <input type="text"/> |
| <input type="text"/> |
| <input type="text"/> |
| <input type="text"/> |
| <input type="text"/> |
| <input type="text"/> |
| <input type="text"/> |

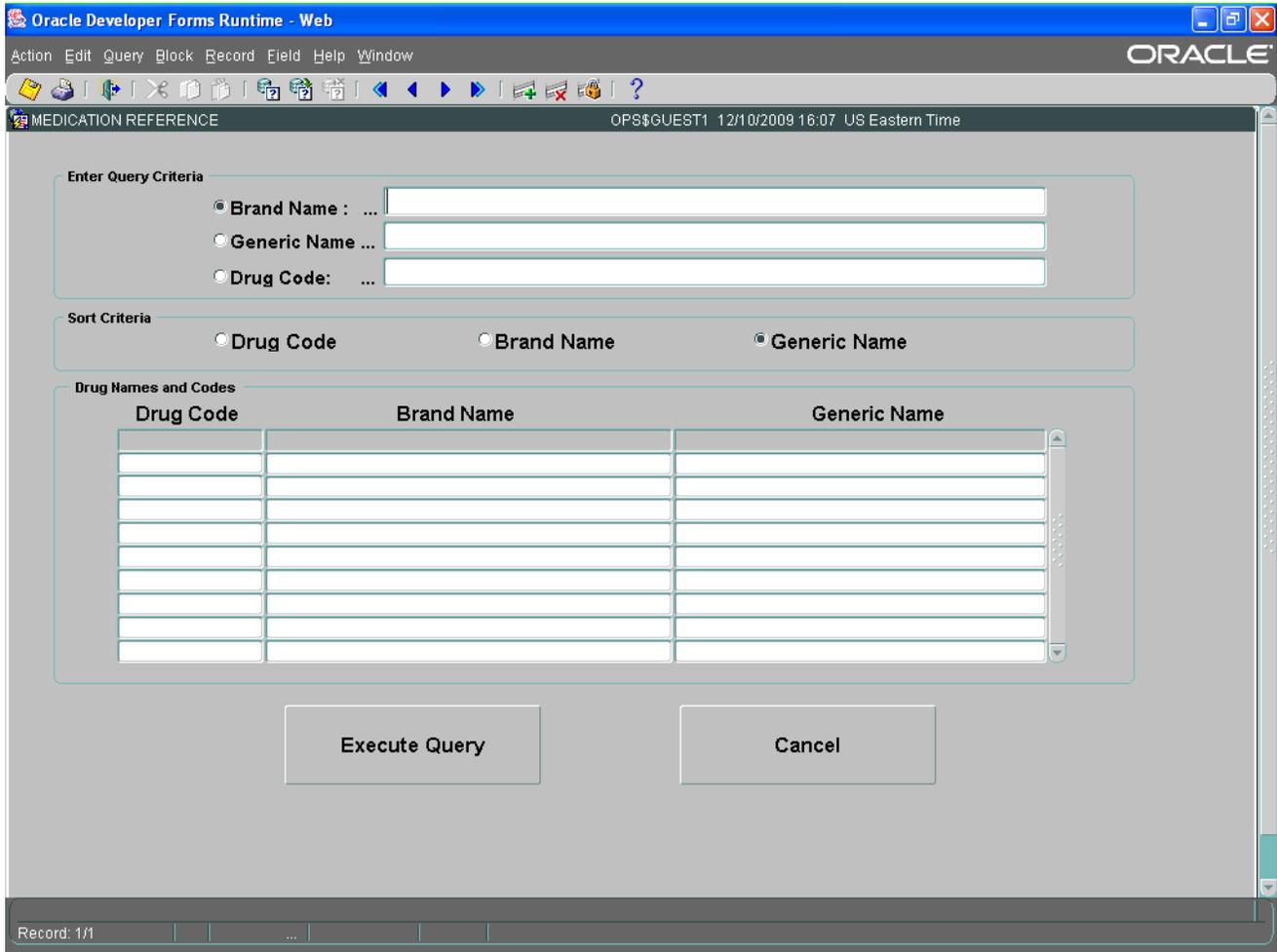
6.E. Specimens Shipment

To access the specimens shipment module, press the “specimens shipment” button on the main menu. This will open the “Specimens Shipment Registration” screen. To create a shipment, select the shipment type (Plasma, Urine, or Cheek Swab), then choose the ID of the person creating the shipment, indicate the FedEx tracking number and the ship date. After entering those items, press the “save” button, which will create a shipping ID. After saving the shipment information, the lower portion of the screen will show the specimens available for shipping from your site. Choose the specimens you want to include in the shipment, and move them to the box on the right hand side. Then press the “save” button.



6.F. Drug Dictionary

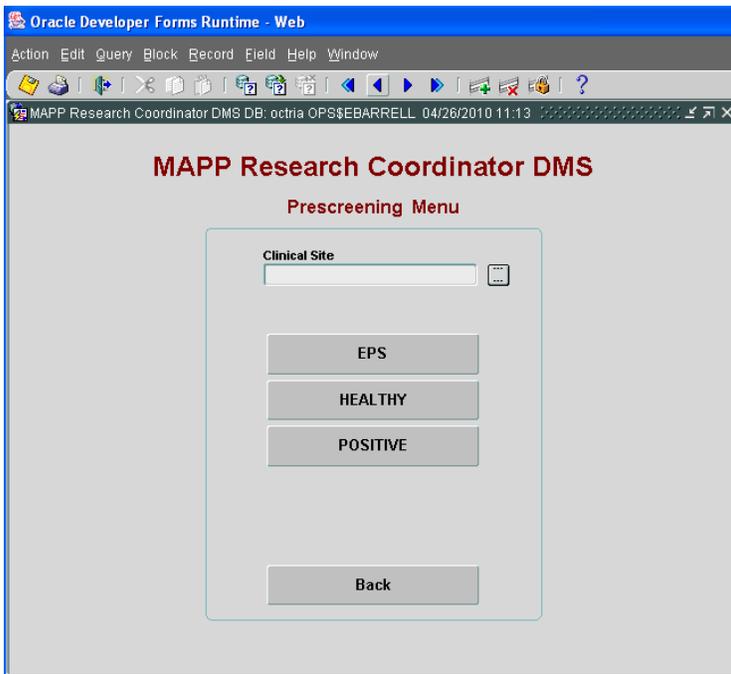
To access the drug dictionary, press the “Drug Dictionary” button on the main menu. Doing so will open the drug dictionary tool which will allow for searching of drug brand names and generic names and corresponding drug codes. To perform a search, enter the search term in the Brand Name or Generic Name field, then press the “execute query” button. All of the drugs that contain the entered Brand Name or Generic Name will be returned in the “Drug Names and Codes” table, along with associated drug codes. Choose the appropriate code for the drug you are searching for, and write the drug code on the case report form.



6.G. Pre-screening

To access the Pre-screening modules select the “Pre-screening Menu” button on the Main Menu. The Pre-screening modules are used to record the monthly Pre-screening data for each of the three different types of potential study participants contacted. In order to access the Pre-screening modules, enter your site number and the study for which you will be entering data.

***Please note:** Pre-screening data entry is due by the 5th of each month for the preceding month. For example, the Pre-screening data for April would be due by the 5th of May.

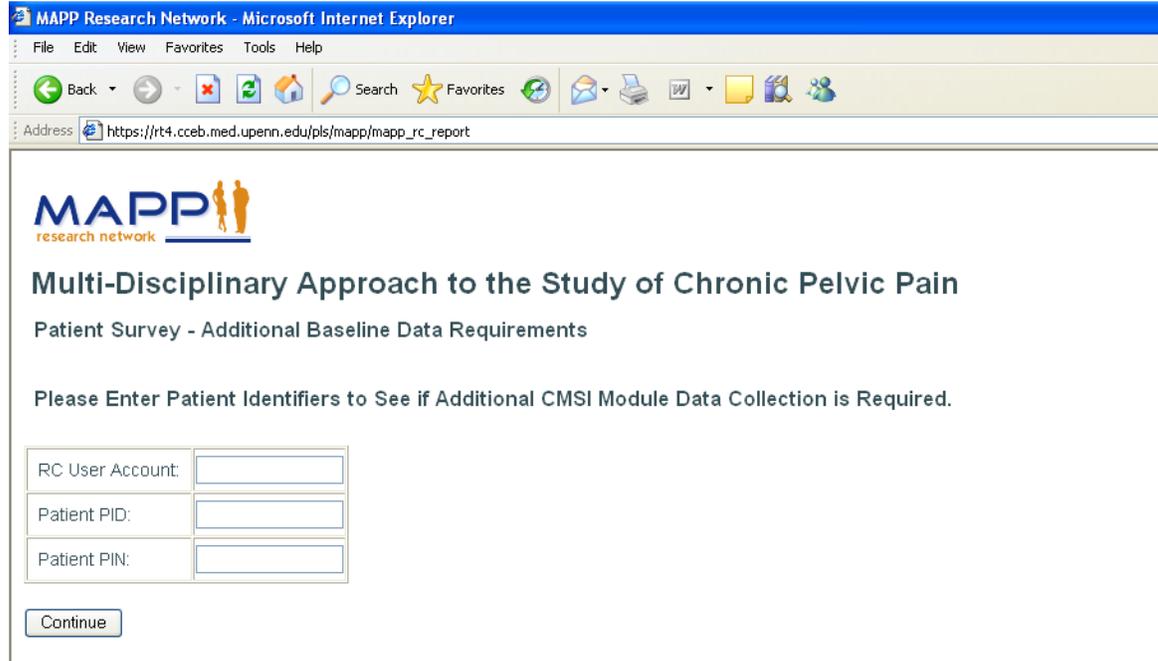


As shown below, the Pre-screening data entry modules appear and collect data in the same fashion as the Pre-screening CRFs.

| Pre-screening Summary for Epidemiology and Phenotyping Study | |
|--|--|
| 1. Month of Report: : <input type="text"/> / <input type="text"/> | |
| 2. Number of subjects with initial contact this month: <input type="text"/> | |
| a. Number who were contacted in person: <input type="text"/> | |
| b. Number who were contacted by phone: <input type="text"/> | |
| c. Number who were contacted in other ways: <input type="text"/> | |
| Status of subjects currently in the pre-screening process: | |
| 3. Number of subjects no longer considered for participation ("Pre-screening failures"): | |
| a. Number of subjects no longer considered due to no internet access, or refusal to use internet for Participant survey: <input type="text"/> | |
| 4. Number of subjects with decision for participation or scheduled consent pending: <input type="text"/> | |
| 5. Number of subjects consented : <input type="text"/> | |
| 6. Number of subjects who declined to consider participation : | |
| a. Number of subjects who are not interested in participating/following protocol: <input type="text"/> | |
| b. Number of subjects who did not consider this study beneficial: <input type="text"/> | |
| c. Number of subjects who have concerns about the research processes: <input type="text"/> | |
| d. Number of subjects who have medical condition(s) unrelated to chronic pain that may interfere with participation: <input type="text"/> | |
| e. Number of subjects who prefer (additional) compensation: <input type="text"/> | |
| f. Number of subjects who have concerns about data privacy/ protection of personal medical information: <input type="text"/> | |
| g. Number of subjects who are not bothered enough by the symptoms to justify participation: <input type="text"/> | |
| h. Number of subjects who refused to provide biomarker specimens (including blood, cheek swab specimen, and/or urine specimen): <input type="text"/> | |
| 7. Number of subjects who learned about this study through: | |
| a. Physician for this study: <input type="text"/> | |
| b. Other physicians: <input type="text"/> | |
| c. Central database: <input type="text"/> | |
| d. Newspaper: <input type="text"/> | |
| e. Internet: <input type="text"/> | |
| f. Other: <input type="text"/> | |
| <input type="button" value="SAVE DATA"/> | |
| <input type="button" value="PRESCR-EPS"/> | |

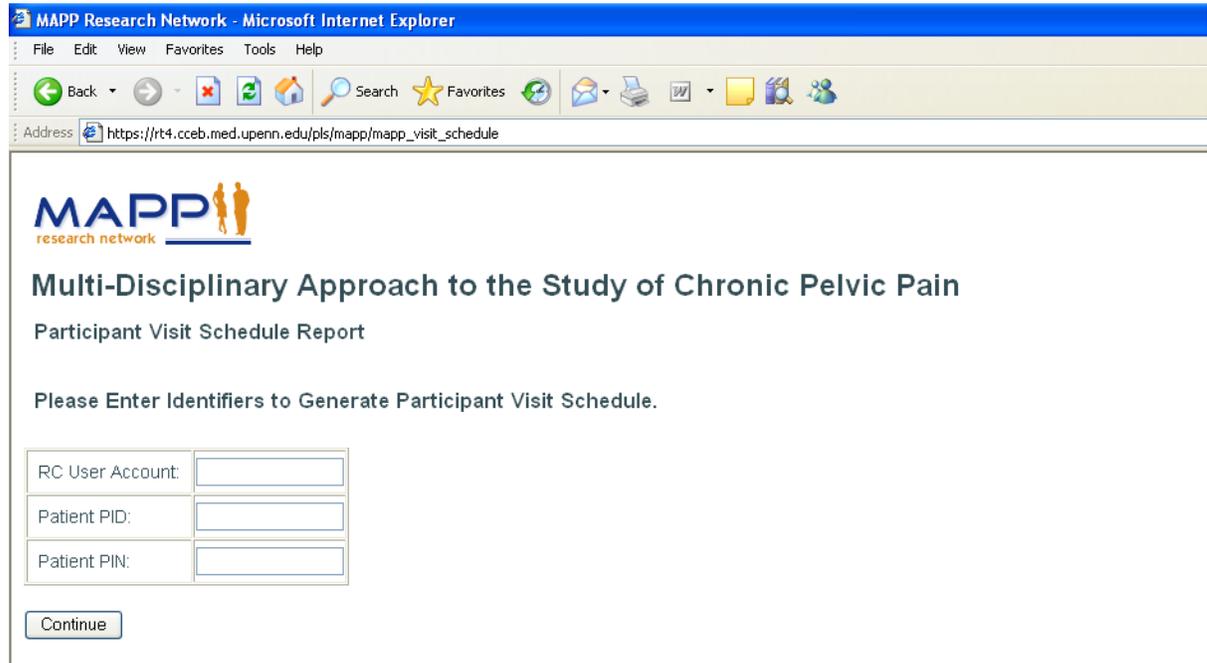
6.H. Participant CMSI and Completion Report Module

To access the Participant CMSI and Completion Report, choose the “Research Coordinator – CMSI” link from the DMS tab of the MAPP network Portal. Doing so will take you to the CMSI module screen. Once there, enter your DMS username the participant’s ID and the Participant’s Pin, then press the “continue” button. This will open up the CMSI and Survey Completion report for the indicated participant.



6.I. Participant Calendar Module

To access the Participant study visit calendar, choose the “Research Coordinator – Generate Visit Schedule” link from the DMS tab of the MAPP network Portal. Doing so will take you to the Participant Visit Schedule Report screen. Once there, enter your DMS username the participant’s ID and the Participant’s Pin, then press the “continue” button. This will open up the Participant Visit Schedule report for the indicated participant.



6.J. Pending Surveys Report

This tool may be used by the RC to monitor the progress of Participants as they complete the bi-weekly and bi-monthly surveys. If a visit window appears to be close to closing and a Participant has not yet completed the follow-up Participant Survey, the RC should contact the Participant with a reminder to complete the pending Participant Survey.

| PID | Site | Visit | Target Date | Earliest Date | Latest Date | Visit Type |
|--------|-----------|-------|-------------|---------------|-------------|------------|
| 100061 | MAPP 0401 | 6 | 26-APR-2010 | 23-APR-2010 | 29-APR-2010 | Bi-Weekly |

6.K. Oracle Clinical DMS Module – See APPENDIX E – Oracle Clinical MOP

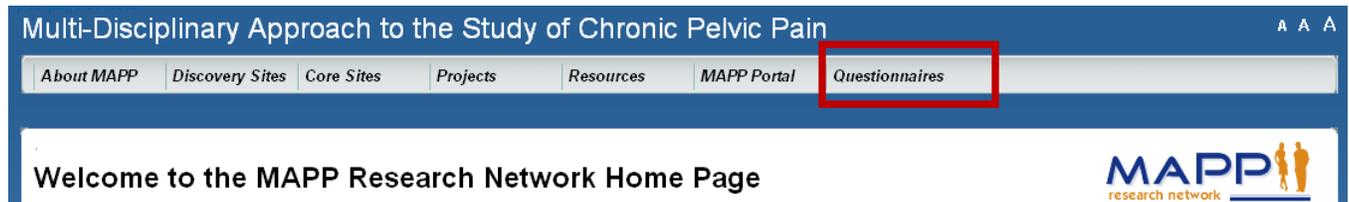
7. PARTICIPANT FOLLOW-UP INTERNET ASSESSMENTS

7.A. Participant Follow- Up

The participant survey is accessible via the study's website, www.MAPPNETWORK.ORG. Participants will be required to log on to the website and enter their PID and PIN to gain access to their biweekly and bimonthly online questionnaires. It is expected that the biweekly questionnaires will take participants about 5-10 minutes to complete; while the bimonthly online questionnaires will take about 15-20 minutes to complete.

7.B. Accessing Participant Follow Up Survey

To access the online questionnaires, participants will need to log onto the MAPP Study website (www.MAPPNETWORK.ORG) from any internet browser, for example Internet Explorer, Firefox, or Safari, and click on the “Questionnaires” tab at the top of the screen.



After clicking on the “Questionnaires” tab, a new screen will appear that will require the participant to enter his/her MAPP Study Participant ID (PID) and PIN to gain access to your questionnaires.

7.C. Completing Participant Internet Survey

Once the participant enters his/her MAPP PID and PIN they will then see the following introduction screen:



Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain

Introduction

Welcome and thank you for participating in the MAPP study.

The following questions are designed to provide details about your urological symptoms, non-urological pain, sexual function, your health, anxiety, depression, anger, fatigue, sleep, perceived stress, and complex medical symptoms. Please answer all questions to the best of your ability. For any questions which you can not or prefer not to answer, please click the "Continue" button and you will be taken to the next question. As you continue through the survey a progress indicator at the bottom of the screen will let you know how much of the survey has been completed. Also, for your reference, the name of the questionnaire will appear at the top of each screen.

If you encounter any difficulties using the MAPP Participant survey, please immediately contact the Research Coordinator at the Clinical Center where you enrolled in the MAPP study.

Progress:



By pressing the 'Continue' button, the survey will start. Once the survey starts, participants will have the ability to move backward and forward within the survey. In addition, participants will be able to stop and return at a later time to complete the questionnaires, if necessary. Hitting the browser "back" button on their computer screen will allow them to go back within the survey to review questions that they previously answered.

Please note that while going back, if they change any of their previous answers, they will be required to answer all of the questions from that point forward. If at anytime a participant needs to end his/her session prior to completing all of the questions, simply inform them to exit out of their internet browser and the session will end.

All of their answers/responses up to the point that they exited the survey will be saved. Once they log back on to complete the survey, the system will start at the very next question following the last question that was completed prior to stopping.

Remind participants, to log back onto the system within the scheduled target window to complete the questionnaires as specified on the participant calendar provided to them at the baseline clinic visit.

7.D. Missed Surveys

The calendar that the RC provides to the participant at the baseline clinic visit will include the target date that the participant is expected to log onto the website to complete each biweekly or bimonthly survey.

Participants are allowed 3 days before and 3 days after the actual scheduled date to log onto the system to complete the necessary questionnaires. Once this seven day period ends, they will not be able to complete another survey until the contact window opens for the next scheduled online survey, as indicated on the participant's study calendar.

7.E. Help Completing Surveys

Participants should be instructed to contact the clinical center for any problems/issues completing their online assessments or if they lost their PID and PIN and require the information again. If necessary, **the RC can contact the DCC Help Desk to provide technical support related to problems and issues that may arise when working with the web based Data Management System.**

8. PARTICIPANT SAFETY

8.A. Risks and Benefits

8.A.1. Risks

Before giving consent to participate in this study, the Research Coordinator must inform the participant of all potential risks related to participation in this study, as outlined in the protocol and informed consent form.

8.A.2. Benefits

There may be no direct benefit to the participant by participating in this study. Participants will be contributing to scientific knowledge and possibly helping other patients with Urologic Pelvic Pain Syndromes.

9. HUMAN SUBJECT CONSIDERATIONS

9.A. Trans-MAPP Participant Considerations

9.A.1. 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.

9.A.2. 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.

9.A.3. 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.

9.A.4. 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.

9.B. Ethical Issues

9.B.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.

9.B.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.

9.C. Participant Confidentiality

Procedures to assure confidentiality will be strictly observed. All identifiable personal health information data should 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.

A log of the participant names, participant ID numbers, and pertinent registration information (e.g., home address, telephone number, and emergency contact information) should be maintained in a locked area at each clinical site. Only the participant ID number and initials are utilized when communicating with the DCC staff or entering data into the study database. Any communication between DCC and clinical sites regarding participant data will occur via the participant ID number. Any forms or documents sent to DCC, IRB or other regulatory authorities should have all personal information removed.

10. STUDY ORGANIZATION AND OVERSIGHT

10.A. 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:

Trans-MAPP EP Study Manual of Operations

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

In addition to these Discovery Sites, 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

10.B. 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

10.C. 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

10.D. 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

10.E. 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

10.F. 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.

11. STUDY MANAGEMENT

11.A. Discovery Site Responsibilities

11.A.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/Recruitment Site is responsible to screen, recruit, enroll and retain a designated number of study participants. It is the responsibility of the Discovery/Recruitment 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.

Each Discovery/Recruitment site is responsible for staffing at least one RC to coordinate all activities at the site level. If an RC leaves the study, however, the on-site investigator is responsible for hiring a replacement immediately to ensure overlap among the relevant individuals. The departing RC is responsible for training the replacement RC on issues concerning the study specific to the clinical site.

The success of the study depends heavily on the ability of the clinical sites to retain enrolled participants throughout their follow-up visits. The onus of keeping participants interested in the study, therefore, resides in the hands of the clinical site staff. Potential ways of accomplishing this are:

- Emphasizing the advantage of having a dedicated RC and/or PI available to answer calls.
- Making a dedicated phone line with voice mail available to study participants.
- It is expected that each site will manage the study with integrity, professionalism, and confidentiality and will adhere to all applicable federal regulations and Good Clinical Practice Guidelines. The RC is expected to provide the most complete and accurate data possible.

The responsibilities of each Discovery/Recruitment Site RC include:

- Recruiting, screening, enrolling, and following participants throughout the course of the study.

- Confirming eligibility of each participant based on the study criteria identified in the Protocol.
- Data entry of Research Coordinated CRFs will be performed at the clinical sites.
- Adhering to study Protocol and the MOP in the implementation of procedures and the acquisition of data.
- Responding to inquiries regarding study information and reporting from the DCC in a timely fashion.
- In-servicing staff at clinical site to the study Protocol.
- Enlisting aid of staff at Discovery/Recruitment sites to assist with identification of potential participants.
- Maintaining approval from regulatory affairs board for study site.
- Completing and submitting annual/final reports to regulatory affairs board for study site.
- Serving as liaison with study site co-investigators.
- Submitting information regarding Procedural or Unanticipated Problems according to study/site policy.
- Maintaining a study follow-up schedule which will plot out the course of visits that the Participant must complete on-line surveys and in-clinic contacts.

11.A.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.

The PI/RC must maintain documentation of appropriate licensure or accreditation for all clinical laboratory facilities used for study samples analysis.

11.A.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.

11.B. Data Coordinating Core responsibilities

11.B.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.

11.B.2. Clinical Site Monitoring

The MAPP Research Network is a cooperative agreement study in which all investigators and the NIDDK have a shared responsibility for the overall quantity and quality of the data collection.

It will be the responsibility of the DCC to monitor the quantity and quality of data being collected throughout the course of the study. However, at the present time, there are no plans for site monitoring.

11.B.3. 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.

11.B.4. 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.

11.B.5. CRCU Software Systems Help Desk

Sponsored Project Help Desk (SPHD)

The SPHD provides technical support to all study personnel using Data Management System (DMS) software developed and distributed by the DCC. This includes all DMS web links available on the study web page, Web Portal, and concerns with DCC-provided hardware. The Help Desk will answer questions concerning the operation of the DMS and will assist in resolving any issues that hinder the effective use of the software.

Technical Support

The Help Desk will provide technical support related to problems and issues that may arise when working with the application provided by the CRCU.

The Help Desk will not be responsible for providing technical support for hardware and/or software that was not provided by the CRCU (e.g. Operating systems, networking/collaborative software, word processors, spreadsheets, modems, printers, and hardware) and has direct local institutional support.

11.B.6. Assignment of DMS Accounts

A DMS account consists of a username and password that uniquely identifies a user. DMS accounts are required for a user to gain access to the data entry area, and are the primary means for ensuring data security and confidentiality. Therefore, it is critically important that all DMS accounts are kept secure and confidential and are not shared with anyone.

NOTE: The username and password used to individually access your project Web site (www.mappnetwork.org) is **not** your DMS username and password. Access to the project Web site infers no access to the project DMS. You may reach the project DMS through a link from within the project Web site but will then be prompted for a specific DMS account username and password.

In addition to providing data security and confidentiality, DMS accounts provide a means to trace all database activities to individual user accounts.

To obtain DMS accounts, a Clinical Center or Site representative should notify the CRCU project manager of the requested user's name and provide a general idea of what functions the user will be performing in the DMS. The CRCU Project Manager will in turn notify the Sponsored Project Help Desk of the new user request.

Important

When a DMS account has been created, the Sponsored Project Help Desk or the CRCU project manager will contact the user with his/her account information.

When personnel leave the project, a representative from the Clinical Center or Site should contact the SDCC Project Manager immediately. The Sponsored Project Help Desk will then take the necessary actions to deactivate that user's database account.

11.B.7. Procedures for Obtaining Help Desk Support

Study personnel can contact the Sponsored Project Help Desk by e-mail or telephone.

E-mail Support

The Sponsored Project Help Desk can be e-mailed at:

sshelpdesk@cceb.med.upenn.edu

When sending e-mail, the following information must be provided:

- Name (User Name)
- Study Name – (Project Name)
- Clinical Center Name / Location
- Phone number
- Detail description of the problem and level of urgency (low, medium, high)

Telephone Support:

- The Sponsored Project Help Desk can be contacted at (215) 573-4623.
- The caller will be forwarded to voicemail. When leaving a voicemail message, the caller **must** provide the following information:
 - 1) Name (User Name)
 - 2) Study Name – (Project Name)
 - 3) Clinical Center Name / Location
 - 4) Phone number (where the user can be reached)
 - 5) Detail description of the problem and level of urgency (low, medium, high)

Help Desk Expected Response Time:

Every effort will be made to respond to voicemail and/or e-mail messages as soon as possible. To facilitate a timely response, help desk personnel are equipped with pagers and will be paged when there is a new voicemail message. Whenever possible, the Sponsored Project Help Desk will attempt to resolve the issue during the initial call. Occasionally, a problem may occur that requires additional interaction between the caller, the Help Desk and the CRCU personnel. Client patience and cooperation is always appreciated during such periods. Our goal is to restore normal operations as quickly as possible.

Help Desk Availability:

The Sponsored Project Help Desk is available during normal business hours (Monday-Friday 0800 – 1700 U.S. Eastern Standard Time).

11.C. Tissue Analysis and Technology Core Responsibilities

11.C.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.

11.C.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.

11.C.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.

11.C.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.

12. APPENDIX A: STUDY VISIT SCHEDULE

13. APPENDIX B: BASELINE VISIT OUTLINE

**Conducting Trans-MAPP EP Study
Screening/Baseline Study Visit (Visit #1)**

PLEASE ALSO REFER TO THE TRANS-MAPP EP STUDY BASELINE VISIT FLOW DIAGRAM (included below), AS WELL AS THE TRANS-MAPP EP STUDY BASELINE VISIT CHECKLIST FOR A DETAILED LIST OF CRFs NEEDED FOR THE BASELINE VISIT FOR TRANS MAPP EP PARTICIPANTS.

1. Scheduling Baseline/Screening Visit

- a. Remind Participant to bring all current medications to the visit to complete the Concomitant Medications (CMED) questionnaire
- b. Remind participants to bring eye glasses if needed for viewing computer screen
- c. Inform participant what to expect during the visit as well as the anticipated length (approx. 2.5 hrs)

2. Obtain Informed Consent:

- a. Confirm that Participant is at least 18 years of age
- b. Confirm that Participant agrees to Trans-MAPP EP Study procedures and follow up.
- c. Confirm that Participant gives permission for use of their DNA for genes related to main goals of this study.

3. DECISION POINT #1

- a. **STOP Visit** – if Participant is under 18yrs of age, does not agree to the study procedures and follow-up, and/or if he/she does not provide permission for use of their DNA for genes related to main goals of this study or to provide biomarker specimens..
- b. **Continue with Visit** – if participant complies/agrees to all of the above, as properly documented on the informed consent document

4. Register Participant via the study's Registration Tool accessible via the study's website, www.MAPPNETWORK.org.

- a. Register the Participant to receive Participant PID# and PIN. Participant must be registered to the Trans-MAPP EP Study in order to proceed with any other study measures/data collection/processes.
- b. Prior to exiting Registration Module, if applicable, register Participant to relevant Site Specific Studies.
- c. Document Participant's computer generated PID # and PIN

5. Proceed with Eligibility Screening

- a. Provide Participant with the following Participant completed questionnaires:
 - ❖ Demographics (DEMO)
 - ❖ SYM-Q- Baseline (SYM-Q-Baseline)
 - ❖ Male/Female Genitourinary Pain Index (MGUPI-Baseline, F-GUPI-Baseline)
 - ❖ Eligibility- (ELIG)

6. Assess inclusion, exclusion, and deferral criteria by reviewing Participants' responses to the above completed forms. In addition to exclusion and deferral criteria, Participant needs to meet the following specific eligibility requirements, per the Eligibility Confirmation-Controls (ELIG-Controls) form:
 - a. To meet all Eligibility Criteria, Male or Female Participants, must have a "YES" response to Questions 5a and 5b of the Eligibility CRF.
 - b. To meet all Eligibility Criteria, Male Participants, with CP/CPPS, inclusion criteria response for question 6a of the Eligibility CRF must be "YES".
7. For both Male and Female Participants, all Exclusion Criteria Responses Must Be "No" For The Participant To Be Eligible For Enrollment
8. For both Male and Female Participants, all deferral criteria responses must be **"NO"** for the participant to be eligible for enrollment.
 - a. If any responses to the deferral criteria are "yes" indicate date participant will become eligible for re-screening.

9. DECISION POINT #2

- a. **Stop Study Visit** – if participant does not meet inclusion criteria
- b. **Stop Study Visit** – if participant satisfies at least one exclusion criterion
- c. **STOP Study Visit and Schedule New Screening/Baseline Visit** – if participant meets one or more deferral criterion

10. If Participant is not excluded or deferred, escort him/her to a designated area (Restroom/Clinic/ect.) to obtain Trans-MAPP Biomarker Urine Sample #1 following the instructions Specimen Tracking Form

- a. Collect clean-catch midstream (VB2) - up to 90cc
- b. Fill the provided urinalysis tube for dipstick analysis. Prior to conducting the urinalysis, aliquot off a small volume into a separate tube for the pregnancy test. **DO NOT PERFORM** Pregnancy test in urinalysis tube and make sure to aliquot out urine sample for pregnancy test prior to placing the dipstick into the urinalysis tube.
- c. Aliquot all but ~5cc into 50cc tubes to ship to the TATC and complete Biomarker Urine Tracking Form (UTRAC).
 - ❖ Send remaining 5cc to onsite lab for 48hr urine culture

11. DECISION POINT #3

- a. **Stop Study Visit** – 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.*
- b. **Stop Study Visit** – if female participant has positive pregnancy test.*
- c. **Proceed with Study Visit** – if participant meets inclusion criteria, does not satisfy any of the exclusion or deferral criteria, and has a negative dip stick result.

* If the visit is stopped, please do not send urine samples to lab, properly dispose of them at the site.

12. Data enter the Eligibility* CRF into the Oracle Clinical System that is accessible via the study's website, www.MAPPNETWORK.org, and Proceed to Assess Participant's Eligibility

- a. Verify that participant meets inclusion criteria
- b. Assess all exclusion criteria

- c. Review urine dip-stick results
- d. Assess remaining exclusion and deferral criteria
- e. Female Participant ONLY – confirm negative pregnancy test result

***The Eligibility CRF must be data entered in order for Participant to access the online questionnaires as well as to run the participant contact schedule. All other baseline data forms should be data entered within 3 days of the baseline visit.**

13. If Participant meets all Eligibility Criteria thus far, proceed with the study visit and escort eligible participants to a quiet comfortable location where he/she can complete the online deep phenotyping baseline assessments.

- a. Review with the participant the “Participant Instructions” for logging onto and completing the online questionnaires

14. Participant will be given a break from the online questionnaire modules, after they complete the Symptoms set of questions, to complete the 2nd Biospecimen Collection and Physical Exam measures. Specifically, the computer will inform the participant “Congratulations! At this time you have reached the mid-way point of the MAPP Participant Survey, and it is time to take a break. Please exit the survey by closing this browser window and contact the Research Coordinator. Once your break has concluded, you will be logged back in and the rest of the MAPP Participant Survey will continue from this point.” During the break, RC will:

- a. Obtain Plasma Sample and Complete Plasma Tracking Form (PTRAC)
- b. Obtain Cheek Swab and Complete Cheek Swab Tracking Form (CTRAC) **Please note:** the RC, or the participant with Research Coordinators guidance and oversight, collect the Cheek Swab sample
- c. Collect Urine Specimen #2- Infectious Etiology Samples (VB1, VB2) Tracking (UMIETRAC, UFIETRAC)
- d. Conduct the Physical Exam and complete the appropriate form (EXAM)
 - a. **Optional for Male Participants:** after physical exam and prostate exam/massage obtain Urine Specimen #3 Infectious Etiology sample (VB3) - and complete the necessary form (UMEITRAC)

15. After biospecimen collection and completion of the physical exam, escort Participant back to computer area, assist participant with logging back into the online system to complete the Non-Urologic assessment (*after the break the RC will need to log the Participant back into the system and press “continue” to advance the participant to last modules of the online questionnaire*).

16. After Participant Completes the Baseline Online Questionnaires :

- a. Run Participant CMSI Report from the RC Data Management Tools screen.
- b. Review the Completeness Report – stress to participant the importance of completing the entire survey/questionnaires. If participant did not complete the entire survey, as indicated on the report, confirm with him/her that they intended to not complete the form, if not, assist participant in logging back onto the system to complete the survey, however please remember that it is not mandatory that he/she completes the session.
- c. Administer the applicable CMSI modules (Fibromyalgia (CMSI-FM), Chronic Fatigue (CMSI-CFS), Irritable Bowel Syndrome (CMSI-IBS), Migraine (CMSI-MI), Vulvodynia (CMSI-

VDYN), Temporomandibular Joint Disorder (CMSI-TMJ)) as indicated on the participant report .

17. Conduct Pressure Pain Threshold (PPT) Procedure - remember to utilize the PPT CRF to record the results

18. End Study Visit – Remember to:

a. Provide Participant with:

- ❖ Two assembled at home collection kits (one set each for collection of the flare/non-flare urine samples when prompted by the computer system) and accompanying instructions. **NOTE:** RC must complete the header information on the linking form (UTRAC_Home_Linking) and pre-record the header information into the DMS prior to providing the kits to the patients. Only Participants PID # and PIN should be recorded on the forms in the places as indicated and no other identifying information
- ❖ Contact Completion Calendar (review target date and visit window for online assessments)
- ❖ Instruction sheet for accessing and completing the online Participant questionnaire
- ❖ A reminder of their study PID# and PIN (this can be included on the Contact Completion Calendar or separate site specific format)
- ❖ The date for next in-clinic (6-month) visit
- ❖ Site specific reimbursement for their time and effort
- ❖ Copy of signed informed consent
- ❖ Site Contact if they have questions
- ❖ Introduce and schedule participant for any site specific studies that he/she may participate

b. Ship the collected Plasma Specimen and the Home Collection Linking Form to the TATC and enter shipping details into the DMS

c. Properly store the other biospecimens at the required temperature as indicated in the lab section of the manual of procedures.

d. Send urine aliquot for 48hr urine culture to local lab/clinic.

19. The completion of the screening/baseline visit, followed by a negative 48 hour urine culture result, defines enrollment in the Trans-MAPP EP Study. Obtain 48 culture results:

- a. If urine **dipstick stick was negative** and **48-hour urine culture is negative** complete and data enter the Urine Culture Result (UCR) form and Enrollment form confirming that all Eligibility Criteria have been met. Ship necessary specimens, and batch others according to lab manual of procedures.
- b. If urine **dipstick was positive** and **48-hour urine culture is negative**, call participant back in ASAP to repeat the screening baseline visit. Repeat the urine dipstick and culture and participant should then proceed with completion of all baseline biospecimen collection, online questionnaires, and the Pressure Pain Threshold Procedure, with the awareness that the urine dipstick may have been a false positive.
- c. If urine **dipstick stick was negative** and **48-hour urine culture is positive** participant will need to be notified, and placed into deferral mode.
- d. If urine **dipstick was positive** and **48-hour urine culture is positive**, participant will need to be notified, and placed into deferral mode. If participant is deferred:

- ❖ Complete the ELIG form deferral section accordingly and data enter the Eligibility Confirmation and Urine Culture Result (UCR) form.
- ❖ Contact Participant and inform him/her of the deferral period, necessary follow-up, and earliest possible date for new screening/baseline visit (when participant returns he/she will maintain the same PID and PIN# but will need to repeat all of the baseline forms, specimen collection, and online questionnaires).
- ❖ Properly dispose of any biospecimens collected; do not send them to the TATC.
- ❖ Please inform the DCC, in writing via email (ebarrell@mail.med.upenn.edu), of specimens or online questionnaires completed for deferred and/or ineligible participants so that the DCC can archive the online questionnaire data and the DCC will inform the TATC to properly dispose of the necessary corresponding biospecimens.
- ❖ Data enter all other baseline CRFs within 3 days of study visit.

14. APPENDIX C: PRESSURE PAIN THRESHOLD (PPT) MANUAL

The PPT study will be performed following the administration of the extensive self-report battery and physical examination at the baseline clinic visit (i.e., at the completion of all other phenotyping testing) for all subjects as well as at the 6 and 12 months clinic visits. The PPT studies take approximately 20 min (total) to conduct, and will be performed using a device engineered and manufactured at the University of Michigan, and made available by the Michigan site to all discovery sites. University of Michigan personnel will be responsible for training all sites on the use of this device at a MAPP face-to-face meeting.

Pressure Pain Testing Equipment

Pressure pain threshold (PPT) testing will be conducted using a Multi-model Automated Sensory Testing (MAST) system. The MAST System is a wirelessly distributed, automated quantitative sensory testing (QST) platform designed for research and clinical applications. This system facilitates the development of various algorithms, transducers and testing protocols in order to further mechanistic pain research and aid in the clinical diagnosis and treatment of chronic pain disorders. It features a central server that coordinates testing protocols and program execution. The testing procedure can be overseen by an operator or run in “kiosk mode”, where the subject can begin or end the testing procedure, but not manipulate any key test variables. Operators are able to custom configure the testing algorithm and monitor test progress in real-time. By automating the testing procedure, experimenter bias and operator variability is significantly reduced over more manual methods. A wireless touch screen panel displays sensory rating scales and requests patient feedback as predetermined times. A wireless thumbnail stimulator (described below) serves as actuator device to evoke pressure pain. The software, however, is generic and can be utilized with other methods of stimulation and patient feedback systems. For instance, the MAST system can incorporate auditory and optical actuators to evoke and measure levels of loudness discomfort and visual distress, respectively. The embedded software has wired and wireless local area network (LAN), wide area network (WAN), and Bluetooth® capability for integrating local feedback from patients and coordinating large scale clinical studies. The system also has the capability to control multiple transducers simultaneously, for example multiple force transducers, thus facilitating the assessment of endogenous modulation networks [ie, diffuse noxious inhibitory controls (DNIC)]. The software can be used to design a testing regime, execute the regime, and compile the resultant data which can then exported in multiple formats (eg, EXCEL, SPSS) for offline analysis.

The pressure stimulator applies an accurately controlled blunt force stimulus to the thumbnail bed. The force profile, including peak force and rate of application, which is set in the software, is ultimately applied by a cylindrical rigid transducer housed in a plastic, “joystick-like” housing ergonomically designed to be held comfortably in either the left or right hand. An adjustable thumb wedge ensures that the thumb remains in a consistent position during testing. Tips of various stiffness and diameter can be placed at the end of the transducer. The system has the functionality to be able to interface with other force transducers suited to other parts of the human body, such as the forearm, leg, jaw, head, or vulva. The stimulator is lightweight, battery powered (4 cell, 14.8V Lithium Polymer) and can be communicated with via a controlling device over a digital wireless Bluetooth® serial port link. The device also has the ability for testing algorithms to be downloaded onto it allowing stand-alone testing to be conducted without the server. Control signals set the stimulation profile (duration, peak force, rate of application, etc). Information corresponding to current sensor values and state of the

device are sent to the controlling device over the same link. The device handles the complete process of stimulation (actuator control) from the “start of stimulus” command signal until the stimulus is removed, to prevent injury to the patient if the communication link is lost. By monitoring the applied force versus position relationship, the correct placement of the thumb can be discerned to ensure repeatable, low variability experimental results are obtained. This architecture allows this device to be controlled from any device that is Bluetooth® capable (such as laptops, PDAs, cell phones or desktop PC’s). Force is applied by controlling the torque supplied by a miniature DC servo-motor and transferred to the pain transducer through a high-ratio gearbox and converted into linear motion by a rack and pinion system. The motor voltage, current and speed are measured, as well as the battery voltage, position and speed of the output shaft of the gearbox and force applied to the thumb. The force applied to the subject is measured using a full-bridge strain gauge load cell. According to Newton’s 3rd law of motion, the plunger asserts a force on the subject and the subject will exert an equal but opposite force on the plunger. This force will compress the plunger and this variation in strain is measured through minute changes in resistance of the sensing elements. These measured signals are used for feedback control of the force, position and speed applied by the plunger. The embedded PID control system incorporates linearized calibration curves to ensure accurate and repeatable testing can be performed. Additionally, the controller parameters can be tuned to customize the force stimulation profile providing added flexibility for research applications.

Participant Safety

Safety of the subject is of key importance and numerous software and hardware based failsafe systems are in place. Firstly, for hardware based safety, the system has been designed to be incapable of producing a force greater than 200 N. Secondly, a kill switch allows the power to the servo motor to be instantly removed. Thirdly, a mechanical knob is directly connected to the plunger and can be used to manually move the plunger once the power to the motor has been removed. Embedded software safety systems in the controller include two adjustable force limits. The first will immediately end the stimulus application should excessive forces be detected. The second is set at a slightly higher force than the first and will remove power to the motor in the event the action taken by the 1st limit fails. Additionally, the stimulus application is controlled by the hand piece and not the server, so that communications problems or disruption will not affect the resolution of the stimulus. Also, once the device is paired with the server, communications are securely encrypted and various error detection algorithms ensure corrupted data will not be acknowledged by the device. This prevents malicious interference with a testing session from a 3rd party or unexpected spurious behavior of the device due to noise sources traditionally associated with wireless communications. Additionally, server based safety systems allow the operator (or subject in the “kiosk mode”) to immediately terminate a test and any stimuli being applied at any moment.

System software requires Windows XP. The MAST System (v1.0) includes 2 mini tablet-PCs with the following specifications: Intel Atom 1.6 GHz processor; 1 GB DDR2-SO DIMM memory; 60 GB, 4200 rpm Hard Drive; Integrated 10/100 Ethernet + WLAN 802.11 b/g/n; 8.9” 1024x600 touch screen; and Bluetooth.

PPT Procedure

Before any testing occurs, participants should be familiarized with the device and thumb pressure, by performing several “practice runs.” The Pressure Pain Threshold will be determined using blunt pressure delivered by a 1-cm² hard-rubber probe to the thumbnail bed of the participant’s non-dominant hand.

The probe delivering pressure to the thumb is attached to a mechanically-driven piston incorporated into a plastic casing. During testing, the thumb is inserted into the casing and pressure is applied to the nail bed by a miniature integrated servo-motor attached to the piston. A miniature digital load-cell measures the exact pressure applied to the thumb to ensure accurate and repeatable testings be performed.

The system delivers an ascending series of 5-s duration stimuli at 20-s intervals, beginning at 0.25 kg/cm^2 and increasing in $0.25 - 0.50 \text{ kg/cm}^2$ intervals, up to tolerance or to a maximum of 10 kg/cm^2 . The patient will rate pain intensity during each stimulus on a 0-100 numerical rating scale (NRS), with '0' representing 'no pain' and '100' representing 'pain as bad as it could be'. System software computes and digitally stores the pain detection, pain tolerance thresholds and the pressure intensity that evoked a pain rating of 60 (PAIN-60) on the NRS. This value (PAIN-60), the amount of pressure in kg required to elicit a pain rating of 60/100, is the primary outcome for this portion of the study, and the amount of pressure in kg at which the participant requests the procedure be stopped (PAIN-Stop) is a secondary outcome.

The PPT procedure will be conducted in triplicate (on the same thumb); participants may choose to stop the testing at any time.

Please be sure to document the results of each of the three runs in the spaces provided on the **Pressure Pain Threshold (PPT) form.**

- 15. APPENDIX D : BIOSPECIMEN COLLECTION MANUAL (SEE SEPARATE DOCUMENT)**

16. APPENDIX E: ORACLE CLINICAL MOP (SEPERATE DOCUMENT)

17. APPENDIX F: CASE REPORT FORMS (SEE SEPARATE DOCUMENT)

18. APPENDIX G: TRANS-MAPP EXTENDED FOLLOW-UP PARTICIPANT LETTER

Date

Name

Address

Dear:

We would like to take this opportunity to express our appreciation for your continued participation in the Multidisciplinary Approach to Chronic Pelvic Pain (MAPP) study and update you on future plans. With the knowledge that we gained from the first series of MAPP studies, we are currently planning another set of studies to better understand Urologic Pelvic Pain Syndrome (UCPPS). During this planning phase, we would like to invite you to continue your participation in the study through extended follow-up internet-only surveys.

The Extended follow-up will consist of the completion of a series of questionnaires online via the study's website every four months and will continue for a period of up to 60 months from your original Baseline visit. The additional information gathered during the extended follow up study will further help us understand symptom profiles of chronic pelvic pain and continue to help guide our planning of the next series of studies of UCPPS.

For the extended follow up, all participants who have completed the 12 month Trans-MAPP Epidemiological Longitudinal Study will be asked to complete additional questionnaires that will be presented via the internet every four months. There will be no additional clinic visits or urine samples collected during this follow up period.

If you agree to participate, we would ask that you log into the secure MAPP portal (www.MAPPNETWORK.Org) every four months to complete a series of questionnaires identical to the bi-monthly questionnaires from the initial Trans-MAPP study. These surveys will ask you questions about your General Health, Quality of Life, IC/CPSS symptoms, Non-

Urologic symptoms, and Body Pain systems. The series of questionnaires contain approximately 175 items and are expected to take approximately 20 minutes. You are not obligated to answer any questions that you prefer not to answer.

Taking part in this research study is completely voluntary and if you choose not to participate, you simply do not have to log into the website above. Agreeing to participate in the extended follow up will not commit you to participate (or not participate) in the next series of MAPP Studies currently being planned.

We plan to phone you once in approximately two weeks to confirm your receipt of this informational letter as well as to answer any questions that you may have in regard to the Extended Follow up or any other information presented in this letter. If you prefer that we not contact you by phone after this mailing please do not hesitate to contact <insert RC name, phone number, and email>

You will not have any costs for participating in this research study.

Taking part in research is always optional and if you decide not to participate in this study, or if you end participation at any time, your decision will have no effect on any care received at your site.

Thank you in advance for your support in planning the next phase of MAPP studies. Please be advised that by logging into the MAPP network portal and completing the questionnaires you will be considered enrolled in the Extended Follow-Up. If you have any questions, please call us at <insert telephone number>. You may also contact us via e-mail or fax at <insert email address and fax number>.

Thank you for your time.

Sincerely,

XXXXX

