Study Title:	**A Clinical and Biosample Database to Enable Discovery of Pathogens and Pathogenic Mechanisms in Chronic Fatigue Syndrome**
Protocol Type:	**Human Material Banking and Data Repository**
Principal Investigator:	**Nancy Klimas, M.D.**
Study Site:	**Chronic Fatigue Clinic, Miami, FL.**

Site Responsible Investigator:	**Donna Felsenstein, M.D.**
Study Site:	**Massachusetts General Hospital, Boston, MA.**
Site Responsible Investigator:	**Lucinda Bateman, M.D.**
Study Site:	**Chronic Fatigue Consultation Clinic, Salt Lake City, UT.**
Site Responsible Investigator:	**Daniel Peterson, M.D.**
Study Site:	**Sierra Internal Medicine, Sierra, NV**
Site Responsible Investigator:	**Sue M. Levine, M.D.**
Study Site:	**Medical Office of Susan M. Levine, M.D. New York, NY**

Assessment Core Co-Investigators:	Nancy Klimas, M.D.
Laboratory Co- Investigators:	W. Ian Lipkin, M.D. (Lab Site Co-PI) Mady Hornig, M.D. (Lab Site Co-PI) David Hirschberg, PhD (Co-Investigator)

Study Laboratories:

Center for Infection and Immunity ("CII")
Mailman School of Public Health
Columbia University
722 West 168th Street, Room 1704
New York, NY 10032
(212) 342-0558

Duke Human Vaccine Institute
Thomas Denny, MSc
106 Research Drive
MSRB II, Room 4083
DUMC Box 103020

Sponsor: **Chronic Fatigue Initiative, Inc.**

TABLE OF CONTENTS **PAGE**

1.0 BACKGROUND/RATIONALE

Chronic Fatigue Syndrome (CFS) is a clinically defined condition characterized by severe, disabling fatigue and a combination of symptoms that prominently features impairment of concentration and short-term memory, sleep disturbances, and musculoskeletal pain. The challenges posed by CFS to the medical community and to the public in general are significant. CFS is a multi-systemic disease of unknown origin affecting between 1 and 4 million Americans (Reeves et al, 2007). More than 25% of those suffering from CFS lose their ability to maintain full-time employment (CDC 2008). The annual cost in the United States of productivity lost is estimated at US $9.1 billion (Reynolds et al, 2004). No pathognomonic signs or diagnostic tests for this condition have been validated across scientific studies. In addition, no definitive treatments are clinically available. Although surveys by the Centers for Disease Control and Prevention (CDC) find that the general medical community regards CFS as a real illness, the absence of definitive diagnostic tests and proven treatments renders health care providers reluctant to care for such patients, and some in the medical community assume that patients with CFS fabricate their symptoms for secondary gain or suffer instead from a primary psychiatric disorder.

The complexity and diversity of the clinical presentation in CFS suggests the disorder may arise through multiple etiologic pathways. To facilitate our understanding of this heterogeneity, we propose to establish the Chronic Fatigue Initiative (CFI) Cohort, comprised of extraordinarily well-characterized subjects with CFS and healthy controls, and the CFI Biobank and Database, housing biologic samples and data acquired from the CFI Cohort. Together, these two resources will create a unique foundation for investigations of CFS pathogenesis. Diagnosis and clinical characterization of cases and controls at geographically-diverse clinical sites, led by clinician-investigators expert in CFS, will be rigorous and standardized. Biologic specimens will be consistently obtained, handled and processed through this multi-center study to ensure maximal sample integrity. The CFI Database will link clinical data from the CFI Cohort, in coded fashion, to biologic samples in the CFI Biobank, as well as to laboratory assay results. This will form a rich resource for the discovery of pathogens and pathogenic mechanisms in CFS for use in qualified research studies selected and supported by the study Sponsor based on reviews and recommendations of an expert scientific review board. The introduction of these tools for CFS research, in the context of the current investigation of pathogenesis and pathogen discovery, will enable expanded analyses focused on putative causal agents and mechanisms of disease in CFS, help to delineate phenotypic subsets among patients with CFS that may be more likely to respond to specific treatments, and open new pathways for the development of quantitative diagnostic tests and therapeutic interventions that will improve the standard of care for this neglected patient population.

2.0 OBJECTIVES

2.1 Establish a rigorously-characterized cohort of subjects diagnosed with CFS and healthy controls by capturing rich clinical data in an integrated database and carefully preserving biologic specimens in a sample repository.

2.2 Investigate the role of microbial and immune factors in the pathogenesis of CFS by applying molecular tools for identification of pathogens and profiling of host responses.

3.0 SUBJECT ELIGIBILITY

3.1 Inclusion Criteria for CFS Cases

3.1.1 Patient is between ≥ 18 and ≤ 65 years of age at time of signing of consent.

3.1.2 Patients with **previously confirmed diagnosis of CFS**[1] as established by the International Chronic Fatigue Syndrome Study Group (Fukuda 1994), **AND/OR** the recently updated Canadian criteria (Jason 2010). Appendix A: Inclusion ME/CFS Clinical Diagnostic Worksheet, (Carruthers et al., 2003)

3.1.2.1 Inclusion Criteria for CFS According to the 1994 Fukuda Criteria

- Clinically evaluated, unexplained, persistent or relapsing fatigue for > 6 months that: a) is of new or definite onset, b) is not the result of ongoing exertion, c) is not substantially alleviated by rest, d) is made worse by exertion, e) results in substantial reduction in previous levels of occupational, educational, social or personal activities.
- Concurrent occurrence of 4 or more of the following symptoms during at least 6 consecutive months and not pre-dating fatigue: a) sore throat, b) tender cervical or axillary lymph nodes, c) muscle pain, d) multiple joint pain without swelling or redness, e) headaches of new type, pattern, or severity, f) unrefreshing sleep, g) post-exertional malaise, h) impaired memory or concentration.

3.1.2.2 Inclusion Criteria for ME/CFS According to the 2003 Canadian Criteria

- Fatigue: Significant degree of new onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level.

---

[1] See Appendix G for list of required labs for documentation of CFS diagnosis

- Post-Exertional Malaise and/or Fatigue: An inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post exertional malaise, and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. Pathologically slow recovery period-usually 24 hours or longer.

- Sleep Dysfunction: Unrefreshed sleep or sleep quantity or rhythm disturbances such as reversed or chaotic diurnal sleep rhythms. If the patient does not have sleep dysfunction, but no other diagnosis fits except ME/CFS – a diagnosis of ME/CFS can be entertained if this patient has an infectious illness type onset.

- Pain: Significant degree of myalgia. Pain experienced in the muscles and/or joints, and often widespread and migratory in nature. Significant headaches of new type, pattern or severity. If the patient does not have pain, but no other diagnosis fits except ME/CFS – a diagnosis of ME/CFS can be entertained if this patient has an infectious illness type onset.

- Neurologic/Cognitive Manifestations: Ataxia, muscle weakness, and fasciculations are common. Overload phenomena (hypersensitivities to stimuli that have changed from pre-illness status): cognitive, sensory – e.g., photophobia and hypersensitivity to noise – and/or emotional overload, which may lead to "crash" periods (temporary period of immobilizing physical and/or cognitive fatigue) and/or anxiety. Two or more of the following difficulties: Confusion, impairment of concentration and short-term memory consolidation, disorientation, difficulty with information processing, categorizing and word retrieval, perceptual and sensory disturbances e.g., spatial instability and disorientation and inability to focus vision.

- At least One Clinical Feature from Two of the Following Three Categories:
    - Autonomic Manifestations: i) orthostatic intolerance, neurally mediated hypotension (NMH), postural orthostatic tachycardia syndrome (POTS), delayed postural hypotension] ii) lightheadedness, iii) extreme pallor, iv) nausea and irritable bowel syndrome, v) urinary frequency and bladder dysfunction, vi) palpitations with or without cardiac arrhythmias, vii) exertional dyspnea.
    - Neuroendocrine Manifestations: i) loss of thermostatic stability (subnormal body temperature and marked diurnal fluctuation, sweating episodes, recurrent feelings of feverishness and cold extremities), ii) intolerance of extremities of heat and cold, iii) marked weight change (anorexia or abnormal appetite), iv) loss of adaptability and worsening of symptoms with stress.
    - Immune Manifestations: i) tender lymph nodes, ii) recurrent sore throat, iii) recurrent flu-like symptoms, iv) general malaise, v) new sensitivities to food, medications and/or chemicals. The illness persists for at least six months. It usually has a distinct onset,** although it may be gradual. Preliminary diagnosis may be possible earlier.

3.1.3 Patient has the following laboratory values measured within 6 weeks of On-Study Visit/blood draw.

Values must be within normal limits for institution unless otherwise indicated below:

- CBC with Differential
- Comprehensive chemistry panel (SMA 18) ALT and AST may be up to 2x the upper limit of normal
- ESR, may be up to 1x the upper limit of normal
- TSH

3.1.4 Negative serology testing for HIV (1 year).
3.1.5 A female subject is eligible to participate if she is not pregnant, not <3 months postpartum, and not currently lactating per self-report.
3.1.6 Patient is able to read, understand and speak English.
3.1.7 Record of laboratory testing results of "required labs" as indicated in Appendix G.
3.1.8 XMRV status, including laboratory where assessed, **if known** (testing is not required for participation).

3.2 Exclusion Criteria for CFS Cases

3.2.1 Patients do not meet the Fukada Criteria or the Canadian Criteria of CFS for inclusion.

3.2.2 Patients meet any of the exclusion criteria associated with the set of inclusion criteria used to establish their diagnosis of CFS (see Appendix B: Exclusion ME/CFS Clinical Diagnostic Worksheet, Carruthers et al.).

3.2.2.1 Exclusion Criteria for the Fukuda Criteria

- Organ failure including emphysema, cirrhosis, cardiac failure, or chronic renal failure.
- Chronic infections including AIDS, hepatitis B, or hepatitis C.
- Rheumatic and chronic inflammatory diseases including systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, inflammatory bowel disease, or chronic pancreatitis.
- Major neurological diseases including multiple sclerosis, neuromuscular diseases, stroke, head injury with residual neurologic deficits, or epilepsy,
- Diseases requiring systemic treatment including organ or bone marrow transplantation, chemotherapy, or radiation of brain, thorax, abdomen, or pelvis.
- Major endocrine diseases including hypopituitarism or adrenal insufficiency.
- Primary sleep disorders including untreated sleep apnea or narcolepsy.
- Sleep disorders such as restless leg syndrome and periodic limb movement, if they are severe, but not if the degree of the sleep problem is insufficient to explain the severity of fatigue.
- Fatigue caused by medications, sleep deprivation, untreated hypothyroidism, untreated or unstable diabetes mellitus, or active infection.
- Females who are pregnant, < 3 months postpartum, or currently lactating.

- Major surgery < 6 months after operation or minor surgery < 3 months after operation.
- Major infections such as sepsis or pneumonia <3 months postresolution.
- Myocardial infarction or heart failure < 5 years after event.
- Morbid obesity BMI>40.
- Psychiatric conditions including lifetime diagnosis of bipolar affective disorders, schizophrenia of any subtype, delusional disorder of any subtype, organic brain disorders, or major depressive disorder with psychotic or melancholic features, anorexia nervosa, or bulimia < 5 years before the onset of chronically fatiguing illness

3.2.2.2 Exclusion Criteria for the Canadian Criteria

- Active diseases processes that explain most of the major symptoms of fatigue, sleep disturbance, pain, and cognitive dysfunction including Addison's disease, Cushing's Syndrome, hypothyroidism, hyperthyroidism, iron deficiency, other treatable forms of anemia, iron overload syndrome, diabetes mellitus, and cancer.
- Untreated sleep disorders such as upper airway resistance syndrome or obstructive or central sleep apnea.
- Rheumatological disorders such as rheumatoid arthritis, lupus, polymyositis and polymyalgia rheumatica.
- Immune disorders such as AIDS.
- Neurological disorders such as multiple sclerosis (MS), Parkinsonism, myasthenia gravis and untreated B12 deficiency
- Infectious diseases such as tuberculosis, chronic hepatitis, acute Lyme disease.
- Primary psychiatric disorders and substance abuse.
- Exclusion of other diagnosis cannot be reasonably excluded by the patient's history and physical examination is achieved by laboratory testing and imaging.

3.2.3 Patients taking immunomodulatory medications and/or medications that cause immunodeficiency or immunosuppression will be excluded. Examples include but are not limited to medications such as: prednisone, cortisone, plaquenil, methotrexate, TNF inhibitors. Limited number of participants on immune enhancing drugs such as Ampligen and Isoprinosone may be included if subject is on stable dosing for more than three months. A list of immunosuppressive drugs by category with examples can be found in the tables "Causes of Secondary Immunodeficiency" and "Some Drugs that Cause Immunosuppression" at this website:
http://www.merck.com/mmpe/sec13/ch164/ch164a.html

3.2.4 Patients treated with long-term (longer than 2 weeks) antiviral medication within the past 6 months.

3.2.5 Patients treated with long-term (longer than 2 weeks) antibiotics within the past three months.

3.2.6 Patients treated with short-term (less than 2 weeks) antiviral or antibiotic medication within the past 30 days.

3.2.7 Patients using antiretroviral medication within the past year.
3.2.8 Patients unable to read, understand, or speak English.
3.2.9 Subject with history of substance abuse in the past year (excluding nicotine and caffeine) as determined by patient self-report.
3.2.10 Subject fails clinical laboratory or physical exam screen.
3.2.11 Patients who in the professional opinion of the PI or attending physician, should not be enrolled.

3.3 Inclusion Criteria for Controls

3.3.1 Person is generally healthy and is ≥18 years ≤ 65 years of age.
3.3.2 Regional controls residing for ≥ 1 year within a 100 mile radius of this clinical location, not residing in the same household, related to and not a sexual partner of any participants or CFS person who is not a participant.
3.3.3 Frequency-match CFS cases by age (within 5 years) and sex.
3.3.4 Control has the following laboratory values measured within 6 weeks of On-Study Visit/blood draw:

Values must be within normal limits for institution:

- CBC with Differential
- Comprehensive chemistry panel (SMA 18)
- ESR
- TSH

3.3.5 Negative serology testing for HIV (within past year).
3.3.6 Person is able to read, understand and speak English.
3.3.7 Record of EBV ea and IgM, HHV6, Coxsackie B panel and XMRV status, including laboratory where assessed, **if known** (testing is not required for participation).

Exclusion Criteria for Controls

3.4.1 Subject meets the clinical criteria for the diagnosis of chronic fatigue syndrome as established by the International Chronic Fatigue Syndrome Study Group (Fukuda 1994) or the revised Canadian criteria (Jason 2010).
3.4.2 Subject has a diagnosis or history of CFS.
3.4.3 Subject with any active or uncontrolled co-morbidities which, according to the investigator or the case definitions referenced in Section 3.4.1, may interfere with the ability of the subject to participate in the study.
3.4.4 Subjects taking immunomodulatory medications and/or medications that cause immunodeficiency or immunosuppression will be excluded. Examples include but are not limited to medications such as: prednisone, cortisone, plaquenil, methotrexate, TNF inhibitors. Immune enhancing drugs such as Ampligen and Isoprinosone may be included if subject is on stable dosing for more than three months. A list of immunosuppressive drugs by category with examples can be found in the tables "Causes of Secondary Immunodeficiency" and "Some Drugs that Cause Immunosuppression" at this website: http://www.merck.com/mmpe/sec13/ch164/ch164a.html

3.4.5 Subject has been treated with long-term (longer than 2 weeks) antiviral medication within the past 6 months.
3.4.6 Subject has been treated with long-term (longer than 2 weeks) antibiotics within the past 3 months.
3.4.7 Subject has been treated with short term (less than 2 weeks) antiviral or antibiotic medication for a condition unrelated to CFS within the past 30 days.
3.4.8 Subject has used antiretroviral medication.
3.4.9 Subject is unable to read, understand, or speak English.
3.4.10 Subject who in the professional opinion of the PI or attending physician, should not be enrolled.
3.4.11 Subject with history of substance abuse in the past year (excluding nicotine and caffeine) as determined by patient self-report.
3.4.12 Subject fails clinical laboratory or physical exam screen.
3.4.13 Subject does not have access to a primary care physician.

4.0 SUBJECT ENROLLMENT

4.1 Subject Enrollment: Number of CFS Cases and Controls

The target number for enrollment is up to 200 CFS cases and up to 200 matched controls. We anticipate that across up to 5 clinical sites, accrual may allow for a target accrual of up to 50 cases and up to 50 controls per site to assure a final total of up to 200 completed, evaluable CFS cases and up to 200 healthy controls.

4.1.1 Guidelines for subset accrual:

4.1.1.1 At each clinical site, up to 50% of total accrual will be comprised of "acute onset" subjects:

a) 25% of cases will meet the criteria for the XMRV study (Appendix C) at each site.

b) 25% of cases will be subjects $\leq$ 3 years since original onset of CFS at each site.

4.1.1.2 The remaining 50% accrual at each clinical site will be comprised of subjects who are $\geq$ 3 years since original onset of CFS, meeting the overall protocol eligibility criteria and in the judgment of the site investigator, representative of that clinical setting's CFS patient population.

4.2 Recruitment – CFS Cases

4.2.1 Patients previously diagnosed with CFS who are in the medical practice of Dr._____ (Site Responsible Investigator) located at the Site Responsible Investigator's CFS clinic (the Study Site) may be considered for eligibility to participate in the study. These potential subjects will be initially identified by the Site Responsible Investigator or members of his or her staff participating in the conduct of the study

(Study Site Team), which shall include a site Clinical Research Coordinator (CRC). The potential subjects will either be approached in clinic, contacted by mail (Physician Letter: Appendix D) or called on the telephone by a Study Site Team member (Telephone Script: Appendix E) to inquire if they are interested in participating in the study.

If a potential subject expresses an interest in study participation, he or she will be asked to participate in a pre-screening interview conducted by a Study Site Team member to help determine eligibility for the study. If the potential subject satisfies the pre-screening criteria, a Study Site Team member will assign a unique subject identifier to the potential subject that will protect the individual identity of the potential subject during the entire study process, and the key linking this unique identifier to the potential subject will be kept securely at the Study Site and accessible only to the Study Responsible Investigator and selected members of the Study Site Team.

The potential subjects with CFS will be recruited and enrolled in the study, as summarized in the following schema:

Figure 1: CFS Subject Schema

	• Subject recruitment by Site Responsible Investigator and Study Site Team using pre-screening questionnaire	
ELIGIBLE ↓ ↓ ↓	↓ ← → 	INELIGIBLE ↓ ↓ ↓
• Study Site Team assigns a unique subject identifier to the prospective subject to protect subject identity, and the linking key is maintained securely at the Study Site only. Study Site Team members instruct prospective subjects to complete a Part I On-Line Consent and Core Questionnaire. These electronic documents are both de-identified, and contain only the subject's unique subject identifier. ↓ ↓		• Pre-screening questionnaire data is destroyed • Ineligibility is recorded by Study Site in secure screening failure log

• Subject completes Part I Consent and Core Questionnaire • CFI Database confirms consent and scores Core Questionnaire • CFI Database communicates subject eligibility status to Study Site Team, using the unique subject identifier ↓		
↓ ELIGIBLE INELIGIBLE ↓ → → → → ↓ ↓ ↓ ↓ ↓		
• Study Site Team schedules On-Study Visit: 1. Part II Consent Session - Signed informed consent 2. History & Physical Exam Includes Tear collection & Rectal swab (optional). 3. Severity of Illness Questionnaire 4. Clinical and Research Blood Draw, Saliva & Urine collection (Samples are identified only by a unique laboratory identification number that is linked to the subject, and the linking key is maintained securely at the Study Site only.) 5. De-identified clinical data provided to the CFI Databank, de-identified blood samples provided to study laboratories for standard disease and other testing, and eligible de-identified blood samples are furnished to the CFI Biobank for processing and storage for further approved research use 6. Subject is reimbursed $50.00 U.S.	• Data remains in CFI Database if Subject consented using Part-I On-Line Consent Form, otherwise data is destroyed • Ineligibility is recorded by Study Site in secure screening failure log • Subject is reimbursed $25 U.S.	

4.2.2 Informed Consent: CFS Subjects

As noted in Figure 1, following identification of potential subjects from medical record review/screening of CFS patients cared for by the Study Responsible Investigator, potential subjects will be approached either in clinic, by phone or by letter from their physician (the Study Responsible Investigator), or by a member of the Study Site Team. If they express an interest in the study, the CRC will assign a unique subject identification number and a unique laboratory identification number, and provide them with a code for access to a secure web-based link to: Part I, the on-line study Consent Form. Upon completing the Consent Form, they will access and complete the on-line Core Questionnaire (Appendix F). The Part I On-Line Study Consent Form and the Core Questionnaire will be self-administered by the CFI Database ***(REDCap).*** No protected health information (PHI) is received by the CFI Database because the Part-I On-Line Consent and Questionnaire bear only unique subject identifying numbers, and the key linking particular subjects to the identifying numbers is kept only at the Study Site, accessible by the Site Responsible Investigator and selected Study Site Team members. Subjects will also be provided with the name and telephone contact information of one or more Study Site Team members who will be available to assist them with questions Monday-Friday, 9:00 AM-5:00 PM EST, and, as necessary, contact the CFI Database on behalf of subjects (whose identify will remain unknown to the CFI Database) to help resolve issues. The on-line activities will be designed such that subjects will have the opportunity to take breaks throughout the process and save their data thus avoiding the risk of losing their entries over separate sessions. CFI Database staff will monitor these sites daily.

These processes may also be completed on paper via standard U.S. mail if subjects do not have internet access. In such cases, Study Site Team members will provide the Part I Consent Form and Core Questionnaire to the subject for completion and return to the Study Site via self-addressed stamped envelope. These paper forms will also only bear the unique subject identifying numbers, and no PHI. All paper copies of the Core Questionnaire, bearing only the unique subject identifying number will be forwarded to the CFI Database. Thus even when completed on paper, Core Questionnaire responses will be available in the CFI Database to the appropriate clinical site.

After completing the Part I Consent Form and Core Questionnaire, they will be informed if they are eligible to participate in the next aspect of the study, which involves an on-site visit at the Study Site (called an On-Study Visit), where over the course of a few hours the subject will: (i) meet with a member of the Study Site Team to review and execute Part II of the study Consent Form, which review will be confirmed by signature, time and date on the Part II Consent Form; (ii) participate in the Study Site physical exam and clinical history; and (iii) provide a blood donation.

4.2.3 Scope of Consent

4.2.3.1 The Part I Consent Form will allow for completion and review of the Core Questionnaire. De-identified responses will be reviewed and scored by the Database staff, and responses may also be reviewed by Study Site Team members who may contact subjects via follow-up phone regarding questions/clarifications as necessary. Subjects meeting the criteria following completion of the Core Questionnaire will be scheduled for a Part II Consent Form meeting and On-Study Visit at the Study Site.

4.2.3.2 When subjects present to the Study Site for their Part II Consent Form meeting and On-Study Visit, they will be presented with Part II of the study Consent Form to allow for the following: 1) allow medical history review and physical exam, including current medical history and a review and summary of information from patient records on the subject held by the CFS Clinic; 2) allow the collection of blood for routine disease and other testing, including HIV testing (if it has not been done in the past year), 3) allow the collection and laboratory/data analysis (including genetic testing) of specimens as described in Sections 6.0 and 7.0 of this protocol, 4) allow the collection and linkage of clinical data/questionnaire responses to the samples and 5) to allow for re-contact by the Site Responsible Investigator and Study Site staff for specified purposes including: a) notification of new clinical studies not covered by this study and informed consent; and b) updating clinical information and c) notice of medical findings indicating significant and material treatment options. The consent status of each subject will be tracked by the Study Site Team. In addition, subjects may notify the Study Site Responsible Investigator in writing at any time that they wish to withdraw consent for ongoing participation and/or to have their specimens removed from the CFI Biobank, as well as have their data deleted from the CFI Database, and the Study Site Responsible Investigator will notify the Principal Investigator, who will implement the subject's withdrawal from the study. However, subjects will not be able to withdraw consent with respect to materials and data that have already been transferred from the CFI Biobank and CFI Database to researchers for use in research studies.

During the consent session, subjects will be given ample opportunity to ask questions and to discuss the study with investigators. Each subject will be provided with a copy of their signed consent form for reference.

4.2.4 Following registration and completion of the Part I, On-Line Consent Form, the subject completes the Core Questionnaire which includes the following components:

- Demographics and Lifestyle
- Medical History
- Past and Current Medical Conditions
- Medications
- Family Health History
- Pittsburgh Sleep Quality Index

4.2.5 The CFI Database Staff will verify completion of the questionnaires, determine eligibility, compile a summary report of each subject's results and send that information

to the Study Site Team, throughout this process using the unique subject identifier provided on the Part I Consent and Core Questionnaire, and having no access to PHI.

4.2.6 The Study Site Team will confirm the consent status and Core Questionnaire data with the Database Coordinator, complete the medical record review summary in the CFI Database (Appendix G) (*CFS subjects only*) and assemble documentation for the Site Responsible Investigator prior to the subject's On-Study Visit.

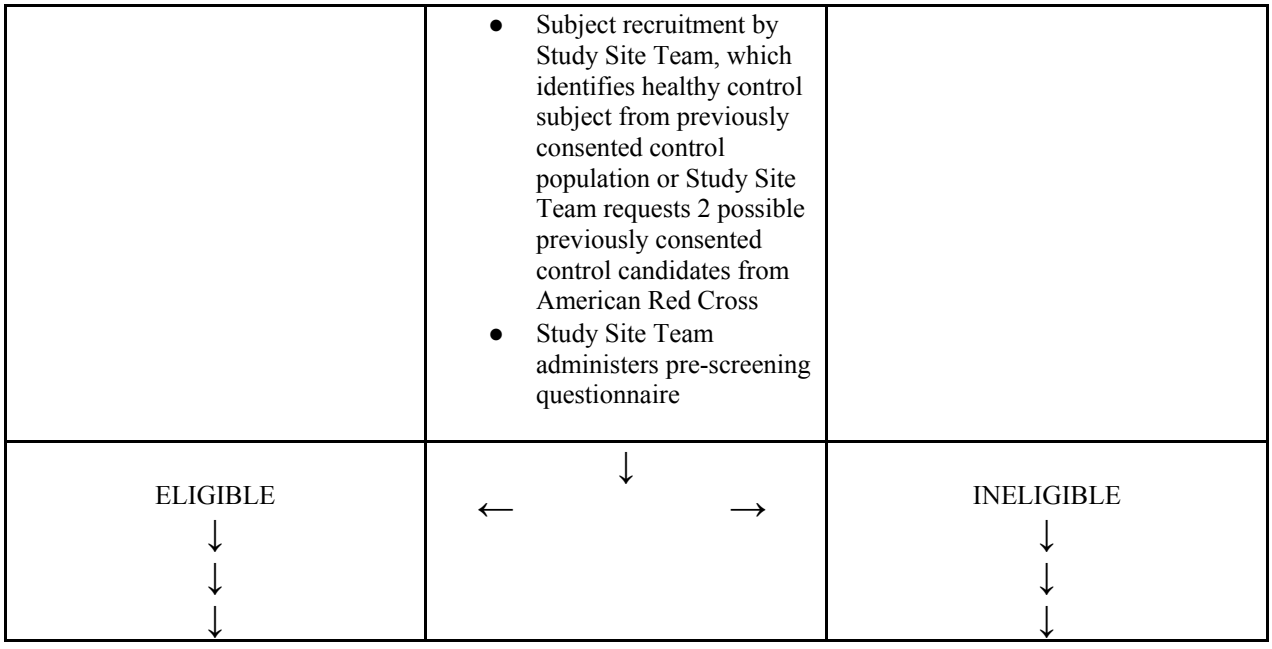
4.3 Recruitment – Controls

For each CFS subject enrolled in the study, we will screen healthy controls in order to match one healthy control subject on the basis of sex and age (within five years). Control subjects from the study site area residing for $\geq$ 1 year within a 100 mile radius of this clinic will be prioritized for recruitment. The expected accrual period for control subjects is the same as that of the cases. Control subjects must have research **labs drawn within 30 days** of their matched CFS case subject.

If a potential subject expresses an interest in study participation, he or she will be asked to participate in a pre-screening interview conducted by a Study Site Team member to help determine eligibility for the study. If the potential subject satisfies the pre-screening criteria, a Study Site Team member will assign unique subject identifier to the potential subject that will protect the individual identity of the potential subject during the entire study process, with the key linking this identifier to the potential subject kept securely at the Study Site and accessible only to the Study Responsible Investigator and selected members of the Study Site Team.

The potential healthy control subjects will be recruited and enrolled in the study, as summarized in the following schema:

Figure 2: Healthy Control Schema



• Study Site Team assigns unique subject identifier to the prospective subject to protect subject identity, and the linking key is maintained securely at the Study Site only. Study Site Team members instruct prospective subjects to complete a Part I On-Line Consent and Core Questionnaire. These electronic documents are both de-identified, and contain only the subject's unique subject identifier. ↓		• Pre-screening questionnaire data is destroyed • Ineligibility is recorded by Study Site in secure screening failure log
• Subject completes Part I Consent and Core Questionnaire • CFI Database confirms consent and scores Core Questionnaire (chooses closest match) • CFI Database communicates subject eligibility status to Study Site Team, using the unique subject identifier ↓		
↓ ELIGIBLE INELIGIBLE ↓ → → → → ↓ ↓ ↓ ↓ ↓ ↓		
• Study Site Team schedules On-Study Visit: 1. Part II Consent Session - Signed informed consent 2. History & Physical Exam Includes Tear collection & Rectal swab (optional). 3. Severity of Illness Questionnaire 4. Clinical and Research Blood Draw, Saliva & Urine collection (samples are identified only by a unique laboratory identification number that is linked to the subject, and	• Subject is reimbursed $25.00 U.S. • Data remains in CFI Database if Subject consented using Part-I On-Line Consent Form, otherwise data is destroyed • Research samples are discarded • Ineligibility is recorded by Study Site in secure screening failure log	

the linking key is maintained securely at the Study Site only). 5. De-identified clinical data provided to the CFI Databank, de-identified blood samples provided to study laboratories for standard disease and other testing, and eligible de-identified blood samples are furnished to the CFI Biobank for processing and storage for further approved research use ● Subject is reimbursed $100.00 U.S.		

4.3.1 Matching healthy controls to CFS cases

To identify control subjects, the Study Site Team will recruit controls using the following selected methods; yoked-controls, healthy donors known to clinicians from previous studies who have given consent for re-contact and healthy blood donors from the American Red Cross and Regional Blood Donor centers who have previously consented to be contacted for research studies.

Specifically, if CFS subjects have previously participated in clinical research at this site, and have previously presented with "yoked-controls" then these healthy controls may also be considered for screening for this study provided that there is previously documented consent for "contact for future studies".

As noted in Figure 2, when an appropriate CFS case subject has been identified, the Study Site Team will contact the designated local Blood Donor Center and request that they contact a potential control candidate matched for age, sex and geographic location. Control candidates will be contacted by the Blood Donor Center and asked to contact the Study Site Team. The Study Site Team will conduct the Telephone pre-screening for Controls (Appendix H), assign the unique study identification number and a laboratory ID number, and document and assist control candidates in accessing the Part I Consent Form and Core Questionnaire.

Also as noted above, "yoked-controls" may also be considered for screening provided there is documented consent for re-contact. The screening process for new controls and previously studied controls will be identical.

4.3.2 Informed Consent – Control Subjects

Via telephone, the Study Site Team provides control candidates with information regarding participation in the study, a code for access to a secure web-based link to the

Part I: Consent Form and the Core Questionnaire to complete on a de-identified basis using only unique subject identifiers, and no PHI. The Part I On-Line Study Consent Form and the Core Questionnaire will be self-administered by the CFI Database. No protected health information (PHI) is received by the CFI Database because the Part-I On-Line Consent and Questionnaire bear only unique subject identifying numbers, and the key linking particular subjects to the identifying numbers is kept only at the Study Site, accessible by the Site Responsible Investigator and selected Study Site Team members. Subjects will also be provided with the name and telephone contact information of one or more Study Site Team members who will be available to assist them with questions Monday-Friday, 9:00 AM-5:00 PM EST, and, as necessary, contact the CFI Database on behalf of subjects (whose identify will remain unknown to the CFI Database) to help resolve issues. The on-line activities will be designed such that subjects will have the opportunity to take breaks throughout the process and save their data thus avoiding the risk of losing their entries over separate sessions. CFI Database staff will monitor these sites daily.

These processes may also be completed on paper via standard U.S. mail if subjects do not have internet access. In such cases, Study Site Team members will provide the Part I Consent Form and Core Questionnaire to the subject for completion and return to the Study Site via self-addressed stamped envelope. These paper forms will also only bear the unique subject identifying numbers, and no PHI. All paper copies of the Core Questionnaire, bearing only the unique subject identifying number will be forwarded to the CFI Database. Thus even when completed on paper, Core Questionnaire responses will be available in the CFI Database to the appropriate clinical site.

After completing the Part I Consent Form and Core Questionnaire, the healthy controls will be informed if they are eligible to participate in the next aspect of the study, which involves an on-site visit at the Study Site (called an On-Study Visit), where over the course of a few hours the subject will: (i) meet with a member of the Study Site Team to review and execute Part II of the study Consent Form, which review will be confirmed by signature, time and date on the Part II Consent Form; (ii) participate in the Study Site physical exam and clinical history; and (iii) provide a blood, urine, saliva, tear & optional fecal donation.

The healthy controls study Consent Form will allow for the following: 1) allow medical history review and physical exam, including current medical history and a review and summary of information from patient records on the subject held by the CFS Clinic; 2) allow the collection of urine, saliva, tear, fecal (optional), and blood for routine disease and other testing, including HIV testing, 3) allow the collection and laboratory/data analysis (including genetic testing) of specimens as described in Sections 6.0 and 7.0 of this protocol, 4) allow the collection and linkage of clinical data/questionnaire responses to the samples and 5) to allow for re-contact by the Site Responsible Investigator and Study Site staff for specified purposes including: a) notification of new clinical studies not covered by this study and informed consent; and b) updating clinical information and c) notice of medical findings indicating significant and material treatment options. The consent status of each subject will be tracked by the

Study Site Team. In addition, subjects may notify the Study Site Responsible Investigator in writing at any time that they wish to withdraw consent for ongoing participation and/or to have their specimens removed from the CFI Biobank, as well as have their data deleted from the CFI Database, and the Study Site Responsible Investigator will notify the Principal Investigator, who will implement the subject's withdrawal from the study. However, subjects will not be able to withdraw consent with respect to materials and data that have already been transferred from the CFI Biobank and CFI Database to researchers for use in research studies.

4.4 Screening Failures

If screening reveals subjects for either the CFS case or control cohorts are ineligible for this study, the reason for screening failure will be recorded in the Study Screening Failure Log. This log will be maintained in a secure, password protected location at the Study Site and will not be entered into the CFI Database. If the subject meets the criteria for CFS but is ineligible for this study, his or her data will also remain in the CFI Database, identified only by his or her applicable unique subject identifier. All standard of care medical information in the patient's medical record will remain as per standard practice.

5.0 STUDY DESIGN AND PROCEDURES

5.1 Core Questionnaire

5.1.1 Following completion of Part I of the On-Line Consent Form and prior to the On-Study Visit, all subjects will complete the following Core Questionnaire:

- Demographics General Information
- Past and Current Medical Conditions
- Medications
- Family Medical History
- Pittsburgh Sleep Quality Index

5.2 On-Study Visit

Following Part I eligibility confirmation by the CFI Database, subjects are contacted by the Study Site Team to return to the clinic for an On-Study Visit.

The following will be conducted during the On-Study Visit:

5.2.1 Informed Consent

At the On-Study Visit this study will be described to all subjects and all subjects will review Part II of the Consent Form with a Study Site Team member and document consent by signature, time and date. Subjects will have an opportunity to ask questions and will be provided with a copy of the signed consent form.

5.2.2 History and Physical Exam

All subjects will meet with the Study Site Responsible Investigator or his or her medically qualified designee for history and physical exam. Physical exam will include: Vital signs including BMI, Skin, Lymphatic System, HEENT, Pulmonary, Cardiac, Abdomen, Musculoskeletal, Neurologic exam for all subjects (Appendix I), as well as a tear collection and optional rectal swab. Tear collection involves the clinician touching a small ($1/8^{th}$ inch x 1 inch) soft paper strip to the corner of the eye (not the eyeball), which wicks tears on to the paper. Stool collection is optional and is collected by a superficial swab of the anal canal.

5.2.3 Severity of Illness Questionnaire:

While in clinic for the On-Study Visit, all subjects will complete the following Severity of Illness Questionnaire via a secure web based program within the CFI Database (Appendix J). This Questionnaire includes the following components:

- General health
- Symptom Questionnaire
- Multidimensional Fatigue Inventory
- Pain Inventory
- BDI
- Beck Anxiety Q

* Responses will be reviewed while subjects remain in clinic and staff will be in place to respond and/or make appropriate referrals for any subjects affirming suicidal ideations on the QIDS.

5.2.4 Routine Screening Labs

All subjects will undergo routine screening labs including: CBC with Differential, Comprehensive chemistry panel (SMA 18), ESR, TSH, HIV. Tests results will be reported to subjects. Any positive results for HIV will be subject to institutional, local and state reporting requirements. Further, if the subject tests positive for HIV or other serious diseases, the Study Site Responsible Investigator will provide or arrange for appropriate counseling and referrals.

5.2.5 Labs pertaining to exclusion of other fatiguing illnesses/confirmation of CFS

Appendix G represents the medical history summary which will be collected for all CFS subjects and entered in to the CFS Databank by the Study Site CRC. As well as documenting eligibility by meeting criteria for CFS by CDC or Canadian Criteria, documentation of laboratory studies which are indicated in red font will be “required” data to confirm exclusion of other fatiguing illnesses. If these labs have been tested at any time in the past, they do not need to be repeated and if they have been tested multiple times, the most recent test date and result should be entered.

5.2.6 Research Sample Collection/Blood Draw

As well as blood draw for routine laboratory testing, all subjects will undergo a research blood draw per the then current "Sample Collection Protocol" (Appendix K). **All blood draws will be scheduled during - the visit between 10:00 AM and 2:00 PM.** Every effort will be made to combine any study blood draws with scheduled clinical lab blood draws to limit the number of times subjects are asked to undergo venipuncture. Estimated research blood draw for enrollment will be approximately 80 cc (6 tablespoons). If the subject indicates that he or she is participating in other research studies, the study coordinator will need to ascertain that the amount of blood the subject is having drawn and that the total volume and frequency will not exceed accepted blood sampling guidelines. Saliva and urine collection will take place at this time. Saliva will be collected into a sputum collection container, with a simple spit sample. Urine will be collected as a clean catch in a sterile urine collection device. Subjects will be instructed on cleaning the area and the method to properly collect mid-stream.

5.3 Compensation

Control subjects will be compensated with US $100.00 at the completion of their study participation defined as: screening, consent, completion of questionnaires and sample collection of blood. Control subjects who are found ineligible at the time of completion of the Core Questionnaire will be compensated $25.00 for their time.

CFS patients will be compensated with US $50.00 at the completion of their study participation as defined above for control subjects. CFS patients who are found ineligible at the time of completion of the Core Questionnaires will be compensated $25.00 for their time.

6.0 SPECIMEN/DATA COLLECTION PROCEDURES

6.1 Data Collection

At each Study Site, Study Site Team members will assign to each subject a unique subject identification number and if blood samples are collected, a unique laboratory ID number. The file linking the unique subject identification code and the unique laboratory ID number to personally identifiable information will be maintained at the Study Site in a secure, password protected location accessible only by the Site Responsible Investigator and authorized Study Site team members. The unique subject identification number will be used on all screening tools (e.g. telephone screening questionnaires) and for subjects to gain password protected access to the secure, web-linked Phase I Consent, Core Questionnaire and the Severity of Illness Questionnaire. The unique laboratory identification number will serve as the only link to an individual subject's urine, saliva, tear, fecal and blood samples provided to laboratories for routine disease and other testing. No one other than the Site Responsible Investigator and authorized Study Site Team members (and their direct staff needing access to such information in order to perform duties associated with this study) will have access to the link between a subject's unique subject identifier number, unique laboratory identification number, and his or her individually identifying information.

6.2 Biosample Collection

All samples procured for this study will be collected at the Study Site by a Study Site Team member, in accordance with generally accepted good laboratory practices, who is a certified phlebotomist or other medical professional.

Samples will be collected between 10:00 AM and 2:00 PM. When the order for sample collection from a study subject is provided, the Study Site Team will select a sample collection kit for that subject. A Study Site Team member will label the individual subject's pre-assembled kit with the subject's unique laboratory identification number. Each kit will also have a pre-printed set of bar-coded labels for application to the individual samples tubes (and eventual aliquots) from each subject. For CFI Biobank and Database purposes, the unique barcodes from the kit will be the subject's unique laboratory identification number in the system. No personal identifiers will travel with the kits or on the tubes. The file linking the unique laboratory identification code to personally identifiable information will be maintained at the Study Site in a secure, password protected location accessible only by the Site Responsible Investigator and authorized Study Site team members. No one other than the Site Responsible Investigator and authorized Study Site Team members (and their direct staff needing access to such information in order to perform duties associated with this study) will have access to the link between a subject's unique laboratory identifier number and their individually identifying information.

6.3 Sample Processing

Once the samples are collected, they will be immediately transferred to the Study Site Team members who will prepare the samples for initial processing per the study SOPs and then shipped accordingly to the CFI Biobank.

6.4 Sample Storage

De-identified biologic samples will be stored in the CFI Biobank, Duke Human Vaccine Institute. De-identified related clinical and laboratory data will be stored in the CFI Database, REDCap via Partners Healthcare. Password protection, access control and subject confidentiality for all aspects of sample and data storage will be integral. The key matching the subject's identification with the pairing of the unique subject identification number for the clinical data and the laboratory identification number for the sample data will be kept secure at the Study Site. To allow access by authorized investigators to coded clinical and laboratory data, the software for the CFI Database will include industry standard encryption algorithms to ensure data security while allowing remote access via the internet. These elements will allow for the optimal acquisition, storage and management of biosamples and related data for each CFS subject and control subject who has consented to be enrolled in this study.

All samples will be processed and maintained according to documented SOPs that follow generally accepted good laboratory practices in order to assure sample quality, integrity and long-term stability.

7.0 LABORATORY/DATA ANALYSIS

All samples released from the Biobank are de-identified and coded; the key matching the subject's identification with the pairing of the unique subject identification number for the clinical data and the laboratory identification number for the sample data will be kept securely at the Study Site, accessible only by the Study Site Investigator and authorized Study Site Team members. Duke Human Vaccine Institute will function as the Biobank, for sample collection, maintenance and release for research studies selected and supported by the Sponsor. Sponsor research selection will be made based on the review and recommendation of a CFI scientific review board, with the study's Principle Investigator responsible for assuring adherence to protocol guidelines.

7.1 Pathogen Discovery

The first use of the samples collected in this study is in a study being supported by the Sponsor to identify known and unknown pathogens in patients with CFS. Drs. Mady Hornig and W. Ian Lipkin and their colleagues at the Center for Infection and Immunity at Columbia University will analyze the subjects' blood for known and unknown pathogens and related immune function markers using state of the art molecular techniques (mass spectroscopy, microarrays, pyrosequencing, RT-PCR, etc.).

7.1.2 Known Pathogens

Primary analysis will show the frequency and distribution of known pathogens within the study cohort and matched controls. The study will conduct two phases of analysis, wherein each analysis will provide two sets of odds ratios. The odds ratios will reflect the association between the presence of the pathogen of interest and a diagnosis of CFS. Additional sets of odds ratios will be generated in the second phase of analysis to distinguish the differences, if any, in the association of a specific pathogen, or set of pathogens with different CFS subsets.

7.1.3 Unexpected or Novel Pathogens

Samples from patients with significant deviations from normal levels of immune or metabolic markers, that tested negative for known pathogens, will be analyzed along with representative samples of patients who tested positive for known pathogens and healthy controls. GreeneChip microbial microarray will be used to interrogate samples for the presence of unexpected pathogens or microbial agents with sequences sufficiently divergent from those represented in methods to be employed in the first stage (section 7.1.2, Known Pathogens; includes MassTag, real time and standard PCR). Samples negative on GreeneChip will proceed to a third stage: pyrosequencing of DNA to identify unique or unusual non-human sequences consistent with presence of a pathogen. Positive findings with any of these strategies will be followed up by quantitative PCR or real time PCR to confirm the presence of the pathogen and estimate its burden in the biological sample (e.g., viral load). Once these pathogens and their unique gene sequences have been identified, appropriate probes will be added to the panel of known pathogens so population statistics, such as those described in Section 7.1.2, can be derived as new samples are analyzed.

7.1.4 Immunological Markers

Each case sample and a matched control will be analyzed for expression of a range of immune and metabolic markers previously reported to be altered in CFS study populations or hypothesized to be altered based on pathway analysis or on data from studies of other populations with overlapping clinical features. Graphical techniques such as QQ-plots and histograms will be applied to assess distributions of continuous variables for deviation from normality. The data will be analyzed to determine descriptive statistics (means and standard deviations or standard error of the mean, or medians and interquartile ranges, as appropriate for the data distribution) will be generated for all continuous variables. Frequency tables will be generated for categorical and discrete variables. Other statistical strategies (*t* tests or nonparametric techniques for group comparisons; ANOVA, regression, or mixed models for more complex datasets; or principal components analysis for derivation of host response profiles) may be applied in later phases of the project.

7.1.5 Matching Considerations

As described above each case will be matched for geographic location ($\leq$ 100 mile radius), sex and age ($\pm$ 5 years) to one control.

Control subject bloods to be drawn within 12 weeks of the matched CFS subject blood draw.

7.1.6 Future Studies

In order to optimize the value of the subject samples and clinical data collected as part of this study, the Sponsor will invite proposals from investigators who wish to access the biosample collection in the CFI Biobank and the clinical data in the CFI Database to study mechanisms of disease in CFS. Any further proposals, outside the scope of the work described in the objectives of this protocol, will require separate research proposals, and also IRB review and approval as required by law and professional standards. No subject-identifying information will be shared with outside investigators.

8.0 STATISTICAL ANALYSIS

8.1 Descriptive Statistics

The study will amass a large database including clinical and standard laboratory test data on patients with CFS, over time. The data will be collected systematically, according to protocol. Descriptive statistics such as means, medians, standard deviations, standard errors, interquartile ranges will be generated for all continuous variables. Frequency tables will be provided for all categorical and discrete variables. Graphical techniques such as QQ-plots and histograms will be applied to assess distributions of continuous variables.

8.2 Comparative Statistics

The study will collect clinical data, standard laboratory test data, and experimental laboratory data on both CFS Case Subjects and Healthy Control Subjects that are frequency matched by age

(within 5 years) and gender. Cases will be compared to controls on many different measures. For example, we anticipate that comparisons will include but not be limited to:

- Clinical data other than the data used to define a case or a control
- Exposures (diseases, lifestyle information)
- Instruments that measure various qualities such as pain, sleep, lifetime psychiatric illness, cognition
- Particular pathogens (present or absent)
- Pathogen burden, with ubiquitous pathogens (e.g., viral load, evidence of viral reactivation)
- Immunologic markers

All case-control comparisons will employ comparative statistics:

- Parametric statistics for normally distributed continuous variables and nonparametric statistics for non-normally distributed continuous variables;
- Proportions will be compared using tests such as chi-square and Fisher exact test.

9.0 Regulatory requirements

This study will be conducted in compliance with this protocol, GCP and all applicable law and professional standards, such as embodied in the standards for clinical research guidelines established by the Code of Federal Regulations (Title 45 CFR Part 46), the International Conference on Harmonization (ICH) Guidelines, and the Health Insurance Portability and Accountability Act of 1996, as amended and the rules and regulations promulgated there under (HIPAA).

9.1 Quality Assurance

The Study Site may be subject to review by the IRB and/or to inspection by appropriate regulatory authorities. Members of the study personnel will routinely conduct quality assurance inspection of the records.

9.2 Data Handling and Record Keeping

9.2.1 Retention of and Direct Access to Source Data/Documents

The Site Responsible Investigators and their institutions will permit, and the subject consent forms will authorize in compliance with HIPAA, trial-related monitoring, oversight, audits, IRB/IEC review, Sponsor and regulatory inspection(s) by providing direct access to source data and documents. All source data and documents will be retained for as long as is required by law and local regulation. Source documents will be kept confidential in locked and otherwise secure storage facilities.

9.2.2 Database

All Case Report Forms (CRF) and other clinical data will be entered into the CFI Database in a de-identified manner, which shall comply with all applicable privacy and security laws and professional standards, including, as applicable, HIPAA. Only the specified Study Site will have password-protected access to patient identifiers.

9.3 Funding

This study is sponsored by the Chronic Fatigue Initiative, Inc. (New York, NY), a private not-for-profit foundation incorporated in the State of Delaware under Section 501(c)(3) of the Internal Revenue Code of 1986. CFI's mission is to foster and support collaboration among the world's premier medical research, treatment and public health organizations in understanding the causes, therapies and epidemiology of Chronic Fatigue Syndrome. There are no costs to participants for the research components of this study.

9.3.1 Subject Injury or Illness

If an illness or injury is directly caused by the subject's participation in the study, the Site Responsible Investigator and the Study Site Team will assist the subject in obtaining appropriate medical treatment for the illness or injury. Reimbursement for all costs of such treatment first will be sought from the subject's insurer, managed care plan, or other health benefits program. The subject will be responsible for any associated co-payments, co-insurance or deductibles. Some insurers, managed care plans or other health benefits programs may not cover costs associated with research studies. If costs of care or other losses related to such injury or illness are not covered by the subject's insurer, managed care plan or other benefits or insurance program, he or she may be responsible for these costs, and no additional financial compensation will be provided by the Sponsor, the Site Responsible Investigator, or the Study Site. If the subject is unable to pay for the costs of medical treatment, the Site Responsible Investigator responsible for the subject's enrollment to this protocol will assist him or her in applying for supplemental benefits and explain how to apply for available patient financial assistance. Additionally, neither the Site Responsible Investigator, the Study Site nor the Sponsor is responsible for research and medical care by other institutions or personnel participating in this study.

10.0 REFERENCES

Carruthers, B.M., A.K. Jain, et al (2003). "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols." Journal of Chronic Fatigue Syndrome 11(1): 7-36.

CDC. (2008, May 6, 2006). "Chronic Fatigue Syndrome: Basic Facts." Retrieved September 9, 2008.

Fukuda, K., S. E. Straus, et al. (1994). "The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group." Annals of Internal Medicine 121(12): 953-9.

Jason, L. A., K. Corradi, et al (2005). "Chronic Fatigue Syndrome: The Need for Subtypes." Neuropsychology Review 15(1): 29-58.

Reynolds, W. J., S.D. Vernon, et al (2004). "The Economic Impact of Chronic Fatigue Syndrome." Cost Effectiveness and Resource Allocation 2.

Simon, R. et al (2002). "Design of Studies Using DNA Microarrays." Genetic Epidemiology 23:21-36.

11.0 List of Appendices

Appendix A: ME/CFS Clinical Diagnostic Worksheet, (Carruthers et al., 2003)

1. **Fatigue**: Patient must have a significant degree of new onset, unexplained, persistent or recurrent physical and mental fatigue that substantially reduces activity level.
2. **Post-Exertional Malaise and Fatigue**: There is an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post-exertional fatigue and/or malaise and/or pain and a tendency for other associated symptoms within the patient's cluster to worsen. There is a pathological slow recovery period–usually 24 hours or longer.
3. **Sleep Dysfunction**:[2] There is unrefreshed sleep or sleep quantity or rhythm disturbance such as reversed or chaotic diurnal sleep rhythm.
4. **Pain**:[2] There is a significant degree of myalgia. Pain can be experienced in the muscles and joints and is often migratory in nature. Often there are significant headaches of new type, pattern or severity.
5. **Neurological/Cognitive Manifestations**: Two or more of the following difficulties should be present: confusion, impairment of concentration and short-term memory consolidation, disorientation, difficulty with information processing, categorizing and word retrieval, and perceptual and sensory disturbances–e.g., spatial instability, and inability to focus vision. Ataxia, muscle weakness and fasciculations are common. There may be overload phenomena: cognitive, sensory–e.g., photophobia and hypersensitivity to noise–and/or emotional overload, which may lead to "crash"[3] periods and/or anxiety.
6. **At Least *One* Symptom from *Two* of the Following Categories**:

   ____ **Autonomic Manifestations**: orthostatic intolerance–NMH, POTS, delayed postural hypotension, vertigo; light-headedness, extreme pallor; nausea and IBS; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmia; palpitations, and exertional dyspnea.

   ____ **Neuroendocrine Manifestations**: loss of thermostatic stability–subnormal body temperature and/or marked diurnal fluctuation, sweating episodes, recurrent feeling of feverishness and cold extremities; intolerance to heat and cold; marked weight change–anorexia or abnormal appetite; loss of adaptability and tolerance for stress, worsening of symptoms with stress and a slow recovery.

   ____ **Immune Manifestations**: tender lymph nodes, recurrent sore throat and flu-like symptoms, general malaise, new sensitivities to food, medications and/or chemicals.
7. **The illness persists for at least six months. It usually has a distinct onset**,[4]** although it may be gradual. Preliminary diagnosis may be possible earlier. Three months is appropriate for children.

To be included, the symptoms must have begun or have been significantly altered after the onset of the illness. It is unlikely that a patient will suffer from all symptoms in criteria 5 and 6. The disturbances tend to form symptom clusters that are often unique to a particular patient. The manifestations fluctuate and may change over time.

[1] There is a small number of patients who have no pain or no sleep dysfunction but no other diagnosis fits except ME/CFS. A diagnosis of ME/CFS should only be entertained when this group has an infectious illness type onset.
[2] "Crash" refers to a temporary period of immobilizing physical and/or mental fatigue.
[3] Some patients have been unhealthy for other reasons prior to the onset of ME/CFS and lack detectable triggers at onset and/or have more gradual or insidious onset.

Appendix B: ME/CFS Clinical Diagnostic Worksheet, Carruthers et al.

Exclusions: Confirm active disease processes that explain most of the major symptoms of fatigue, sleep disturbance, pain, and cognitive dysfunction. It is essential to exclude certain diseases, which would be tragic to miss: Addison's disease, Cushing's syndrome, hypothyroidism, hyperthyroidism, iron deficiency, iron overload syndrome, other treatable forms of anemia, diabetes mellitus, and cancer. It is also essential to exclude treatable sleep disorders such as upper airway resistance syndrome and obstructive or central sleep apnea; rheumatological disorders such as rheumatoid arthritis, lupus, polymyositis, and polymyalgia rheumatica; immune disorders such as AIDS; neurological disorders such as MS, Parkinsonism, myasthenia gravis and B12 deficiency; infectious diseases such as tuberculosis, chronic hepatitis, Lyme disease, etc.; primary psychiatric disorders and substance abuse. Exclusion of other diagnoses, which cannot be reasonably excluded by the patient's history and physical examination, is achieved by laboratory testing and/or imaging. If a potentially confounding medical condition is under control, then the diagnosis of ME/CFS can be entertained if the patient meets the criteria otherwise.

Co-Morbid Entities: Fibromyalgia syndrome, myofascial pain syndrome, temporomandibular joint syndrome, irritable bowel syndrome, interstitial cystitis, irritable bladder syndrome, Raynaud's phenomenon, prolapsed mitral valve, migraine, allergies, multiple chemical sensitivities, thyroiditis, sicca syndrome, depression, Hashimoto's, etc. Such co-morbid entities may occur in the setting of ME/CFS. Others such as IBS may precede the development of ME/CFS by many years, but then become associated with it. The same holds true for migraines and depression. Their association is thus looser than between the symptoms within the syndrome. ME/CFS and FMS often closely connect and should be considered to be "overlap syndromes."

Idiopathic Chronic Fatigue: If the patient has unexplained prolonged fatigue but has insufficient symptoms to meet the criteria for ME/CFS, it should be classified as idiopathic chronic fatigue.

_____ Patient meets the criteria for ME/CFS

_____ Patient meets the criteria for Idiopathic Chronic Fatigue

Appendix C: XMRV Study Inclusion/Exclusion Criteria

Inclusion Criteria General:

Inclusion Criteria for CFS Subjects

A subject will be eligible for inclusion in this study if s/he has previously been diagnosed with CFS, meets both the Fukuda and Canadian consensus criteria, is currently unable to work due to illness, reports a 'viral like' prodrome (3 out of 8 of the following clinical features: fever, headache, gastrointestinal discomfort/upset, malaise, sore throat, myalgias, arthralgias, tender lymph nodes) prior to onset of CFS. CFS cases must meet both the 1994 Fukuda and Canadian case definitions. In addition, cases must have a history of acute onset of viral syndrome as described above, and currently be unable to work due to the illness.

Additional Criteria include:

SF36 meets 2 of the 3 criteria: vitality <35, social functioning <62.5, role physical <50.
Age between 18 and 65 years at the time of signing the informed consent.
A female subject is eligible to participate if she is not pregnant, not <3 months postpartum, and not currently lactating per self-report.
Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

Inclusion criteria for CFS according to the 1994 Fukuda criteria:

Clinically evaluated, unexplained, persistent or relapsing fatigue for > 6 months that: a) is of new or definite onset, b) is not the result of ongoing exertion, c) is not substantially alleviated by rest, d) is made worse by exertion, e) results in substantial reduction in previous levels of occupational, educational, social or personal activities.
Concurrent occurrence of 4 or more of the following symptoms during at least 6 consecutive months and not predating fatigue: a) sore throat, b) tender cervical or axillary lymph nodes, c) muscle pain, d) multiple joint pain without swelling or redness, e) headaches of new type, pattern, or severity, f) unrefreshing sleep, g) postexertional malaise, h) impaired memory or concentration.

Inclusion criteria for CFS according to the 2003 Canadian criteria:

Fatigue: Significant degree of new onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level.
Post Exertional Malaise and/or Fatigue: An inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post exertional malaise, and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. Pathologically slow recovery period usually 24 hours or longer.
Sleep Dysfunction: Unrefreshed sleep or sleep quantity or rhythm disturbances such as reversed or chaotic diurnal sleep rhythms. If the patient does not have sleep dysfunction, but no other diagnosis fits except ME/CFS a diagnosis of ME/CFS can be entertained if this patient has an infectious illness type onset.
Pain: Substantial myalgia. Pain experienced in the muscles and/or joints, and often widespread and migratory in nature. Headaches of new type, pattern or severity. If the patient does not have pain, but no other diagnosis fits except ME/CFS a diagnosis of ME/CFS can be entertained if this patient has an infectious illness type onset.

Neurologic/Cognitive Manifestations: Ataxia, muscle weakness, and fasciculations are common. Overload phenomena (hypersensitivities to stimuli that have changed from preillness status): cognitive, sensory e.g., photophobia and hypersensitivity to noise and/or emotional overload, which may lead to "crash" periods (temporary period of immobilizing physical and/or cognitive fatigue) and/or anxiety. Two or more of the following difficulties: Confusion, impairment of concentration and short term memory consolidation, disorientation, difficulty with information processing, categorizing and word retrieval, perceptual and sensory disturbances e.g., spatial instability and disorientation and inability to focus vision.
At least one clinical feature from two of the following three categories:
Autonomic Manifestations: i, orthostatic intolerance [neurally mediated hypotension (NMH), postural orthostatic tachycardia syndrome (POTS), delayed postural hypotension], ii) lightheadedness, iii) extreme pallor, iv) nausea and irritable bowel syndrome, v) urinary frequency and bladder dysfunction, vi) palpitations with or without cardiac arrhythmias, vii) exertional dyspnea.
Neuroendocrine Manifestations: i) loss of thermostatic stability (subnormal body temperature and marked diurnal fluctuation, sweating episodes, recurrent feelings of feverishness and cold extremities), ii) intolerance of extremities of heat and cold, iii) marked weight change (anorexia or abnormal appetite), iv) loss of adaptability and worsening of symptoms with stress.
Immune Manifestations: i. tender lymph nodes, ii. recurrent sore throat, iii. recurrent flulike symptoms, iv. General malaise, v. new sensitivities to food, medications and/or chemicals.
If a potentially confounding medical condition is under control, then the diagnosis of ME/CFS can be entertained if patients meet the criteria otherwise.
Diagnosis present for at least 6 months.

Inclusion criteria for controls:
Neighborhood or regional controls with residence within the same geographic region and not residing in the same household. Controls will be selected for phlebotomy within 12 weeks of the blood draw for a case using a frequency matching strategy that considers region, sex, and age in 5year intervals. Controls will also be matched to case race/ ethnicity based upon the following categories: Asian, white, black, Hispanic, Pacific Islander, using a frequency matching strategy.

Exclusion criteria for CFS subjects:
A subject will not be eligible for inclusion in this study if s/he does not meet the Fukuda criteria and the Canadian criteria or if the following general exclusion criteria apply.

General Exclusion Criteria for Controls and CFS Subjects
Control subjects do not have a disorder causing immunosuppression including, but not limited to cancer, severe infections, HIV, or other immunosuppressive disorders.
Alcohol or substance abuse or dependence < 2 years before onset of chronic fatiguing illness (DSMIVTR criteria, see Appendix) One drink is equivalent to 12 g of alcohol: 12 ounces (360 ml) of beer, 5 ounces (150 ml) of wine or 1.5 ounces (45 ml) of 80 proof distilled spirits.
Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56-day period.
Unwillingness or inability to follow the procedures outlined in the protocol.
Subject is mentally or legally incapacitated.
For controls, explicit denial of CFS symptoms.
Subject does not have access to primary care physician.

Exclusion Criteria for the Fukuda Criteria:
Organ failure including emphysema, cirrhosis, cardiac failure, or chronic renal failure.
Chronic infections including AIDS, hepatitis B, or hepatitis C.
Rheumatic and chronic inflammatory diseases including systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, inflammatory bowel disease, or chronic pancreatitis.
Major neurological diseases including multiple sclerosis, neuromuscular diseases, stroke, head injury with residual neurologic deficits, or epilepsy.
Diseases requiring systemic treatment including organ or bone marrow transplantation, chemotherapy, or radiation of brain, thorax, abdomen, or pelvis.
Major endocrine diseases including hypopituitarism or adrenal insufficiency.
Primary sleep disorders including untreated sleep apnea or narcolepsy.
Sleep disorders such as restless leg syndrome and periodic limb movement, if they are severe, but not if the degree of the sleep problem is insufficient to explain the severity of fatigue.
Fatigue caused by medications, sleep deprivation, untreated hypothyroidism, untreated or unstable diabetes mellitus, or active infection.
Females who are pregnant, < 3 months postpartum, or currently lactating.
Major surgery < 6 months after operation or minor surgery < 3 months after operation.
Major infections such as sepsis or pneumonia <3 months postresolution.
Myocardial infarction or heart failure < 5 years after event.
Morbid obesity BMI>40.
Psychiatric conditions including lifetime diagnosis of bipolar affective disorders, schizophrenia of any subtype, delusional disorder of any subtype, organic brain disorders, or major depressive disorder with psychotic or melancholic features, anorexia nervosa, or bulimia < 5 years before the onset of chronically fatiguing illness.

Exclusion criteria for the Canadian criteria:
Active diseases processes that explain most of the major symptoms of fatigue, sleep disturbance, pain, and cognitive dysfunction including Addison's disease, Cushing's Syndrome, hypothyroidism, hyperthyroidism, iron deficiency, other treatable forms of anemia, iron overload syndrome, diabetes mellitus, and cancer.
Untreated sleep disorders such as upper airway resistance syndrome or obstructive or central sleep apnea.
Rheumatological disorders such as rheumatoid arthritis, lupus, polymyositis and polymyalgia rheumatica.
Immune disorders such as AIDS.
Neurological disorders such as multiple sclerosis (MS), Parkinsonism, myasthenia gravis and B12 deficiency.
Infectious diseases such as tuberculosis, chronic hepatitis, Lyme disease.
Primary psychiatric disorders and substance abuse.
Exclusion of other diagnosis, which cannot be reasonably excluded by the patient's history and physical examination is achieved by laboratory testing and imaging.

Appendix D: Physician Letter to CFS Subjects

Dear_____:

I am writing to invite you to participate in a new study for patients diagnosed with CFS entitled, "A Clinical and Biosample Database to Enable Discovery of Pathogens and Pathogenic Mechanisms in Chronic Fatigue Syndrome". If you are eligible for the study and agree to participate, you would provide us updated and somewhat more extensive information about your symptoms and medical conditions. Finally, you would provide a blood sample (about 5-6 tablespoons), as well as samples of urine, saliva, tear and optional rectal swab, to be sent to our Biobank. These blood samples would be used for experimental tests, and would typically be obtained at the same time you are having regular blood tests.

The experimental blood tests will include measurement of chemicals in your blood, measurement of the number and function of cells in your blood, identification of infectious agents in your blood, genetic studies to identify genes that might be linked to CFS, and studies of the genes that are turned on in your white blood cells.

While the research teams will make use of information you have given to us, and the blood samples you provide, your identity will remain unknown to all but me and the members of my research team. For example, questionnaires you complete and any blood and laboratory samples that are tested will contain only a study number entered into the study Database, referred to as a Unique Subject Identification Number, not your name or other identifying information.

The visit to the clinic will be free of charge. The experimental blood, urine, saliva, tear and optional rectal swab tests done at any time during the study also will be free of charge.

If you are interested in participating in this new study, please call _____ at _____. If you are not interested in the study or do not wish to participate, please do not be concerned. You are not required to do so and your decision will in no way affect care that you already receive or are entitled to receive from Dr. _____ at _____.

Thank you very much for your time and consideration and I look forward to hearing about your interest in participating in the research study.

Sincerely,

Appendix E: Telephone Script for CFS Subjects/Screen

Screener: Date: Subject ID Number: Subject Age: Gender: M F

Hi, my name is _____ and I am a Clinical Research Coordinator from Dr. _____'s CFS Clinic.

The purpose of this screening interview is to see if you may meet the criteria for a new study that Dr. _____is participating in called, "A Clinical and Biosample Database to Enable Discovery of Pathogens and Pathogenic Mechanisms in Chronic Fatigue Syndrome".

If you are eligible to participate in the study and agree to participate we will ask you to provide updated and somewhat more extensive information about your symptoms and medical conditions. We will also ask you to provide a blood sample (about 5-6 tablespoons) to be sent to the study's Biobank. These blood samples would be used for experimental tests, and would typically be obtained at the same time you are having regular blood tests drawn.

The experimental blood tests will include measurement of chemicals in your blood, measurement of the number and function of cells in your blood, identification of infectious agents in your blood, genetic studies to identify genes that might be linked to CFS, and studies of the genes that are turned on in your white blood cells. During this time you will also be asked to provide a simple urine and saliva sample as well as a tear collection and an optional rectal swab.

While the research team will make use of information you and the laboratory samples you provide, your identity will remain unknown to all but Dr. _____ and the members of his/her research team. For example, questionnaires you complete will contain only a Unique Study ID Number which the members of Dr. _____'s research team will assign, and this Unique Study ID Number will be entered into the study Database, not your name or other identifying information. When you donate blood or other laboratory samples they will only be labeled with a laboratory identification number. The link between the unique study identification number, the laboratory identification number and your identifying information will be restricted and, for example, will not be shared either the Biobank or with outside investigators conducting studies involving your donated samples.

The visit to the clinic will be free of charge. The experimental blood, urine, saliva or optional fecal tests done at any time during the study also will be free of charge.

If you are interested in possibly participating in this study, first I have to ask you several questions to determine if it is appropriate to proceed. This screening interview will take approximately 20 minutes. I am going to go through a list of questions. You may choose not to answer these questions. You also may choose to stop participating in this interview at any time; if you want to stop, please tell me. The screening interview is not designed to ask you for sensitive personal information, but it is possible that some people may feel uncomfortable answering these questions about their health with a person they do not know.

Information about you that you give me during this interview will be kept confidentially and securely at the ____ Clinic premises, with access limited to selected ____ Clinic personnel to the extent permitted by law. If this interview information shows that you are not eligible for the study, or if you choose not to participate in the study, the information will be destroyed. If you are eligible for the study and choose to

participate, any information that identifies you will be kept confidential in accordance with the terms of an informed consent document and authorization that you sign.
If you are *interested* in taking part in this screening, then I will record your name and information; this will be kept confidential, but there is a small risk that people outside of the Center could learn this information. If you are *not interested* in participating in the study, there will be no penalty, and you will not lose any benefits to which you otherwise would be entitled. CFS participants who complete Part I On-Line Consent and Core Questionnaires and but for some reason are not eligible to continue will be reimbursed $25.00 U.S. In addition if you remain eligible for the study and complete Part II Consent, History & Physical Exam, as well as provide blood, urine, saliva and tear samples, and optional rectal swab, you will be paid an additional $25.00 U.S.

If you have any questions, concerns, or complaints about this interview, you may contact Dr. _____ at: _____. If you want to talk to someone separate from the research team about a concern or complaint or your rights as a possible research subject, please contact the _____Institutional Review Board (IRB) at _____.

Script completed prior to Eligibility Screening Form Initials: _____
ELIGIBLE for Referral to CFI Database:

Based on the information you gave me, it looks like you may be eligible for participation in the study. If you would like to continue, you will be contacted by our Study Site Clinical Research Coordinator named, _____ at Dr. _____'s CFS Clinic _____ during business hours within the next 3 days?

Yes _____ No _____

If yes, then the Clinical Research Coordinator will give you the specifics about the study and to get you started in the process. If you have questions about this process or about the questionnaire, you may contact the Clinical Research Coordinator M-F 9:00 am – 5:00 pm EST at _____.

The Database Staff reviews the responses to the Questionnaire(s) within 24 hours of receiving them, Monday-Friday. If we have any questions or concerns about your responses we will call you by phone. Thank you for your time. Good-bye.

NOT ELIGIBLE for Referral to Biobank:
Based on the information you gave me, unfortunately it does not appear that you meet the requirements for this study.

_____ NOT ELIGIBLE

Screener: **Date:** **Subject ID Number:** **Subject Age:** **Gender: M F**

Some of these questions are about chronic fatigue, which we define as the same thing as a chronic lack of energy, or chronic feeling of tiredness. Please answer every question that applies. Use a "best guess" for dates and details you cannot remember precisely. You may skip any question you do not choose to answer.

1. When did the fatigue begin? Month_____ Year_____

2. Is the fatigue a new condition, or have you experienced similar fatigue at other times earlier in your life?

1 ☐ Yes
2 ☐ No

3. How did your fatigue **START**?

1 ☐ Gradually, no clear onset.
2 ☐ Suddenly with a "flu", cold or "virus" characterized by two or more of the following: fever, headache, muscle aches, earache, sore throat, congestion, runny nose, cough, diarrhea or fatigue.
3 ☐ Suddenly, with no other symptoms.
4 ☐ I cannot remember.

4. Which of the following statements best describes the severity of your fatigue **ON AN AVERAGE DAY** over the past months (check ONLY ONE):

1 ☐ I am bedridden and can do virtually nothing.
2 ☐ I am shut-in: I can walk around the house but cannot even do light housework or its equivalent.
3 ☐ I can work only part-time at my work or on family responsibilities.
4 ☐ I can do all the things I usually do at home or work, but I feel much more easily fatigued from them and don't do things as well as I should.
5 ☐ I can do all the things I want to do, even though I am fatigued.

5. Have you been so fatigued that you have had to reduce your average activity level below half of what was your normal level before you became ill?

1 ☐ Yes, all the time
2 ☐ Yes, some of the time
3 ☐ Yes, but rarely
4 ☐ No

6. Over the **PAST 6 MONTHS** have you had any of these symptoms **FREQUENTLY OR CONSTANTLY**:

1 ☐ Difficulty concentrating bad enough to interfere with your life.

2		Memory problems bad enough to interfere with your life.
3		Difficulty thinking bad enough to interfere with your life.
4		Difficulty finding the right word.
5		Trouble with math or numbers.
6		Unusually absent minded.
7		Need to focus on one thing at a time.
8		Trouble expressing your thoughts.
9		Difficulty understanding things.
10		Frequently lose your train of thought.
11		Very sensitive to bright lights and/or to noises.
12		Loss of depth perception in your vision.
13		Difficulty focusing your vision.
14		Palpitations of your heart.
15		Dizziness.
16		Fainting or feeling like you are about to faint.
17		Feeling unsteady on your feet.
18		Shortness of breath.
19		Cramping abdominal pains.
20		Nausea.
21		Diarrhea.
22		Constipation.
23		Difficulty controlling your urine (leakage, severe urges).
24		Difficulty starting urination.
25		Feel hot (feverish).
26		Measured fevers (temperature greater than 99.6^0 F).
27		Measured low temperature (below 97.0^0 F).
28		Cold hands and feet.
29		Sweat very easily and for no apparent reason during days.
30		Sweat during sleep, making bed clothes and sheets wet.
31		Cannot tolerate hot weather.
32		Cannot tolerate cold weather.
33		Gained weight without trying.
34		Lost weight without trying.
35		No appetite.
36		Appetite too good: cannot stop eating.
37		Unusually sensitive to odors and chemicals.
38		New sensitivities to foods.
39		Sore throat.
40		Swollen glands in your neck, under your arms or in your groin.
41		Glands are tender to the touch.
42		Aching muscles.
43		Aching, stiff or tender joints (more than one joint).
44		Joints that get red and enlarged or swollen.
45		Headaches that are new or different from past headaches.
46		Awakening unrested, difficulty falling or staying asleep.
47		Abdominal pain
48		Unusually thirsty

49 ☐ Urinating large amounts of fluid each day.

7. If you try to exercise or exert yourself even a little (check **ONE**):

1 ☐ Do you feel terrible only during exercise.
2 ☐ Do you feel terrible only after exercise.
3 ☐ Do you feel terrible both during and after exercise.
4 ☐ Do not feel terrible either during or after exercise.
5 ☐ I do not exercise.

8. If you feel bad after exertion, which of the following statements applied to you (check **ANY** that apply):

1 ☐ Only the muscles I used to exercise ache.
2 ☐ All my muscles ache.
3 ☐ My fatigue gets much worse for at least the next 24 hours.
4 ☐ I get new or worse fevers.
5 ☐ I get new or worse swelling of my lymph glands.
6 ☐ I get new or worse sore throat.
7 ☐ I get new or worse trouble thinking/concentrating.
8 ☐ I never had this reaction to exercise before I got sick.

9. Have you ever been diagnosed with any of these conditions:

1 ☐ Hypothyroidism (underactive thyroid)
2 ☐ Diabetes
3 ☐ Hepatitis
4 ☐ Lupus (systemic lupus erythematosus)
5 ☐ Multiple sclerosis
6 ☐ Rheumatoid arthritis (adult)
7 ☐ Juvenile rheumatoid arthritis (began in childhood)
8 ☐ Anorexia nervosa or bulimia
9 ☐ Dementia
10 ☐ Cancer of any type (not including basal cell or squamous skin cancer)
11 ☐ Anemia
12 ☐ Depression
13 ☐ Bipolar disorder
14 ☐ Schizophrenia
15 ☐ Alcohol or other drug abuse
16 ☐ Chronic lung disease
17 ☐ HIV/AIDS
18 ☐ Lyme disease
19 ☐ Celiac disease
20 ☐ Severe obesity
21 ☐ Sleep apnea
22 ☐ Narcolepsy

Appendix F: Core Questions

To be completed <u>prior</u> to On-Study Visit

Demographics and Lifestyle

Date Questionnaire was started: _____

1. Male_____ Female_____
2. Height_____ Weight_____
3. Body Mass Index (BMI) if known_____

4. Do you consider yourself Hispanic/Latino? _____Yes _____No

If you selected No, please go to #7. If you selected "Yes", please select the group that represents your Hispanic origin or ancestry:

_____ Puerto Rican
_____ Mexican or Mexicano
_____ Chicano
_____ Cuban American
_____ Other Latin American
_____ Do not know
_____ Refuse to answer
_____ Dominican Republic
_____ Mexican American
_____ Cuban
_____ Central or South American
_____ Other Hispanic

5. What race do you consider yourself to be?

_____ White
_____ American Indian
_____ Native Hawaiian
_____ Samoan
_____ Asian Indian
_____ Filipino
_____ Korean
_____ Other Asian
_____ Do not know
_____ Refuse to answer
_____ Black or African American
_____ Alaska Native
_____ Guamanian
_____ Other Pacific Islander
_____ Chinese
_____ Japanese
_____ Vietnamese

6. Where were you born ?

7. Has the nature of your illness changed since onset ? If yes, how has it changed ?

8. Over what time period did this change occur ? (i.e. weeks, months, years, etc.)

What are the first 3 digits of your current zip code?	
How long have you lived here?	
If you have lived here less than 1 year, what where the first three digits of your ZIP code where you lived before?	
Are you pregnant or currently lactating?	_____ Yes _____ No _____Not applicable
Have you had a baby in the past 3 months?	_____ Yes _____ No _____Not applicable
Are you now:	_____ Single _____Married _____Widowed _____ Divorced _____ Separated _____ Live in partner _____ Refuse to answer
Check the highest grade or level of school you have completed or the highest degree you have received.	_____ High School Graduate _____ GED or Equivalent _____ Some College _____College Graduate _____ Graduate Degree _____ Professional Degree _____ Refuse to answer
We would like to know what you do. Check the one that best describes your current situation.	_____ Working now _____ Temporarily laid off _____ Sick _____Maternity leave _____ Looking for work, unemployed _____ Retired _____ Disabled, permanently or temporarily _____ Keeping house _____ Student _____ Other, specify _____
If you stopped working was this because of illness ? If yes, was this due to CFS? If yes, how long ago did you stop working ?	_____ Yes _____ No _____ Other, specify _____ Yes _____ No _____ Other, specify _____ Years _____ Months
Including yourself, how many people (related or not) are living or staying at your home?	
Are you covered by health insurance or some other kind of health care plan?	_____ Yes _____ No _____ Don't know _____ Refuse to answer
What kind of health insurance or health care coverage do you have?	_____ Private health insurance _____ Medicare _____ Medi-Gap _____ Medicaid _____ SCHIP (CHIP, Children's Hlth Ins. Prog.)

	_____ Military Health Care (Tricare, VA, CHAMP) _____ Indian Health Service _____ State-sponsored health plan _____ Other government program _____ Single service plan (e.g., prescription drug) _____ No coverage of any type _____ Refuse to answer _____ Don't know
Do you drink alcoholic beverages?	_____ Yes _____ No _____ Don't know _____ Refuse to answer
How many alcoholic beverages do you drink?	_____ in a day _____ in a week
Do you now smoke cigarettes?	_____ Every day _____ Some days _____ Not at all
Did you smoke cigarettes in the past?	_____ Yes _____ No _____ Don't know _____ Refuse to answer
What kind of house do you currently live in?	_____ Detached house _____ Duplex or Triplex _____ Row house _____ Low rise apartment (1-3 floors) _____ High rise apartment (>3 floors) _____ Mobile home or trailer _____ Other
Is this property actively used as a farm or ranch?	_____ Yes _____ No _____ Don't know _____ Refuse to answer
Approximately how old is the house/building you live in (in years)?	_____ years
Is there an enclosed garage attached to this (house/apartment)?	_____ Yes _____ No _____ Don't know _____ Refuse to answer
Are automobiles, vans, trucks or other motor vehicles parked in this attached garage?	_____ Yes _____ No _____ Don't know _____ Refuse to answer
Are <u>any</u> gas powered devices stored in any room, basement, or attached garage in this (house/apartment)?	_____ Yes _____ No _____ Don't know _____ Refuse to answer
During the past 12 months, has there been water or dampness in your home from broken pipes, leaks, heavy rain, or floods?	_____ Yes _____ No _____ Don't know _____ Refuse to answer

Does your home frequently have a mildew odor or musty smell?	_____ Yes _____ No _____ Don't know _____ Refuse to answer
Is air conditioning (refrigeration) used to cool this (house/apartment)?	_____ Yes _____ No _____ Don't know _____ Refuse to answer

What is the primary fuel used for heating this (house/apartment)?	_____ Gas from underground pipes serving the neighborhood _____ Gas from bottled, tank or liquid propane _____ Electricity _____ Fuel oil, kerosene, etc. _____ Coal or coke _____ Wood _____ Solar Energy _____ Other fuel _____ No fuel used _____ Don't know
Does this (house/apartment) have a central heating system with ducts that blow air into most rooms?	_____ Yes _____ No _____ Don't know _____ Refuse to answer
In the last 12 months, did any dogs, cats or other small furry animals, such as a rabbit, guinea pig or hamster, live or spend time inside your home?	_____ Yes _____ No _____ Don't know _____ Refuse to answer
If yes, what kind of pet?	_____ Dog _____ Cat _____ Small furry animal _____ Other _____
What is the primary source of drinking water at your home?	_____ Private well _____ Community supply _____ Bottled water _____ Other
Have you EVER consumed unpasteurized dairy products (e.g., milk, cheese, goat cheese, etc.)?	_____ Yes _____ No _____ Don't know _____ Refuse to answer
Have you ever donated blood? If yes, please answer remaining questions	_____ Yes _____ No _____ Don't know _____ Refuse to answer
Have you donated blood or blood products in excess of 500 ml within the past 56 days?	_____ Yes _____ No _____ Don't know _____ Refuse to answer
How many times have you donated blood or blood products in the past 12 months?	_____ 1 time _____ 2 times _____ 3 times _____ 4 times _____ 5 times _____ more than 5 times
How many times have you donated blood or blood products in the past 10 years?	_____ 1 to 5 times _____ 6 to 10 times _____ 11 to 20 times _____ more than 20 times

Appendix G (Part A): Medical History and Labs

Medical History

1. Do you have CFS? _____ Yes _____ No

(If no and you are a healthy participant, please proceed to the next page of Past and Current Medical Conditions)

2. Did a physician or health care provider diagnose you with CFS? _____ Yes _____ No

3. Do you have documentation of a CFS diagnosis from your physician or health care provider? _____ Yes _____ No

4. Do you remember how old you were when CFS first appeared? _____ Yes _____ No

5. If yes, how old were you when CFS first appeared? _____

6. Do you remember how old you were when you were first diagnosed with CFS by a health care provider? _____ Yes _____ No

7. If yes, how old were you when you were first diagnosed with CFS by a health care provider?

_____

8. How would you describe the onset of your CFS?

_____ Less than 24 hours

_____ Over 48 hours

_____ A week

_____ A month

_____ Longer than a month

_____ Don't know

9. Select the primary factor that you believe contributed to your GETTING CFS:

_____ Infection _____ Toxic exposure _____ Vaccination _____Physical trauma

_____ Emotional trauma _____ Other (please specify) _____

10. Select the primary factor that you believe contributed to your staying ill with CFS (or becoming more ill):

_____ Infection _____ Toxic exposure _____ Vaccination _____Physical trauma

_____ Emotional trauma _____ Other (please specify) _____

11. Was your CFS linked to travel outside of the U.S.? _____ Yes _____ No

12. If yes, in what country do you think you acquired CFS? _____

13. If no, where in the U.S. do you think you acquired CFS (e.g., home, work, school, etc.)?

Past and Current Medical Conditions

		Mark "X" if Ever Diagnosed	*Mark "X" if Controlled*	*Mark "X" if Cured*
	Brain Conditions			
1	Seizure disorder or epilepsy			
2	Migraine			
3	Other headache syndrome			
4	Multiple sclerosis			
5	Neuritis			
6	Peripheral neuropathy			
7	Head injury with loss of consciousness			
8	Head injury with continuing neurologic problems			
9	Schizophrenia			
10	Depression			
11	Major depressive disorder with psychotic features			
12	Major depressive disorder with melancholic features			
13	Bipolar disorder			
14	Anxiety			
15	Post-traumatic stress disorder (PTSD)			
16	Dementia (Alzheimer's disease)			
17	Dementia (other type)			
18	Stroke			
19	Anorexia nervosa within the past 5 years			
20	Bulimia within the past 5 years			
21	Sleep apnea			
22	Narcolepsy			
23	Restless leg syndrome			
24	Periodic limb movement			
25	Myasthenia gravis			
26	Alcohol or drug abuse			
27	Hyperventilation syndrome			

28	Autonomic nervous system disease			
29	Other, specify: _____			
	Eye Conditions			
30	Require glasses (myopia or astigmatism)			
31	Glaucoma			
32	Cataracts			
33	Optic neuritis			
34	Eye infections			
35	Sjögren's syndrome			
36	Dry eye			
37	Other, specify: _____			
	Ear, Nose, Throat Conditions			
38	Chronic sinusitis			
39	Chronic rhinitis (runny nose)			
40	Impaired hearing			
41	Easy nasal bleeding			
42	Nasal allergies			
43	Tonsillectomy			
44	Hay fever			
45	Other, specify: _____			
	Heart Conditions			
46	Heart murmur			
47	Angina			
48	High blood pressure			
49	Disease of arteries or veins in arms/legs			
50	Heart attack			

51	Heart failure			
52	Heart block			
53	Postural orthostatic tachycardia syndrome (POTS)			
54	Neurally mediated hypotension (NMH)			
55	Atrial fibrillation or flutter			
56	Ventricular arrhythmia			
57	Cardiomyopathy			
58	Other, specify:_____			
	Lung Conditions			
59	Pneumonia, ever			
60	Pneumonia in the past 3 months			
61	Pleurisy			
62	Asthma (as a child)			
63	Asthma (as an adult)			
64	Bronchitis			
65	Emphysema			
66	Chronic obstructive lung disease (COPD or COLD)			
67	Chronic restrictive lung disease			
68	Silicosis			
69	Asbestosis			
70	Other, specify: _____			
	Gut Conditions			
71	Peptic ulcer			
72	Hiatus hernia			
73	Hepatitis, type unspecified			
74	Hepatitis A			
75	Hepatitis B			

76	Hepatitis C			
77	Gall bladder disease			
78	Liver disease			
79	Cirrhosis			
80	Pancreatitis			
81	Chronic pancreatitis			
82	Celiac disease			
83	Irritable bowel syndrome			
84	Crohn's disease			
85	Ulcerative colitis			
86	Other, specify: _____			
	Kidney/Bladder Conditions			
87	Nephritis			
88	Kidney disease			
89	Chronic renal (kidney) failure			
90	Repeated urinary infection			
91	Kidney/bladder stones			
92	Vasectomy			
93	Blood or protein in the urine			
94	Venereal disease: Type _____			
95	Son or daughter of mother on DES *(diethylstilbestrol - synthetic estrogen)*			
96	Yeast infections of vagina			
97	Dysuria (painful urination)			
98	Interstitial cystitis			
99	Other, specify:_____			
	Skin Conditions			
100	Hives			

101	Psoriasis			
102	Eczema			
103	Contact dermatitis			
104	Dermatomyositis			
105	Vasculitis			
106	Other allergic skin reactions			
107	Other, specify: _____			
	Blood and Immune System Conditions			
108	Anemia			
109	Sickle cell disease			
110	Thalassemia			
111	Hemochromatosis			
112	Myeloproliferative disorders (myelodysplasia)			
113	Other, specify: _____			
	Bone, Joint and Muscle Conditions			
114	Rheumatoid arthritis			
115	Juvenile rheumatoid arthritis			
116	Other arthritis			
117	Fibromyalgia			
118	Reiter's syndrome			
119	Temporomandibular joint syndrome (TMJ)			
120	Lupus (systemic lupus erythematosus)			
121	Back injury			
122	Low back pain			
123	Neck pain/injury			
124	Degenerative disc disease			
125	Muscular dystrophy			
126	Sciatica/disc herniation			

127	Bone lesion/ infections			
128	History of broken bones			
129	Other, specify: _____			
	Hormone/Metabolic Conditions			
130	Hypothyroidism (underactive thyroid)			
131	Hyperthyroidism (overactive thyroid)			
132	Thyroiditis			
133	Adrenal insufficiency (Addison's disease)			
134	Cushing syndrome			
135	Hyperparathyroidism			
136	Hypopituitarism (panhypopituitarism)			
137	Diabetes (diabetes mellitus)			
138	Diabetes insipidus			
139	Ovarian failure			
140	Abnormal blood sodium levels			
141	Abnormal blood potassium levels			
142	Abnormal blood magnesium levels			
143	Abnormal blood calcium levels			
144	Abnormal blood phosphate levels			
	Infections			
145	Mononucleosis			
146	Lyme disease			
147	HIV/AIDS			
148	Fungal disease (not including fungus skin infection)			
149	Chronic parasitic infection			
150	Tuberculosis			
151	Syphilis			
152	Subacute bacterial endocarditis			

153	Sepsis, ever			
154	Sepsis in the past 3 months			
155	Osteomyelitis			
	Cancers			
156	Lung			
157	Esophagus			
158	Stomach			
159	Liver			
160	Pancreas			
161	Colon and Rectum			
162	Prostate			
163	Ovarian			
164	Uterine			
165	Cervical			
166	Leukemia			
167	Lymphoma			
168	Melanoma			
169	Other type of cancer: _____			
	Miscellaneous			
170	Multiple chemical sensitivities (MCS)			
171	Sarcoidosis			
172	Wegener granulomatosis			
173	Severe obesity			

Current Medication Use

It is important that we record the types of medications you take so that research investigators can control for the effect of medications on the research they conduct. For example, samples from patients taking prednisone could not be used in an immune function study. Check any of the medications you are currently taking and rate the effect this medication has for you by circling: 1 = significant improvement, 2 = some improvement, 3 = no change, 4 = somewhat worse, 5 = significantly worse.

Central Nervous System: Anti-anxiety	**Effect**	**consistently** or **as needed**
___alprazolam (Xanax)	1 2 3 4 5	
___chlordiazepoxide (Librium)	1 2 3 4 5	
___diazepam (Valium)	1 2 3 4 5	
___lorazepam (Ativan)	1 2 3 4 5	
___meprobamate with aspirin (Equagesic)	1 2 3 4 5	
___Other, specify_____	1 2 3 4 5	
Central Nervous System: Anti-depressant		
___amitriptyline (Elavil, Endep)	1 2 3 4 5	
___bupropion (Wellbutrin, Wellbutrin SR)	1 2 3 4 5	
___citalopram (Celexa)	1 2 3 4 5	
___desipramine (Norpramin)	1 2 3 4 5	
___doxepin (Sinequan)	1 2 3 4 5	
___fluoxetine (Prozac, Prozac Weekly, Sarafem)	1 2 3 4 5	
___imipramine (Norfranil, Tipramine, Tofranil)	1 2 3 4 5	
___nortriptyline (Pamelor)	1 2 3 4 5	
___paroxetine (Paxil, Paxil CR)	1 2 3 4 5	
___sertraline (Zoloft)	1 2 3 4 5	
___venlafaxine (Effexor, Effexor XR)	1 2 3 4 5	
___Other, specify_____	1 2 3 4 5	
Central Nervous System: Anti-seizure		
___carbamazepine (Atretol, Carbatrol, Epitol,	1 2 3 4 5	
Tegretol, Tegretol-XR)	1 2 3 4 5	
___clonazepam (Klonopin, Rivotril)	1 2 3 4 5	
___gabapentin (Neurontin)	1 2 3 4 5	
___oxcarbazepine (Trileptal)	1 2 3 4 5	
___phenytoin (Dilantin – any kind)	1 2 3 4 5	
___Other, specify_____	1 2 3 4 5	
Central Nervous System: Miscellaneous		
___chlorpromazine (Thorazine)	1 2 3 4 5	
___fluvoxamine maleate (Luvox)	1 2 3 4 5	
___pimozide (Orap)	1 2 3 4 5	
___zolpidem tartrate (Ambien)	1 2 3 4 5	
___Other, specify_____	1 2 3 4 5	

Cardiovascular System:	**Effect**	**consistently** or **as needed**
___atenolol (Tenormin)	1 2 3 4 5	
___clopidogrel bisulfate (Plavix)	1 2 3 4 5	
___digoxin (Digitek, Digoxin, Lanoxicaps,	1 2 3 4 5	
Lanoxin)	1 2 3 4 5	
___lidocaine (Xylocaine)	1 2 3 4 5	
___pravastatin sodium (Pravachol)	1 2 3 4 5	
___propranolol (Inderal, Inderal LA)	1 2 3 4 5	
___quinapril (Accupril)	1 2 3 4 5	
___timolol maleate (Blocadren)	1 2 3 4 5	
___Other, specify_____	1 2 3 4 5	

Cholesterol-lowering drugs	
___atorvastatin (Lipitor)	1 2 3 4 5
___fluvastatin (Lescol)	1 2 3 4 5
___lovastatin (Mevacor, Altoprev)	1 2 3 4 5
___pravastatin (Pravachol)	1 2 3 4 5
___rosuvastatin calcium (Crestor)	1 2 3 4 5
___simvastatin (Zocor)	1 2 3 4 5
___combination statins (Advicor, Vytorin)	1 2 3 4 5
___ezetimibe (Zetia)	1 2 3 4 5
___cholestyramine (Questran, Questran Light,	1 2 3 4 5
Prevalite, Locholest, Locholest Light)	1 2 3 4 5
___colestipol (Colestid)	1 2 3 4 5
___colesevelam hcl (WelChol)	1 2 3 4 5
___gemfibrozil (Lopid)	1 2 3 4 5
___fenofibrate (Antara, Lofibra, Tricor, and	1 2 3 4 5
Triglide)	1 2 3 4 5
___clofibrate (Atromid-S)	1 2 3 4 5
___Other cholesterol lowering medications	1 2 3 4 5

Gastrointestinal System (GI):	
___loperamide (Imodium)	1 2 3 4 5
___Meclizine(Antivert)	1 2 3 4 5
___Misoprostol (Cytotec)	1 2 3 4 5
___Rabeprazol sodium (Aciphex)	1 2 3 4 5
___ranitidine (Zantac)	1 2 3 4 5
___Other, specify_____	1 2 3 4 5

Non-steroidal Anti-inflammatory Drugs:	
___celecoxib (Celebrex)	1 2 3 4 5
___etodolac (Lodine, Lodine XL)	1 2 3 4 5
___ibuprofen (Advil, Excedrin IB, Motrin)	1 2 3 4 5
___indomethacin (Indocin, Indocin SR)	1 2 3 4 5
___naproxen (Aleve, Anaprox, Naprosyn)	1 2 3 4 5
___rofecoxib (Vioxx)	1 2 3 4 5
___Other, specify_____	1 2 3 4 5

Non-narcotic Pain Relievers:	**Effect**	**consistently** or **as needed**
___acetaminophen (Tylenol, Tylenol Extra	1 2 3 4 5	
Strength)	1 2 3 4 5	
___aspirin (any brand such as Bayer, Ecotrin,	1 2 3 4 5	
Empirin, etc.)	1 2 3 4 5	
___Excedrin (any kind except Excedrin IB)	1 2 3 4 5	
___Fioricet	1 2 3 4 5	
___Fiorinal	1 2 3 4 5	
___Other, specify_____	1 2 3 4 5	

Narcotic & Opioid Pain Relievers:	
___butorphanol tartrate (Stadol, Stadol NS)	1 2 3 4 5
___codeine	1 2 3 4 5
___Darvocet	1 2 3 4 5
___Duragesic	1 2 3 4 5
___Fioricet with codeine	1 2 3 4 5
___Fiorinal with codeine	1 2 3 4 5
___methadone (Dolophine, Methadose)	1 2 3 4 5
___morphine (any kind including MS Contin)	1 2 3 4 5
___oxycodone (OxyContin)	1 2 3 4 5
___Percocet	1 2 3 4 5
___Percodan	1 2 3 4 5
___tramadol (Ultram)	1 2 3 4 5
___Vicodin	1 2 3 4 5
___Other, specify_____	1 2 3 4 5

Skeletal Muscle Relaxants:	
___baclofen (Lioresal)	1 2 3 4 5
___carisoprodol(Soma)	1 2 3 4 5
___cyclobenzaprine (Flexeril)	1 2 3 4 5
___methocarbamol (Robaxin)	1 2 3 4 5
___Other, specify	1 2 3 4 5

Hormonal Drugs:	
___cortisone	1 2 3 4 5
___estrogen (Climara, Premarin)	1 2 3 4 5
___levothyroxine (Levothroid, Levoxine,	1 2 3 4 5
Levoxyl, Synthroid)	1 2 3 4 5
___prednisone	1 2 3 4 5
___Other, specify	1 2 3 4 5

Antimicrobial drugs	
___antibiotics (penicillin, doxycyclin, etc.)	1 2 3 4 5
___antivirals (Acyclovir, Valcyte, Valtrex, etc.)	1 2 3 4 5
___amantidine (Symadine, Symmetrel)	1 2 3 4 5

Miscellaneous Drugs:	**Effect**	**consistently** or **as needed**
___Beconase	1 2 3 4 5	
___Enbrel	1 2 3 4 5	
___Fosamax	1 2 3 4 5	
___pseudoephedrine (Sudafed)	1 2 3 4 5	
___Singulair	1 2 3 4 5	
___sumatriptan succinate (Imitrex)	1 2 3 4 5	
___Other, specify_____	1 2 3 4 5	

List any over the counter (OTC) medication not noted:

OTC 1_____	1 2 3 4 5
OTC 2_____	1 2 3 4 5
OTC 3_____	1 2 3 4 5
OTC 4_____	1 2 3 4 5
OTC 5_____	1 2 3 4 5
OTC 6_____	1 2 3 4 5
OTC 7_____	1 2 3 4 5

List any supplements you may be taking (dietary, herbal, etc.):

Supplement 1_____	1 2 3 4 5
Supplement 2_____	1 2 3 4 5
Supplement 3_____	1 2 3 4 5
Supplement 4_____	1 2 3 4 5
Supplement 5_____	1 2 3 4 5
Supplement 6_____	1 2 3 4 5
Supplement 7_____	1 2 3 4 5

1. What medications, herbs, supplements have helped you and why ? (list all)

2. What medications, herbs, supplements have hurt you and why ? (list all)

Family Health History

Participant ID: _____

1. What is your immediate family size (you, your spouse, your children OR your parents and siblings) ?

2. What is your extended family size (aunts, uncles, cousins, grandparents, nieces, and nephews)?

3. How many siblings do you have?

4. Are you a twin? Yes No

5. Are you adopted Yes No

Continue to next page and please complete the following questions about your family health history for BLOOD RELATIVES

Your Family Health History		you	spouse	son	daughter	sister	brother	mother	father	mgmother	mgfather	pgmother	pgfather
Cancer													
	bone												
	breast												
	colon												
	esophageal												
	gastric												
	kidney												
	leukemia												
	lung												
	ovarian												
	prostate												
	skin												
	thyroid												
	uterine												
	other												
GI (gastrointestinal) Disorders													
	colon polyp												
	Crohn's disease												
	IBS												
	ulcerative colitis												
	other												
Urologic Disorders													
	Dysuria (painful urination)												
	Interstitial cystitis (painful bladder)												
	other												
Diabetes													
	Type 1 diabetes												
	Type 2 diabetes												
	gestational diabetes												
	diabetes												
Heart													
	heart disease												
	heart attack												
	hypertension												
	high cholesterol												
	Postural orthostactic tachycardia syndrome (POTS)												
	Neurally mediated hypotension (NMH)												
	Vasovagal syncope (fainting)												
	Palpitations												
Clotting disorder													
	deep vein thrombosis												
	pulmonary embolism												
	clotting disorder												
Lung													
	asthma												
	chronic bronchitis												
	chronic lower respiratory disease												
	COPD												
	emphysema												
	influenza												
	pneuomnia												
Kidney disease													
	cystic kidney disease												
	diabetic kidney disease												
	nephritis												
	kidney nephrosis												
	nephotic syndrome												
	unknown kidney disease												
	kidney disease from birth												
	other kidney disease												
Psychological disorders													
	anxiety												
	attention deficit disorder												
	autism												
	biopolar disorder												
	dementia												
	depression												
	eating disorder												
	obsessive complusive disorder												
	panic disorder												
	personality disorder												
	post traumatic stress disorder												
	schizophrenia												
	social phobia												
	mental disorder												
Pain Disorders													
	Tension headaches												
	Migraine												
	Fibromyalgia (FM or FMS)												
	Temporo-mandibular joint disorder (TMJ)												
	Chronic pelvic pain												
	Vulvodynia (painful vaginal area)												
Other													
	septecemia												
	stroke												
	osteoporosis												
	Chronic fatigue syndrome (CFS)												
	Multiple chemical sensitivities (MCS)												
	Chronic rhinitis (constant runny nose)												

Pittsburg Sleep Questionnaire

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,
1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. When have you usually gotten up in the morning? _____
4. How many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed) _____

5. During the past month, how often have you had trouble sleeping because you …	Not during the past month	Less than once a week	Once or twice a week	There or more times a week
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
6. During the past month, how often have you taken medicine (prescribed or “over the counter”) to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
	Very good	Fairly good	Fairly bad	Very bad
9. During the past month, how would you rate your sleep quality overall?				

Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s):

_____

Date Questionnaires were completed: _____

Appendix G (Part B): Medical Hx and Labs – Chart Review & Meds

Note: **Red Text = Required data**, **Green text = If Available**, "Y/N" = YES or No. If you have this information in the record please scan and retain a copy of the initial and most current version. **Black Text** = Remove the patients name, add study identifier number, scan and upload specific forms on REDCap or send pdf via email to: cfinitiativemiami@gmail.com

Medical Record Abstraction Process: Chart Review

How many years of chart review? _____

Number of visits? ____

Chart Review-ROS for most recent and ROS for patient first visit

Review Of Systems:	Description (text)	Last date
Constitutional		
Head and Neck		
Respiratory		
Cardiovascular		
Gastrointestinal		
Genitourinary		
Skin		
Musculoskeletal		
Hematology		
Neurology		
Psychology		
Other		

Physical Exam Date of most current: _____	Normal/ Abnormal	Last date
General		
Vitals:		
HEENT		
Nodes		
Lungs		
Heart		
Abdomen		
Extremities		
Neurological exam		
Affect		
Skin		
tender points (specify how many number: 0 -18)		
lymph node exam		
Other		

Go through with patient

MEDICATION	EVER TRIED?	DATE STARTED
Antibiotic	Y/N	MM/DD/YYYY
Anti-Viral		
Acyclovir	Y/N	MM/DD/YYYY
Amantadine	Y/N	MM/DD/YYYY
Alferon N Injection, *Interferon alfa-n3*	Y/N	MM/DD/YYYY
Cytovene, *Ganciclovir*	Y/N	MM/DD/YYYY
Epzicom, *Abacavir Lamivudine*	Y/N	MM/DD/YYYY
Famvir, *Famciclovir*	Y/N	MM/DD/YYYY
Flumadine, *Rimantadine*	Y/N	MM/DD/YYYY
Hepsera, *Adefovir Dipivoxil*	Y/N	MM/DD/YYYY
Infergen, *Interferon alfa-n3*	Y/N	MM/DD/YYYY
Intron, *Interferon alfa-2b*	Y/N	MM/DD/YYYY
Norvir, *Ritonavir*	Y/N	MM/DD/YYYY
PegIntron, *Peginterferon alfa-2b*	Y/N	MM/DD/YYYY
Rebetol, *Ribavirin*	Y/N	MM/DD/YYYY
Rebetron, *Rebetol, Intron A*	Y/N	MM/DD/YYYY
Relenza Rotadisk, *Zanamivir*	Y/N	MM/DD/YYYY
Rescriptor, *Delavirdine Mesylate*	Y/N	MM/DD/YYYY
Symmetrel, *Amantidine*	Y/N	MM/DD/YYYY
Tamiflu, *Oseltavimir*	Y/N	MM/DD/YYYY
Tyzeka, *Telbivudine*	Y/N	MM/DD/YYYY
Valcyte, *Valganciclovir HCL*	Y/N	MM/DD/YYYY
Valtrex, *Valacyclovir*	Y/N	MM/DD/YYYY
Virazole, *Ribavirin*	Y/N	MM/DD/YYYY
Ziagen, *Abacavir Sulfate*	Y/N	MM/DD/YYYY
Zovirax, *Acyclovir*	Y/N	MM/DD/YYYY
Anti-retroviral	Y/N	MM/DD/YYYY
Immunosuppressant		
Gengraf, *Cyclosporine*	Y/N	MM/DD/YYYY
Myfortic, *Mycophenolic Acid*	Y/N	
Neoral, *Cyclosporine*	Y/N	MM/DD/YYYY
Orthoclone, *Muromonab-CD3*	Y/N	MM/DD/YYYY
Prograf, *Tacrolimus*	Y/N	MM/DD/YYYY
Papamune, *Sirolimus*	Y/N	MM/DD/YYYY
Sandimmune, *Cyclosporine*	Y/N	MM/DD/YYYY
Simulect, *Basiliximab*	Y/N	MM/DD/YYYY

Thymoglobulin, *Anti-thymocyte Globulin (Rabbit)*	Y/N	MM/DD/YYYY

Central Nervous System: Anti-anxiety Effect

alprazolam (Xanax)	Y/N	MM/DD/YYYY
chlordiazepoxide (Librium)		Y/N
diazepam (Valium)	Y/N	MM/DD/YYYY
lorazepam (Ativan)	Y/N	MM/DD/YYYY
meprobamate aspirin (Equagesic)	Y/N	MM/DD/YYYY
Other, specify_____	Y/N	MM/DD/YYYY

Central Nervous System: Anti-depressant

amitriptyline (Elavil, Endep)	Y/N	MM/DD/YYYY
bupropion (Wellbutrin, Wellbutrin SR)		Y/N
citalopram (Celexa)	Y/N	MM/DD/YYYY
desipramine (Norpramin)	Y/N	MM/DD/YYYY
Duloxetine (Cymbalta)	Y/N	MM/DD/YYYY
doxepin (Sinequan)	Y/N	MM/DD/YYYY
fluoxetine (Prozac, Prozac Weekly, Sarafem)	Y/N	MM/DD/YYYY
imipramine (Norfranil, Tipramine, Tofranil)	Y/N	MM/DD/YYYY
nortriptyline (Pamelor)	Y/N	MM/DD/YYYY
paroxetine (Paxil, Paxil CR)	Y/N	MM/DD/YYYY
sertraline (Zoloft)	Y/N	MM/DD/YYYY
venlafaxine (Effexor, Effexor XR)	Y/N	MM/DD/YYYY
Other, specify_____	Y/N	MM/DD/YYYY

Central Nervous System: Anti-seizure

carbamazepine (Atretol, Carbatrol, Epitol, Tegretol, Tegretol-XR)	Y/N	MM/DD/YYYY
clonazepam (Klonopin,Rivotril)		Y/N
gabapentin (Neurontin)	Y/N	MM/DD/YYYY
oxcarbazepine (Trileptal)	Y/N	MM/DD/YYYY
phenytoin (Dilantin – any kind)	Y/N	MM/DD/YYYY
Other, specify _____	Y/N	MM/DD/YYYY

Central Nervous System: Miscellaneous

chlorpromazine (Thorazine)	Y/N	MM/DD/YYYY
Divalproex (Depakote)		Y/N
fluvoxamine maleate (Luvox)	Y/N	MM/DD/YYYY
Hydergine	Y/N	MM/DD/YYYY
Lamotrigine (Lamictal)	Y/N	MM/DD/YYYY
Levetiracetam (Keppra)	Y/N	MM/DD/YYYY
Naltrexone	Y/N	MM/DD/YYYY
Phenobarbital	Y/N	MM/DD/YYYY
pimozide (Orap)	Y/N	MM/DD/YYYY
Pregabalin (Lyrica)	Y/N	MM/DD/YYYY
Primidone (Mysoline)	Y/N	MM/DD/YYYY
Tiagabine (Gabitril)	Y/N	MM/DD/YYYY

Topiramate (Topamax)	Y/N	MM/DD/YYYY
Trazodone (Deseryl)	Y/N	MM/DD/YYYY
Valproate (Depacon)	Y/N	MM/DD/YYYY
Valproic Acid (Depakene)	Y/N	MM/DD/YYYY
zolpidem tartrate (Ambien)	Y/N	MM/DD/YYYY
Zonisamide (Zonegram)	Y/N	MM/DD/YYYY
Other, specify_____	Y/N	MM/DD/YYYY

Cardiovascular System:

atenolol (Tenormin)	Y/N	MM/DD/YYYY
clopidogrel bisulfate (Plavix)		
digoxin (Digitek, Digoxin, Lanoxicaps, Lanoxin)	Y/N	MM/DD/YYYY
lidocaine (Xylocaine)	Y/N	MM/DD/YYYY
Pentoxifylline (Trental)	Y/N	MM/DD/YYYY
pravastatin sodium (Pravachol)	Y/N	MM/DD/YYYY
propranolol (Inderal, Inderal LA)	Y/N	MM/DD/YYYY
quinapril (Accupril)	Y/N	MM/DD/YYYY
timolol maleate (Blocadren)	Y/N	MM/DD/YYYY
Other, specify_____	Y/N	MM/DD/YYYY

Cardiovascular System: Statins

Atorvastatin (Lipitor ®)	Y/N	MM/DD/YYYY
Fluvastatin (Lescol ®)		Y/N
Lovastatin (Mevacor ®)	Y/N	MM/DD/YYYY
Pravastatin (Pravachol ®)	Y/N	MM/DD/YYYY
Rosuvastatin (Crestor ®)	Y/N	MM/DD/YYYY
Simvastatin (Zocor ®)	Y/N	MM/DD/YYYY
Advicor ® (lovastatin + niacin SR)	Y/N	MM/DD/YYYY
Vytorin ® (simvastatin +ezetimibe)	Y/N	MM/DD/YYYY
ezetimibe (Zetia ®)	Y/N	MM/DD/YYYY
Niacin (Vitamin B3)	Y/N	MM/DD/YYYY

Cardiovascular System: Ant- hypertension

Ace Inhibitors

Benazepril (Lotensin ®)		Y/N
Captopril (Capoten ®)	Y/N	
Enalapril (Vasotec ®)	Y/N	MM/DD/YYYY
Fosinopril (Monopril ®)	Y/N	MM/DD/YYYY
Lisinopril (Prinivil ®, Zestril®)	Y/N	MM/DD/YYYY
Moexipril (Univasc ®)	Y/N	MM/DD/YYYY
Perindopril (Aceon ®)	Y/N	MM/DD/YYYY
Quinapril (Accupril ®)	Y/N	MM/DD/YYYY
Ramipril (Altace ®)	Y/N	MM/DD/YYYY
Trandolapril (Mavik ®)	Y/N	MM/DD/YYYY

Angiotensin II inhibitors

candesartan (Atacand ®)	Y/N	MM/DD/YYYY
eprosartan mesylate (Teveten®)	Y/N	
irbesartan (Avapro ®)	Y/N	MM/DD/YYYY
losartan (Cozaar ®)	Y/N	MM/DD/YYYY
olmesartan (Benicar ®)	Y/N	MM/DD/YYYY
telmisartin (Micardis ®)	Y/N	MM/DD/YYYY
valsartan (Diovan ®)	Y/N	MM/DD/YYYY

Beta Blockers

atenolol (Tenormin ®)	Y/N	MM/DD/YYYY
betaxolol (Kerlone ®)	Y/N	MM/DD/YYYY
bisoprolol (Zebeta ®)	Y/N	MM/DD/YYYY
carvedilol (Coreg ®, Coreg CR™)	Y/N	MM/DD/YYYY
esmolol (Brevibloc ®)	Y/N	MM/DD/YYYY
labetalol (Normodyne ®)	Y/N	MM/DD/YYYY
metoprolol (Lopressor ®)	Y/N	MM/DD/YYYY
nadolol (Corgard ®)	Y/N	MM/DD/YYYY
pindolol (Visken ®)	Y/N	MM/DD/YYYY
propranolol (Inderal ®)	Y/N	MM/DD/YYYY
sotalol (Betapace ®)	Y/N	MM/DD/YYYY
timolol (Blocadren ®)	Y/N	MM/DD/YYYY

Calcium Channel Blockers

amlodipine (Norvasc®):	Y/N	MM/DD/YYYY
bepridil (Vascor®):	Y/N	
diltiazem (Cardizem ®):	Y/N	MM/DD/YYYY
felodipine (Plendil®):	Y/N	MM/DD/YYYY
isradipine (Dynacirc®):	Y/N	MM/DD/YYYY
nicardipine (cardene®):	Y/N	MM/DD/YYYY
nifedipine (Procardia®):	Y/N	MM/DD/YYYY
nisoldipine (Sular®):	Y/N	MM/DD/YYYY
verapamil (Isoptin ®)	Y/N	MM/DD/YYYY

Gastrointestinal System (GI):

Cimetidine Tagamet)	Y/N	MM/DD/YYYY
loperamide (Imodium)	Y/N	
Meclizine(Antivert)	Y/N	MM/DD/YYYY
Misoprostol (Cytotec)	Y/N	MM/DD/YYYY
Rabeprazol sodium (Aciphex)	Y/N	MM/DD/YYYY
ranitidine (Zantac)	Y/N	MM/DD/YYYY
Other, specify_____	Y/N	MM/DD/YYYY

Non-steroidal Anti-inflammatory Drugs:

celecoxib (Celebrex)	Y/N	MM/DD/YYYY
etodolac (Lodine, Lodine XL)	Y/N	MM/DD/YYYY
ibuprofen (Advil, Excedrin IB, Motrin)	Y/N	MM/DD/YYYY
indomethacin (Indocin, Indocin SR)	Y/N	MM/DD/YYYY
Ketorolac (Toradol)	Y/N	MM/DD/YYYY
naproxen (Aleve, Anaprox, Naprosyn)	Y/N	MM/DD/YYYY
rofecoxib (Vioxx)	Y/N	MM/DD/YYYY
Other, specify_____	Y/N	MM/DD/YYYY

Non-narcotic Pain Relievers:

acetaminophen (Tylenol, etc.)	Y/N	MM/DD/YYYY
aspirin (any brand such as Bayer, Ecotrin, Empirin)	Y/N	MM/DD/YYYY
Excedrin (any kind except ExcedrinIB)	Y/N	MM/DD/YYYY
Fioricet	Y/N	MM/DD/YYYY
Fiorinal	Y/N	MM/DD/YYYY
Other, specify_____	Y/N	MM/DD/YYYY

Narcotic & Opioid Pain Relievers:

butorphanol tartrate (Stadol, Stadol NS)	Y/N	MM/DD/YYYY
Codeine	Y/N	MM/DD/YYYY
Darvocet	Y/N	MM/DD/YYYY
Duragesic	Y/N	MM/DD/YYYY
Fioricet with codeine	Y/N	MM/DD/YYYY
Fiorinal with codeine	Y/N	MM/DD/YYYY
methadone (Dolophine, Methadose)	Y/N	MM/DD/YYYY
morphine (any kind including MS Contin)	Y/N	MM/DD/YYYY
oxycodone (OxyContin)	Y/N	MM/DD/YYYY
Percocet	Y/N	MM/DD/YYYY
Percodan	Y/N	MM/DD/YYYY
tramadol (Ultram)	Y/N	MM/DD/YYYY
Vicodin	Y/N	MM/DD/YYYY
Other, specify_____	Y/N	MM/DD/YYYY

Skeletal Muscle Relaxants:

baclofen (Lioresal)	Y/N	MM/DD/YYYY
carisoprodol(Soma)	Y/N	MM/DD/YYYY
cyclobenzaprine (Flexeril)	Y/N	MM/DD/YYYY
methocarbamol (Robaxin)	Y/N	MM/DD/YYYY
Other, specify_____	Y/N	MM/DD/YYYY

Hormonal Drugs:

Cortisone	Y/N	MM/DD/YYYY
estrogen (Climara, Premarin)	Y/N	MM/DD/YYYY
Fludrocortisone (Florinef)	Y/N	MM/DD/YYYY
levothyroxine (Levothroid, Levoxine,Levoxyl, Synthroid)	Y/N	MM/DD/YYYY
Prednisone	Y/N	MM/DD/YYYY
Other, specify_____	Y/N	MM/DD/YYYY

Miscellaneous Drugs:

Beconase	Y/N	MM/DD/YYYY
Enbrel		
Fosamax	Y/N	MM/DD/YYYY
Marijuana	Y/N	MM/DD/YYYY
pseudoephedrine (Sudafed)	Y/N	MM/DD/YYYY
Singulair	Y/N	MM/DD/YYYY
sumatriptan succinate (Imitrex)	Y/N	MM/DD/YYYY
Other, specify: _____	Y/N	MM/DD/YYYY

OTHER MEDS

Chinese Herbs

OTHER THERAPIES (PT, OT, Pscyh, etc.)

MM/DD/YYYY	MM/DD/YYYY

LABS

Note: Chem 23 must be completed within 6 weeks as per study protocol. Blood can be drawn and shipped within the same day. Required: CBC, Chem 23

Chemistry	Units	Numerical Result	Flag
BUN			Hi/Lo/Normal
Creatinine			Hi/Lo/Normal
Sodium			Hi/Lo/Normal
Potassium			Hi/Lo/Normal
Chloride			Hi/Lo/Normal
CO2			Hi/Lo/Normal
GFR			Hi/Lo/Normal
Cholesterol (Total) (fasting)			Hi/Lo/Normal
Cholesterol, LDL (fasting)			Hi/Lo/Normal
Cholesterol, HDL (fasting)			Hi/Lo/Normal
Triglycerides			Hi/Lo/Normal

AST/SGOT			Hi/Lo/Normal
ALT/SGPT			Hi/Lo/Normal
Bili Total			Hi/Lo/Normal
Bili Direct			Hi/Lo/Normal
Alk Phos			Hi/Lo/Normal
Albumin			Hi/Lo/Normal
LDH			Hi/Lo/Normal
Vit B-12			Hi/Lo/Normal
25-OH Vitamin D			Hi/Lo/Normal
Histamine			Hi/Lo/Normal
Angiot Conv Enzyme			Hi/Lo/Normal
Uric Acid			Hi/Lo/Normal
CPK			

Immunology	Units	Numerical Result	Flag
ANA			Hi/Lo/Normal
RF Titer			Hi/Lo/Normal
CH50			Hi/Lo/Normal
IgG			Hi/Lo/Normal
IgA			Hi/Lo/Normal
IgM			Hi/Lo/Normal
IgD			Hi/Lo/Normal
IgE			Hi/Lo/Normal
IgG 1 Subset			Hi/Lo/Normal
IgG 2 Subset			Hi/Lo/Normal
IgG 3 Subset			Hi/Lo/Normal
IgG 4 Subset			Hi/Lo/Normal
ImM Complexes RL			Hi/Lo/Normal
IL-2 Level			Hi/Lo/Normal
IL-2 Receptor			Hi/Lo/Normal
SPEP			Hi/Lo/Normal
ImM New Assay			Hi/Lo/Normal
PHA Stim			Hi/Lo/Normal
Precipitins			Hi/Lo/Normal
Anti-DNA			Hi/Lo/Normal
Con-A Stim			Hi/Lo/Normal

Hematology	Units	Numerical Result	Flag
Total count			Hi/Lo/Normal
WBC			Hi/Lo/Normal
RBC			Hi/Lo/Normal
HGB			Hi/Lo/Normal
HCT			Hi/Lo/Normal
SED RATE			Hi/Lo/Normal
MCV			Hi/Lo/Normal
MCH			Hi/Lo/Normal
MCHC			Hi/Lo/Normal
RDW			Hi/Lo/Normal
PLT			Hi/Lo/Normal
LYMP %			Hi/Lo/Normal
MONO %			Hi/Lo/Normal
NEUT %			Hi/Lo/Normal
EOS %			Hi/Lo/Normal
BASO %			Hi/Lo/Normal

LYMP #			Hi/Lo/Normal
MONO #			Hi/Lo/Normal
NEUT #			Hi/Lo/Normal
EOS #			Hi/Lo/Normal
BASO #			Hi/Lo/Normal
POLY % (manual diff)			Hi/Lo/Normal
BAND % (manual diff)			Hi/Lo/Normal
LYMP % (manual diff)			Hi/Lo/Normal
MONO % (manual diff)			Hi/Lo/Normal
NEUT % (manual diff)			Hi/Lo/Normal
EOS % (manual diff)			Hi/Lo/Normal
BASO % (manual diff)			Hi/Lo/Normal
ATYP % (manual diff)			Hi/Lo/Normal
PLT EST			Hi/Lo/Normal
FISS LYMPH			Hi/Lo/Normal
POLYCHRO			Hi/Lo/Normal
ANISOCYT			Hi/Lo/Normal

Special Hematology : Include most recent report (upload on REDCap or send pdf).

Flow Cytometry **completed ? Yes No**

NK Cell Function

1. **Lymphocyte Function**
2. **RNAse – L**
3. **Perforin Granzyme Quantification**
4. **Other**
5. **Endocrine**
6. **TSH**

	Units	Numerical Result	
T4			Hi/Lo/Normal
TBG			Hi/Lo/Normal
T3			Hi/Lo/Normal
T3 Up			Hi/Lo/Normal
RT3			Hi/Lo/Normal
FTI			Hi/Lo/Normal
Peroxidase-TPO			Hi/Lo/Normal
ATA			Hi/Lo/Normal
AMA			Hi/Lo/Normal
DHEA			Hi/Lo/Normal
DHEA-S			Hi/Lo/Normal
AM Cortisol			Hi/Lo/Normal
TTG, IgA, IgG			Hi/Lo/Normal
Gliadin			Hi/Lo/Normal

Infectious Disease *most recent upload REDCap or send pdf

	Result	Flag
EBV IgG		Hi/Lo/Normal
EBV IgM		Hi/Lo/Normal
EBV EA		Hi/Lo/Normal
EBV EBNA		Hi/Lo/Normal
Heterophile		Hi/Lo/Normal
Monospot		Hi/Lo/Normal
EBV EA Diffuse		Hi/Lo/Normal
EBV EA Restricted		Hi/Lo/Normal

EBV ELISA		Hi/Lo/Normal
CMV IgG* (*CMV can be IgG, IgM or ELISA)		Hi/Lo/Normal
CMV IgM*		Hi/Lo/Normal
CMV ELISA*		Hi/Lo/Normal
Toxoplasmosis (IgG)		Hi/Lo/Normal
Lyme (WB) or Lyme Elisa		Hi/Lo/Normal
Hep B sAb		Hi/Lo/Normal
Hep B sAg		Hi/Lo/Normal
Hep B cAb		Hi/Lo/Normal
Hep A IgG		Hi/Lo/Normal
Hep A IgM		Hi/Lo/Normal
Hep C		Hi/Lo/Normal
VZV IgG		Hi/Lo/Normal
VZV IgM		Hi/Lo/Normal
HHV6-IgG		Hi/Lo/Normal
HHV6-IgM		Hi/Lo/Normal
HHV6-qPCR		Hi/Lo/Normal
Other HHV6		Hi/Lo/Normal
HHV7-IgG		Hi/Lo/Normal
HHV7-IgM		Hi/Lo/Normal
Parvovirus-IgG		Hi/Lo/Normal
Parvovirus-IgM		Hi/Lo/Normal
C. pneumonia		Hi/Lo/Normal
Coxsackievirus-Ab		Hi/Lo/Normal
Echovirus-Ab		Hi/Lo/Normal
Enterovirus-VP1		Hi/Lo/Normal
Herpes 1		Hi/Lo/Normal
Herpes 2		Hi/Lo/Normal
HIV		Hi/Lo/Normal

Central Nervous System

Autonomic Nervous System (upload REDCap or send pdf)

Date MM/DD/YYYY Location

1. ECG (if abnormal include report)
2. Tilt Table Studies
3. Other Autonomic Testing (such as cardiac stress testing) include report & data if available.

Neuroimaging (upload on REDCap)

MRI	Y/N	Abnormal Y/N
CT Scan	Y/N	Abnormal Y/N
FMRI	Y/N	Abnormal Y/N
PET	Y/N	Abnormal Y/N
SPECT	Y/N	Abnormal Y/N
EEG/qEEG	Y/N	Abnormal Y/N

Sleep Studies Y/N Abnormal Y/N
(upload on REDCap)

Intercurrent Events-Comparative Patient History:

1. How many years of chart review?
2. Number of visits ?
3. Since your patient's first visit, has the patient been hospitalized?
   Please describe any hospitalizations (starting from most recent)
   Please include hospitalization date
   Please describe any hospitalizations
   Please list any additional hospitalizations
4. Since your patient's first visit, has the patient had any outpatient surgeries?
   Please describe any surgeries (starting from most recent)
   Please include most recent outpatient surgery and date
   Please list additional surgeries and dates
5. Since your patient's first visit, has the patient had any new chronic conditions?
   Please describe any chronic conditions (starting from most recent)
   Please include most recent chronic condition
   Please describe any chronic conditions any additional chronic conditions.
6. Since your patient's first visit, has the patient had any new acute conditions/serious illnesses?
   Please describe any new acute conditions/serious illnesses
   Please include most recent new acute conditions/serious illnesses diagnosis date
7. Validation of chart review by PI ?
8. In your clinical judgment of chart review from the first time that you saw the patient, has the patient's illness improved, worsened or stayed the same?
9. Please explain why you think the patient's trajectory has changed or stayed the same since you first saw the patient.
10. In your clinical judgment of chart review in the past 6 months, has the patient's illness improved, worsened or stayed the same ?
11. Please explain why you think the patient's trajectory has changed or stayed the same in the past 6 months.

Appendix H: Telephone Script for Healthy Controls/Screen

Screener: Date: Subject ID Number: Subject Age: Gender: M F

Hi, my name is _____ and I am a Clinical Research Coordinator for Dr. _____ at the CFS Clinic in _____.

Thank you for responding to our request to the _____{Blood Donor Center} seeking healthy volunteers in a research study collecting data and biological samples from Chronic Fatigue Syndrome or CFS patients to compare to healthy controls subjects like yourself. The goal of this study is to gather information to improve future diagnosis and treatment of CFS. Having data and samples from people such as you, who do not have Chronic Fatigue Syndrome is essential to understanding how people who have this disease differ from those who do not; thus the success of this study also depends upon the participation of healthy control subjects.

The purpose of this telephone screening interview is to see if you meet the selection criteria for control subjects in this study. If you do, we will ask you to contact our Clinical Research Coordinator at Dr. _____'s CFS Clinic, _____ at _____ during business hours in the next three days. If you give your permission, then that Clinical Research Coordinator will give you further information about the study and help you to get started with the process.

If you are interested in possibly participating in this study, first I have to ask you several questions to determine if it is appropriate to proceed. This screening interview will take approximately 20 minutes. I am going to go through a list of questions. You may choose not to answer these questions. You also may choose to stop participating in this interview at any time; if you want to stop, please tell me. The screening interview is not designed to ask you for sensitive personal information, but it is possible that some people may feel uncomfortable answering these questions about their health with a person they do not know.

Information about you that you give me during this interview will be kept confidentially and securely at the ____ Clinic premises, with access limited to selected ____ Clinic personnel to the extent permitted by law. If this interview information shows that you are not eligible for the study, or if you choose not to participate in the study, the information I collect from you in this interview will be destroyed. If you are eligible for the study and choose to participate, any information that identifies you will be kept confidential in accordance with the terms of an informed consent document and authorization that you sign.

If you are *interested* in taking part in this screening, then I will record your name and information; this will be kept confidential, but there is a small risk that people outside of the Center could learn this information. If you are *not interested* in participating in the study, there will be no penalty, and you will not lose any benefits to which you otherwise would be entitled

If you are eligible for the next step, you will be asked to contact the folks at Dr. _____'s CFS Clinic who will ask you to complete a health history questionnaire. If you complete that Core Questionnaire but for some reason are not eligible to proceed with the study then you will be paid $25.00 US for your participation. In addition, if you remain eligible for the study and come to the CFS Clinic for a physical exam, blood draw of about 5-6 tablespoons, provide urine and tear sample, optional rectal swab, and completion of another questionnaire, you will be paid an additional $75.00 US.

If you have any questions, concerns, or complaints about this interview, you may contact Dr. _____ at: _____. If you want to talk to someone separate from the research team about a concern or complaint or your rights as a possible research subject, please contact the _____Institutional Review Board (IRB) at _____.

Script completed prior to Eligibility Screening Form Initials: _____

ELIGIBLE- SCRIPT 1

Based on the information you gave me, it looks like you may be eligible to participate as a Control Subject for this study. May we contact you sometime during business hours in the next 3 days? (*Or you can also make an appointment at this time.*)

_____ Yes
_____No

NOT ELIGIBLE - SCRIPT 2

Based on the information you gave me, unfortunately it does not appear that you are eligible to serve as a control subject for this study.

Do you have any further questions?
Thank you for your time and your willingness to do this screening interview.

_____ NOT ELIGIBLE

Screener:	Date:	Study ID Number:	Subject Age:	Gender: M F

As we discussed previously, you may skip any question you do not choose to answer, and you may stop at any time. This will take about 5-10 minutes.

Age: _____ Height: _____ ft _____ in Weight: _____ lbs

Education (check highest level):

1 ☐ Less than high school
2 ☐ High school graduate
3 ☐ College training, not graduate
4 ☐ College graduate
5 ☐ Advanced degree

Race (check one only):

1 ☐ White
2 ☐ Black or African American
3 ☐ Native Hawaiian, Pacific Islander
4 ☐ Asian
5 ☐ American Indian, Alaskan Native
6 ☐ More than one race/Other please specify

_____

Ethnicity (check one only):

1 ☐ Hispanic or Latino
2 ☐ Not Hispanic or Latino

YES	NO	
☐	☐	Do you currently, or have you at any time in the past, suffered from unexplained fatigue that is not the result of exertion, is not relieved by rest, and that has substantially interfered with your job, school, personal or social activities?

YES	NO	
☐	☐	Are you currently living with someone who has CFS ?

If yes, what is your relation: _____

(<u>If YES, **STOP**</u>. If NO, continue)

6. Have you had any of these symptoms **FREQUENTLY OR CONSTANTLY FOR THE PAST 6 MONTHS**:

1	☐	Difficulty concentrating bad enough to interfere with your life.
2	☐	Memory problems bad enough to interfere with your life.
3	☐	Difficulty thinking bad enough to interfere with your life.
4	☐	Difficulty finding the right word.
5	☐	Trouble with math or numbers.
6	☐	Unusually absent minded.
7	☐	Need to focus on one thing at a time.
8	☐	Trouble expressing your thoughts.
9	☐	Difficulty understanding things.
10	☐	Frequently lose your train of thought.
11	☐	Very sensitive to bright lights and/or to noises.
12	☐	Loss of depth perception in your vision.
13	☐	Difficulty focusing your vision.
14	☐	Palpitations of your heart.
15	☐	Dizziness.
16	☐	Fainting or feeling like you are about to faint.
17	☐	Feeling unsteady on your feet.
18	☐	Shortness of breath.
19	☐	Cramping abdominal pains.
20	☐	Nausea.
21	☐	Diarrhea.
22	☐	Constipation.
23	☐	Difficulty controlling your urine (leakage, severe urges).
24	☐	Difficulty starting urination.
25	☐	Feel hot (feverish).

26	☐	Measured fevers (temperature greater than 99.6^0 F).
27	☐	Measured low temperature (below 97.0^0 F).
28	☐	Cold hands and feet.
29	☐	Sweat very easily and for no apparent reason during days.
30	☐	Sweat during sleep, making bed clothes and sheets wet.
31	☐	Cannot tolerate hot weather.
32	☐	Cannot tolerate cold weather.
33	☐	Gained weight without trying.
34	☐	Lost weight without trying.
35	☐	No appetite.
36	☐	Appetite too good: cannot stop eating.
37	☐	Unusually sensitive to odors and chemicals.
38	☐	New sensitivities to foods.
39	☐	Sore throat.
40	☐	Swollen glands in your neck, under your arms or in your groin.
41	☐	Glands are tender to the touch.
42	☐	Aching muscles.
43	☐	Aching, stiff or tender joints (more than one joint).
44	☐	Joints that gets red and enlarged or swollen.
45	☐	Headaches that is new or different from past headaches.
46	☐	Awakening unrested, difficulty falling or staying asleep.
47	☐	Abdominal pain
48	☐	Unusually thirsty
49	☐	Urinating large amounts of fluid each day.
50	☐	Fatigue or feeling sick for at least 24 hours after you exercise or exert yourself.

Please continue to the next page.

Please answer the following general health questions.

YES	NO	
☐	☐	Are you in good general health?
☐	☐	Do you smoke? If YES, how many packs per day:
☐	☐	Do you drink alcohol? If YES, how much weekly:
☐	☐	Have you used illicit drugs in the past two years?
☐	☐	Are you on any medications currently (include over-the-counter medications)? If YES, please list below.
☐	☐	Have you ever been hospitalized? If YES, please give date and diagnosis below.
☐	☐	Do you have any chronic medical illnesses? If YES, please list below.
☐	☐	Do you have any psychiatric illnesses? If YES, please list below.

Interviewer Initials: _____ Date: _____

Appendix I: Physical Exam Checklist

Investigator Name:	Study ID:	Date of Visit (mm/dd/yy):

VITAL SIGNS:	
Height: _____ **Weight**: _____ **BMI**: _____	
Temperature _____ °F • Abnormal temperature: 97.0 F < Temperature > 99.6 F *Abnormal temperature indicates subject meets criterion* **Neuroendocrine-Canadian**	❑ Normal ❑ Abnormal **Comments:** **if abnormal:** **Low** **high**
Pain [0,1,2,3,4,5,6,7,8,9,10] • (Circle one. 0=no pain, 10=severe pain)	❑ Normal (0) ❑ Abnormal (1-10) **Comments:**
Cold hands/feet • *Cold extremities indicate subject meets criterion* **Neuroendocrine-Canadian**	❑ Normal ❑ Abnormal **Comments:**
Respiratory Rate _____ --- (*Supine-record after laying down for 5 minutes; Standing-record after 3 minutes*) **Seated BP: _**_____/_____ **Pulse**: _____ **Supine BP:** _____/_____ **Pulse**: _____ **Standing BP: _**_____/_____ **Pulse**: _____ • Signs of Neurally mediated hypotension (NMH): drop in systolic BP > 20-25 mm of mercury upon standing with at least 1 of the associated symptoms: lightheadedness, dizziness, visual changes, syncope, slow response to verbal stimuli, or subject feels an urgency to lie down *NMH indicates subject meets criterion* **Autonomic-Canadian** • Signs of Postural orthostatic tachycardia syndrome (POTS): drop in systolic BP > 20-25 mm of mercury upon standing AND an increase in heart rate > 30 beats per minute *POTS indicates subject meets criterion* **Autonomic-Canadian**	❑ Normal ❑ Abnormal **Comments:** ---

HEENT	
Head • Normal – Normocephalic, normal thyroid	❑ Normal ❑ Abnormal **Comments:**
Ears • Normal – tympanic membranes or tm's flat and no trophi	❑ Normal ❑ Abnormal **Comments:**
Eyes • Sclerae anicteric • Sensitivity to light or diminished pupillary accommodation *Sensitivity to light indicates subject meets criterion* **Neurological (Overload Phenomena)-Canadian**	❑ Normal ❑ Abnormal **Comments:**
Nose • Normal – pink nasal mucosa	❑ Normal ❑ Abnormal **Comments:**
Throat • Normal – no erythema	❑ Normal ❑ Abnormal **Comments:** **Exudate y n** **Tonsilar/adenoid enlargement y n** **:ccrimson cresent" anterior pharynx ring of erethema)** **y n**
Tongue • Normal – not enlarged/smooth	❑ Normal ❑ Abnormal **Comments:**

SKIN AND HAIR	
Skin • Normal – no rash • Comment on dry skin, folliculitis	❑ Normal ❑ Abnormal **Comments:**
Hair • Normal – no alopecia • Comment on thinning, change in texture, etc.	❑ Normal ❑ Abnormal **Comments:**
LYMPH NODES *Lymphadenopathy of any region indicates subject meets criterion* **Immune-Canadian**	
Anterior cervical • Right/Left _____ • Size _____ • Number _____ • Consistency _____ • Fixed_____	❑ Normal ❑ Abnormal **Comments:**
Posterior cervical • Right/Left _____ • Size _____ • Number _____ • Consistency _____ • Fixed_____	❑ Normal ❑ Abnormal **Comments:**
Submandibular • Right/Left _____ • Size _____ • Number _____ • Consistency _____ • Fixed_____	❑ Normal ❑ Abnormal **Comments:**
Submental • Right/Left _____ • Size _____ • Number _____ • Consistency _____ • Fixed_____	❑ Normal ❑ Abnormal **Comments:**

Pre-auricular • Right/Left _____ • Size _____ • Number _____ • Consistency _____ • Fixed_____ Always abnormal if present	❑ Normal ❑ Abnormal **Comments:**
Post-auricular • Right/Left _____ • Size _____ • Number _____ • Consistency _____ • Fixed_____ Always abnormal if present	❑ Normal ❑ Abnormal **Comments:**
Occipital • Right/Left _____ • Size _____ • Number _____ • Consistency _____ • Fixed_____	❑ Normal ❑ Abnormal **Comments:**
Supraclavicular • Right/Left _____ • Size _____ • Number _____ • Consistency _____ • Fixed_____ Always abnormal if present	❑ Normal ❑ Abnormal **Comments:**
Axillary • Right/Left _____ • Size _____ • Number _____ • Consistency _____ • Fixed_____ Always abnormal if present	❑ Normal ❑ Abnormal **Comments:**

Epitrochlear • Right/Left_____ • Size _____ • Number _____ • Consistency _____ • Fixed_____ Always abnormal if present	❑ Normal ❑ Abnormal **Comments:**
Inguinal • Right/Left _____ • Size _____ • Number _____ • Consistency _____ • Fixed_____ Femoral right /left (always abnormal if present)	❑ Normal ❑ Abnormal **Comments:** présent absent
PULMONARY	
Pulmonary (after 1") • Pulmonary dysfunction: irregular breathing, or holding the breath inappropriately *Pulmonary dysfunction indicates subject meets criterion* **Autonomic-Canadian**	❑ Normal ❑ Abnormal **Comments:**
CARDIAC *Rapid/Irregular heartbeat indicates subject meets criterion* **Autonomic-Canadian**	
Cardiac • Rate _____ • Rhythm __reg irreg_____ • Murmur _____	❑ Normal ❑ Abnormal **Comments:**
ABDOMINAL	
Abdominal • *Increased bowel sounds, abdominal tenderness and mild bloating indicates subject meets criterion* **Autonomic-Canadian**	❑ Normal ❑ Abnormal **Comments:**

Hepatomegaly	❑ Normal ❑ Abnormal **Comments:**
Splenomegaly • Normal – not larger than 2 finger breaths • *Splenomegaly indicates subject meets criterion* **Immune-Canadian** (specifically indicate that it does not appear to be pathologically enlarged and require further w/u like a Cat Scan)	❑ Normal ❑ Abnormal **Comments:**

MUSCULOSKELETAL

Musculoskeletal • Normal – no tenderness (Measure tenderness and perhaps location)	❑ Normal ❑ Abnormal **Comments:**
Fibromyalgia (refer to FM diagram with trigger points) • FM number • Location of trigger points	❑ Normal ❑ Abnormal **Comments:**

NEUROLOGICAL EXAM

Neurologic (3-5/5) Upper Extremities: R_____ L_____ Lower Extremities: R _____ L_____ • Muscle weakness, twitching or ataxia *Muscle weakness, twitching or ataxia indicate subjects meets criterion* **Neurological (Motor disturbance)-Canadian** • Hypersensitivity to vibration sense *Hypersensitivity to vibration sense indicates subject meets criterion* **Neurological (Overload phenomena)-Canadian**	❑ Normal ❑ Abnormal **Comments:**

Reflexes • Achilles, biceps and patellar • Attention to delayed relaxation phase (hypothyroidism sign)	❑ Normal ❑ Abnormal **Comments:**
Tandem Gait • Abnormal Tandem Gait – unable to walk heel-to-toe without corrective footing *Abnormal Tandem gait indicates subjects meets* **Neurological (Motor disturbance)-Canadian**	❑ Normal ❑ Abnormal **Comments:**
Rhomberg • Abnormal Romberg – unable to maintain balance with closed eyes and arms extended for 10 seconds without corrective footing *Abnormal Romberg indicates subject meets criterion* **Neurological (Motor disturbance)-Canadian**	❑ Normal ❑ Abnormal **Comments:**
Serial 7 (start at number 49) • Abnormal Serial 7's, performed with > 2 errors *Abnormal Serial 7's indicates subject meets* **Neurological (Impairment of concentration)-Canadian**	❑ Normal ❑ Abnormal **Comments:**

Physical Exam Completed By:_____

Appendix J: Severity of Illness Questionnaire
To be completed during on-site visit:

General Health Questionnaire (SF36)

In general, would you say your health is:				
_____ Excellent	_____ Very Good	_____ Good	_____ Fair	_____ Poor
Compared to one year ago, how would you rate your health in general **now**?				
___ Much better	___ Somewhat better	___ Same	___ Somewhat worse	Much worse

The following items are about activities you might do during a typical day. Does your health now limit you in these activities and if so, how much? Check the appropriate box			
	Yes limited a lot	Yes limited a little	No not limited at all
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports			
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
Lifting or carrying groceries			
Climbing **several** flights of stairs			
Climbing **one** flight of stairs			
Bending, kneeling, or stooping			
Walking **more** than a mile			
Walking **several** blocks			
Walking **one** block			
Bathing or dressing yourself			

*During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?*		
	Yes	No
Cut down the **amount of time** you spent on work or other activities		
Accomplished less than you would like		
Were limited in the **kind** of work or other activities		
Had **difficulty** performing the work or other activities (for example, it took extra effort)		

*During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?*		
	Yes	No
Cut down the **amount of time** you spent on work or other activities		
Accomplished less than you would like		
Didn't do work or other activities as **carefully** as usual		

During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?				
____ Not at all	____ Slightly	____ Moderately	___ Quite a bit	___ Extremely

How much **bodily pain** have you had during the **past 4 weeks**?					
____ None	____ Very Mild	____ Mild	___ Moderate	___ Severe	___ Very Severe

During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?				
____ Not at all	____ Slightly	____ Moderately	___ Quite a bit	___ Extremely

*These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks:***

	All of the time	Most of the time	Good bit of the time	Some of the time	A little bit of the time	None of the time
Did you feel full of pep?						
Have you been a very nervous person?						
Have you felt so down in the dumps that nothing could cheer you up?						
Have you felt calm and peaceful?						
Did you have a lot of energy?						
Have you felt downhearted and blue?						
Did you feel worn out?						
Have you been a happy person?						
Did you feel tired?						
During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?						

How TRUE or FALSE is each of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
I seem to get sick a little easier than other people					
I am as healthy as anybody I know					
I expect my health to get worse					
My health is excellent					

Symptom Questionnaire

Put a check in the box if you had this symptom before CFS. Circle one number for <u>how often</u> and <u>how much</u> each symptom has bothered you over the past 6 months. Go from left to right.

Symptoms	Before?	Over the **<u>past 6 months</u>**, **how <u>often</u>** have you had this symptom? **0 = none of the time** **1 = a little of the time** **2 = about half the time** **3 = most of the time** **4 = all of the time**					Over the **<u>past 6 months</u>**, **how <u>much</u>** has this symptom bothered you? **0 = symptom not present** **1 = mild** **2 = moderate** **3 = severe** **4 = very severe**				
Fatigue/extreme tiredness		0	1	2	3	4	0	1	2	3	4
Dead, heavy feeling after starting to exercise		0	1	2	3	4	0	1	2	3	4
Next day soreness or fatigue after non-strenuous, everyday activities		0	1	2	3	4	0	1	2	3	4
Mentally tired after the slightest effort		0	1	2	3	4	0	1	2	3	4
Minimum exercise makes you physically tired		0	1	2	3	4	0	1	2	3	4
Physically drained or sick after mild activity		0	1	2	3	4	0	1	2	3	4
Feeling unrefreshed after you wake up in the morning		0	1	2	3	4	0	1	2	3	4
Need to nap daily		0	1	2	3	4	0	1	2	3	4
Problems falling asleep		0	1	2	3	4	0	1	2	3	4
Problems staying asleep		0	1	2	3	4	0	1	2	3	4
Waking up early in the morning (e.g. 3am)		0	1	2	3	4	0	1	2	3	4
Sleep all day and stay awake all night		0	1	2	3	4	0	1	2	3	4
Pain or aching in your muscles		0	1	2	3	4	0	1	2	3	4
Pain/stiffness/tenderness in more than one joint without swelling or redness		0	1	2	3	4	0	1	2	3	4
Eye pain		0	1	2	3	4	0	1	2	3	4

Symptoms	Before?	Over the **past 6 months**, **how often** have you had this symptom? **0 = none of the time** **1 = a little of the time** **2 = about half the time** **3 = most of the time** **4 = all of the time**					Over the **past 6 months**, **how much** has this symptom bothered you? **0 = symptom not present** **1 = mild** **2 = moderate** **3 = severe** **4 = very severe**				
Chest pain		0	1	2	3	4	0	1	2	3	4
Bloating		0	1	2	3	4	0	1	2	3	4
Abdomen/stomach pain		0	1	2	3	4	0	1	2	3	4
Headaches		0	1	2	3	4	0	1	2	3	4
Muscle twitches		0	1	2	3	4	0	1	2	3	4
Muscle weakness		0	1	2	3	4	0	1	2	3	4
Sensitivity to noise		0	1	2	3	4	0	1	2	3	4
Sensitivity to bright lights		0	1	2	3	4	0	1	2	3	4
Problems remembering things		0	1	2	3	4	0	1	2	3	4
Difficulty paying attention		0	1	2	3	4	0	1	2	3	4
Difficulty finding the right word to say or expressing thoughts		0	1	2	3	4	0	1	2	3	4
Difficulty understanding things		0	1	2	3	4	0	1	2	3	4
Only can focus on one thing at a time		0	1	2	3	4	0	1	2	3	4
Unable to focus vision and attention		0	1	2	3	4	0	1	2	3	4
Loss of depth perception		0	1	2	3	4	0	1	2	3	4
Slowness of thought		0	1	2	3	4	0	1	2	3	4
Absent-mindedness or forgetfulness		0	1	2	3	4	0	1	2	3	4
Bladder problems		0	1	2	3	4	0	1	2	3	4
Irritable bowel problems		0	1	2	3	4	0	1	2	3	4
Nausea		0	1	2	3	4	0	1	2	3	4

Symptoms	Before?	Over the **past 6 months**, **how often** have you had this symptom? **0 = none of the time** **1 = a little of the time** **2 = about half the time** **3 = most of the time** **4 = all of the time**					Over the **past 6 months**, **how much** has this symptom bothered you? **0 = symptom not present** **1 = mild** **2 = moderate** **3 = severe** **4 = very severe**				
Feeling unsteady on your feet, like you might fall		0	1	2	3	4	0	1	2	3	4
Shortness of breath or trouble catching your breath		0	1	2	3	4	0	1	2	3	4
Dizziness or fainting		0	1	2	3	4	0	1	2	3	4
Irregular heart beats		0	1	2	3	4	0	1	2	3	4
Losing or gaining weight without trying		0	1	2	3	4	0	1	2	3	4
No appetite		0	1	2	3	4	0	1	2	3	4
Sweating hands		0	1	2	3	4	0	1	2	3	4
Night sweats		0	1	2	3	4	0	1	2	3	4
Cold limbs (e.g. arms, legs, hands)		0	1	2	3	4	0	1	2	3	4
Feeling chills or shivers		0	1	2	3	4	0	1	2	3	4
Feeling hot or cold for no reason		0	1	2	3	4	0	1	2	3	4
Feeling like you have a high temperature		0	1	2	3	4	0	1	2	3	4
Feeling like you have a low temperature		0	1	2	3	4	0	1	2	3	4
Alcohol intolerance		0	1	2	3	4	0	1	2	3	4
Sore throat		0	1	2	3	4	0	1	2	3	4
Tender/sore lymph nodes		0	1	2	3	4	0	1	2	3	4
Fever		0	1	2	3	4	0	1	2	3	4
Flu-like symptoms		0	1	2	3	4	0	1	2	3	4
Some smells, foods, medications, or chemicals make you feel sick		0	1	2	3	4	0	1	2	3	4

How often have you felt the strong need to urinate with little or no warning ?

0. Not at all
1. Less than 1 time in 5
2. Less than half the time
3. About half the time
4. More than half the time
5. Always

Have you had to urinate less than 2 hours after you finished urinating ?

0. Not at all
1. Less than 1 time in 5
2. Less than half the time
3. About half the time
4. More than half the time
5. Always

How often did you most typically get up at night to urinate ?

0. None
1. Once
2. 2 times
3. 3 times
4. 4 times
5. 5 or more times

Have you experienced pain or burning in your bladder ?

0. Not at all
2. A few times
3. Fairly often
4. Usually

Multidimensional Fatigue Inventory

The next questions are about how you have been feeling lately. If you completely agree with the statement, select 1. If you completely disagree with the statement, select 5.					
	Completely agree 1	Agree 2	Neutral 3	Disagree 4	Completely disagree 5
I feel fit.					
Physically I feel only able to do a little.					
I feel very active.					
I feel like doing all sorts of nice things.					
I feel tired.					
I think I do a lot in a day.					
When I am doing something, I can keep my thoughts on it.					
Physically I can take on a lot.					
I dread having to do things.					
I think I do very little in a day.					
I can concentrate well.					
I am rested.					
It takes a lot of effort to concentrate on things.					
Physically I feel I am in a bad condition.					
I have a lot of plans.					
I tire easily.					
I get little done.					
I don't feel like doing anything.					
My thoughts easily wander.					
Physically I feel I am in an excellent condition.					

Pain

Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain, other than these everyday kinds of pain during the past 24 hours?	__Yes __ No
Would you consider your pain to be widespread and occurring in more than one spot on your body?	__Yes __ No

	With 0 being no pain and 10 being the worst pain you can imagine, please choose the one number that best describes your pain in the past 24 hours.										
	0	1	2	3	4	5	6	7	8	9	10
Pain at its **worst**											
Pain at its **least**											
Pain on the **average**											
Pain you have **right now**											

Do you take any medications or receive any treatments for your pain? If so, write the treatments or medications you are taking or receiving for your pain in the box to the right.	
In the past 24 hours, how much relief have pain treatments or medications provided? 0% is no relief and 100% is complete relief	%

	With 0 being does not interfere and 10 being completely interferes, choose the one number that describes how, during the past 24 hours, pain has interfered with your:										
	0	1	2	3	4	5	6	7	8	9	10
General activity											
Mood											
Walking ability											
Normal work											
Relations with other people											
Sleep											
Enjoyment of life											

Questions About Depressive Symptoms

Check the one response to each item that best describes you for the <u>past seven days</u>.

1. Falling Asleep:
___ I never take longer than 30 minutes to fall asleep.
___ I take at least 30 minutes to fall asleep, less than half the time.
___ I take at least 30 minutes to fall asleep, more than half the time.
___ I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night
___ I do not wake up at night.
___ I have a restless, light sleep with a few brief awakenings each night.
___ I wake up at least once a night, but I go back to sleep easily.
___ I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:
___ Most of the time, I awaken no more than 30 minutes before I need to get up.
___ More than half the time, I awaken more than 30 minutes before I need to get up.
___ I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.
___ I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping Too Much:
___ I sleep no longer than 7-8 hours/night, without napping during the day.
___ I sleep no longer than 10 hours in a 24-hour period including naps.
___ I sleep no longer than 12 hours in a 24-hour period including naps.
___ I sleep longer than 12 hours in a 24-hour period including naps.

5. Feeling Sad:
___ I do not feel sad.
___ I feel sad less than half the time.
___ I feel sad more than half the time.
___ I feel sad nearly all of the time.

Please complete either 6 <u>or</u> 7 (not both)

6. Decreased Appetite:
___ There is no change in my usual appetite.
___ I eat somewhat less often or lesser amounts of food than usual.
___ I eat much less than usual and only with personal effort.
___ I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

- OR -

7. Increased Appetite:
___ There is no change from my usual appetite.
___ I feel a need to eat more frequently than usual.
___ I regularly eat more often and/or greater amounts of food than usual.
___ I feel driven to overeat both at mealtime and between meals.

Please complete either 8 <u>or</u> 9 (not both)

8. Decreased Weight (Within the Last Two Weeks):
___ I have not had a change in my weight.
___ I feel as if I have had a slight weight loss.
___ I have lost 2 pounds or more.
___ I have lost 5 pounds or more.

- OR -

9. Increased Weight (Within the Last Two Weeks):
___ I have not had a change in my weight.
___ I feel as if I have had a slight weight gain.
___ I have gained 2 pounds or more.
___ I have gained 5 pounds or more.

10. Concentration / Decision Making:
___ There is no change in my usual capacity to concentrate or make decisions.
___ Most of the time, I struggle to focus my attention or to make decisions.
___ I occasionally feel indecisive or find that my attention wanders.
___ I cannot concentrate well enough to read or cannot make even minor decisions.

11. View of Myself:
___ I see myself as equally worthwhile and deserving as other people.
___ I am more self-blaming than usual.
___ I largely believe that I cause problems for others.
___ I think almost constantly about major and minor defects in myself.

12. Thoughts of Death or Suicide:
___ I do not think of suicide or death.
___ I feel that life is empty or wonder if it's worth living.
___I think of suicide or death several times a week for several minutes.
___ I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

13. General Interest
___ There is no change from usual in how interested I am in other people or activities.
___ I notice that I am less interested in people or activities.
___ I find I have interest in only one or two of my formerly pursued activities.
___ I have virtually no interest in formerly pursued activities.

14. Energy Level:
___ There is no change in my usual level of energy.
___ I get tired more easily than usual.
___ I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking, or going to work).
___ I really cannot carry out most of my usual daily activities because I just don't have the energy.

15. Feeling Slowed Down:
___ I think, speak, and move at my usual rate of speed.
___ I find that my thinking is slowed down or my voice sounds dull or flat.
___ It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.
___ I am often unable to respond to questions without extreme effort.

16. Feeling Restless:
___ I do not feel restless.
___ I'm often fidgety, wringing my hands, or need to shift how I am sitting.
___ I have impulses to move about and am quite restless.
___ At times, I am unable to stay seated and need to pace around.

Beck Anxiety Inventory

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not At All	Mildly but it didn't bother me much	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst Happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky / unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint / lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3
Column Sum				

Appendix K: Sample Collection Protocol

The Clinical Research Coordinator (CRC) will select a CFI Biobank sample kit for each CFS Subject and healthy control subject consented and enrolled in, "**A Clinical and Biosample Database to Enable Discovery of Pathogens and Pathogenic Mechanisms in Chronic Fatigue Syndrome",** and match the unique subject ID number for that kit to the study subject ID in the Study Log. Following confirmation of eligibility and signed, informed consent, the CRC will escort the subject to the phlebotomy station for the collection of blood samples.

Blood:

Routine Laboratory Testing:
If ordered by the provider, the phlebotomist shall make a single venipuncture when possible and draw any samples required for routine laboratory testing before drawing the research samples for this protocol.

CFI Biobank Research Samples:

1.0 Purpose

The purpose of this procedure is to define how samples should be processed, at collections sites, upon collection for the Chronic Fatigue Initiative (CFI). This procedure also defines how to package samples for return to the Immunology and Virology Quality Assessment Center (IVQAC, Biorepository). For the CFI project, the IVQAC will be responsible for preparing 400 sample collection kits to be sent to 5 domestic clinical sites. Kits will be sent every other week in bulk. When a clinical site identifies a new donor, they will use two kits for each donor, and return the kits for processing at the IVQAC.

2.0 Scope and Application

This SOP applies to the CFI project only.

3.0 Safety (if applicable)

3.1 Universal precautions should be taken when working with human tissue and bodily fluids

4.0 Reagents and Materials

4.1 Ambient Shipment Kit (Box A)
- 4.1.1 Prelabeled Ambient shipping system (STP-100)—
- 4.1.2 Outerbox, Secondary vessel, Saf-T-Pouch Bubble wrap, absorbent strip, UN 3373 Marking, Shipping Address Marking, Consignee Address Marking, "EMPTY" label
- 4.1.3 Data Logger
- 4.1.4 Four Prelabeled 10mL green top sodium heparin tubes (BD Cat 367874)
- 4.1.5 Pre-printed Fed Ex Way Bill

4.2 Wet Ice Shipment Kit (Box B)
- 4.2.1 Prelabeled Category B Shipping Overpack, Insulated (STP-308)

4.2.2 10-15 gel packs
4.2.2.1 Gel Packs should be kept at 2-8°C upon receipt until ready to use for a send-out
4.2.3 Sealable biohazard bag
4.2.4 Data Logger (DeltaTrak FlashLink® VU)
4.2.5 100mL Absorbent paper
4.2.6 Two Saf-T-Raps for holding a total of 13 tubes
4.2.7 Four 15mL conical tubes
4.2.8 One 50mL conical tube
4.2.9 1* 10mL SST™ Tube with Silica Clot Activator, Double Polymer Gel, Silicone-Coated Interior (BD Cat# 367985)
4.2.10 1*10mL lavender top EDTA blood collection tube (BD Cat 366643)
4.2.11 1*8.5mL PaxGene DNA (Qiagen #761115)
4.2.12 3 *2.5mL PaxGene RNA collection tubes (BD Cat 762165)
4.2.13 Saliva collection kit (Salivettes-Cotton swab with citric acid preparation #51.1534.001)
4.2.14 Urine collection kit (BD #364954)
4.2.15 Tear collection Schirmer strips-2 packets (TearFlo™)
4.2.16 Two tear collection tubes (Corning Cryovials)
4.2.17 Rectal Swab (DNA/RNA Buccal Swab Kit, Isohelix, SK-2)
4.2.18 Instructions for kit return
4.2.19 Pre-printed Fed Ex Way Bill
4.2.20 Extra labels

5.0 Equipment

5.1 2-8°C Refrigerator for gel packs
5.2 Pipettes
5.3 Centrifuge

6.0 Donor Schedule

6.1 Each Friday, please email the Biorepository with your donor schedule for the next week.
6.2 Please include your site name and number of donors per day. Email to cfi.biorepository@mc.duke.edu

7.0 Sample Collection

7.1 Select a Box A and Box B for the donor.
7.1.1 Each sample ID (CFI###) has both a Box A and Box B. These must be matched per donor. Only one donor may be shipper per box.
7.1.2 Record the sample ID number in the electronic manifest.
7.1.3 All tubes are prelabeled. If you need to use a replacement tube or collection item, extra labels are provided. Please write-in the sample information on these labels.
7.2 Blood samples should be drawn with a standard 21-gauge butterfly collection needle set. Vacutainers tubes should be drawn in the following order by a

phlebotomist. Tubes should be slowly inverted the indicated number of times immediately upon collection (Refer to table below).

Order of Draw Closure Color	Collection Tube	Mix by Inverting (Upon Collection)
Red Top	BD Vacutainer ® SST™	5 Times
Green Top	Heparin Tube	8-10 Times
Lavender Top	EDTA Tube	8-10 Times
Clear Top	PAXGene RNA	10 Times
Clear Top	PAXGene DNA	10 Times

7.3 Upon completion of the blood draw, the collection tubes for research shall be given to the Clinical Research Coordinator for further processing, packaging and shipping (see below).

7.4 Additional Specimens should be collected in the following order (see below for specific collection instructions):

7.4.1 2 packets – Tear collection Schirmer strips (TearFlo™)

7.4.2 1 – Urine collection kit (BD #364954)

7.4.3 1 – Saliva collection kit (Salivettes-Cotton swab with citric acid preparation #51.1534.001)

7.4.4 Rectal Swab (DNA/RNA Buccal Swab Kit, Isohelix, SK-2)

8.0 Sample Processing at Collection Sites

8.1 Serum (BD Vacutainer ® SST™)

8.1.1 Slowly invert tube five times immediately upon collection.

8.1.2 Store tube upright at room temperature for a minimum of 30 minutes and a maximum of 60 minutes to allow clot formation.

8.1.3 Centrifuge IMMEDIATELY after clotting of specimen (30-60 minutes) at 1100-1300 g in a centrifuge for 20 minutes at room temperature (in the event of unavoidable delay in centrifuging blood immediately after clotting time (i.e., 30-60 minutes at room temperature), tubes can be refrigerated (4°C), but no longer than 4 hours.

8.1.4 Gently pipette all of the serum (~3-4 mls) into pre-labeled serum tube (15mL conical) provided with kit.

8.1.5 Label tube with the collection date.

8.2 PBMCs (Green top)

8.2.1 Slowly invert tubes 8-10 times immediately after collection.

8.2.2 Label tubes with the collection date.

8.3 Plasma (Lavender top)

8.3.1 Invert tube slowly, 8-10 times immediately after collection.

8.3.2 Centrifuge within 30 minutes of collection at 1100-1300 g in a centrifuge for 20 minutes at room temperature (in the event of unavoidable tubes can be refrigerated (4 deg C), but no longer than 4 hours.
8.3.3 Gently pipette all of the plasma (~3-4 mls) into pre-labeled plasma tube (15mL conical) provided with kit.
8.3.4 Label tube with the collection date.

8.4 **PaxGene RNA**
8.4.1 Slowly invert 10 times immediately after collection.
8.4.2 Label tubes with the collection date.

8.5 **PaxGene DNA**
8.5.1 Slowly invert 10 times immediately after collection.
8.5.2 Label tube with the collection date.

8.6 **Tear sample collection (Two Schirmer strips and collection tube)**
8.6.1 Put on sterile gloves.
8.6.2 Remove a Schirmer filter paper strip from the packet.
8.6.3 Insert the strip over the lid margin at the junction of the lateral and middle thirds of the lower eyelid of the RIGHT eye taking care not to touch the conjunctiva.
8.6.4 Hold the filer strip in place for 5 minutes while the subject closes their eyes.
8.6.5 Remove the Schirmer strip and record the tear volume in millimeters.
8.6.6 Immediately place the strip in the 2mL tube labeled “Tear-Right”.
8.6.7 The vial should then be placed in the labeled 15mL conical.
8.6.8 Remove the sterile gloves and replace.
8.6.9 Repeat with left eye.
8.6.10 Label both vials with collection date.

8.7 **Urine Collection (Urine Collection Kit)**
8.7.1 The healthcare professional obtains a cup for the patient and cautions patient not to remove the yellow cap label to protect against needlestick from the “sharp” contained in the integrated transfer device.
8.7.2 The healthcare professional should remove the Vacutainer Tube and place them in a protected location before giving the cup to the patient for urine collection.
8.7.3 The patient should be directed to follow instructions for proper collection of a clean-voided, midstream urine specimen.
8.7.4 Patient is instructed to give the urine specimen to the healthcare professional immediately after collection.
8.7.5 Place cup upright on clean, flat surface. Container may be tipped at an angle if specimen volume is limited.
8.7.6 Peel back label on cap to expose the integrated transfer device.

8.7.7 Place evacuated tube into cavity on cap, stopper down. Advance the tube over puncture point to pierce stopper.
8.7.8 Hold tube in position until filled.
8.7.9 Remove tube from integrated transfer device.
8.7.10 Mix the tube 8 - 10 times by inversion.
8.7.11 Replace label over integrated transfer device cavity and reseal. Use caution to avoid contact with needle when replacing label.
8.7.12 Label the collection tube with the provided label containing the sample ID and add the collection date.
8.7.13 Treat the screw cap of the cup as a contaminated sharp and discard in biohazard container approved for sharps disposal as per your facility's recommended procedure.

8.8 **Saliva (Salivette)**

8.8.1 Have the donor place the salivette cotton wool swab in his/her mouth.
8.8.2 The donor should chew on the swab for 30 seconds. The swab contains citric acid to stimulate saliva.
8.8.3 The donor should keep the swab in his/her mouth for another two minutes.
8.8.4 The donor should then spit the swab back into the small collection tube.
8.8.5 Replace the lid of the collection tube. The whole salivette collection kit should be returned.
8.8.6 Label the salivette with the collection date.

8.9 **Rectal (Rectal Swab)**

8.9.1 While wearing gloves, pull open the package from one end.
8.9.2 Remove the swab from the tube, taking care not to touch the white swab head with your fingers.
8.9.3 Insert the swab into the rectal area and rub firmly against the rectal vault. Swab area for a minimum of 20 seconds. Important – use reasonable, firm and solid pressure.
8.9.4 Slide the plastic cap over the swab handle with the flat side of the cap facing upwards and the swab facing downwards.
8.9.5 Insert the swab into the clear plastic tube and push the cap into place. Next, hold the cap while pulling the swab handle outwards to release the swab material into the tube.
8.9.6 Close the cap by pushing the stopper fully into the cap ensuring the stopper is fully flush with the cap. The tube is now completely sealed.
8.9.7 Label the tube with the collection date.
8.9.8 The tube should be placed in the pre-labeled 50mL conicals.

9.0 Specimens (Upon Processing using 7 above)

9.1 **Box A**

9.1.1 Prelabeled, filled 4* 10mL green top sodium heparin (4)

9.2 **Box B**

9.2.1 Prelabeled 15mL conical tube with 3-4mL serum (1)
9.2.2 Prelabeled 15mL serum tube with 3-4mL plasma (1)
9.2.3 Prelabeled, filled PaxGene DNA (1)
9.2.4 Prelabeled, filled PaxGene RNA (3)
9.2.5 Prelabeled, filled Salivette (1)
9.2.6 Prelabeled, filled urine tube (1)
9.2.7 Prelabeled conical tubes with 2mL cyrovials containing the tear collection Schirmer strips (2)
9.2.8 Prelabeled rectal swab tube in 50mL conical (1)

10.0 Procedure (Box A)

10.1 Complete the electronic manifest on the RedCap system and print it out.
10.2 Ensure that the absorbent strip is at the bottom of the secondary container.
10.3 Wrap the four green top tubes in bubble-wrap and place in the secondary container.
10.4 Turn the data logger on by depressing the "start" button and place it in the secondary container.
10.5 Put the lid on the secondary container.
10.6 Put the secondary container in the cardboard ring.
10.7 Place the secondary container and cardboard ring into the outer box.
10.8 Place the manifest into the outer box.
10.9 Seal the box.
10.10 Remove "EMPTY" Label from outer box exposing the UN3373 sticker needed for Category B shipment.
10.11 Using the pre-printed FedEx label, fill-out the "From" information**.**
10.12 Affix the label on the shipping box.
10.13 The shipment should be kept at ambient temperature and needs to be shipped for next day, first delivery. **Shipments should not go out on Thursdays or Fridays.**

11.0 Procedure (Box B)

11.1 The gel packs must be pre-cooled (NOT FROZEN) before packaging.
11.2 Complete the electronic manifest and print it out.
11.3 Wrap the 11 processed tubes in the pre-labeled self-sealing bubble wrap pouches (two pouches).
11.3.1 Note that each pouch is labeled for the specific tube that should go in the pouch.
11.3.2 Remove the white strips on the pouch to expose the adhesive. Seal each pouch.
11.4 Put the wrapped tubes and absorbent strip into the provided clear biohazard bag. Put the printed manifest in the secondary pouch (pouch without samples).
11.5 Turn the data logger on by depressing the "start" button and place it in the secondary pouch of the biohazard bag along with the paperwork.
11.6 Seal the biohazard bag.
11.7 Put six gel packs on the bottom of the inner Styrofoam box.
11.8 Put the biohazard bag on top of the gel packs in the box.
11.9 Put the remaining gel packs on top of and around the samples.

11.10 Put the lid on the Styrofoam box.
11.11 Seal the outer cardboard box
11.12 Remove "EMPTY" Label from outer box exposing the UN3373 sticker needed for Category B shipment
11.13 Using the pre-printed FedEx label, fill-out the "From" information**.**
11.14 Affix the label on the shipping box.
11.15 The shipment should be kept at 2-8°C temperature (if possible) and needs to be shipped for next day, first delivery. **Shipments should not go out on Fridays.**

12.0 Emailing IVQAC about shipments

12.1 Upon completion of the electronic manifests (Box A and B have separate manifests) and FedEx labels, email an electronic copy of the manifests and the FedEx tracking numbers to cfi.biorepository@mc.duke.edu

---

[1] Robert N. Sfuchell,* James J. Feldmon,* R. Linsy Forrist and Irwin D. Mandel*Invest *The Effect of Collection Technique on Tear Composition* Ophthalmol Vis Sci 25:374-377, 1984