

Multi-site Clinical Assessment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (MCAM)

Request for OMB approval of an Existing Collection in Use
without an OMB Control Number

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Supporting Statement A

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- **Goal of the study:**

The goal of the present study is to use standardized approaches to measure illness characteristics and domains of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and evaluate the heterogeneity of patients with ME/CFS.

- **Intended use of the resulting data:**

Provide insights on how to improve measures of illness domains (questionnaires and biologic) and allow patients to be phenotypically sub-grouped in a way that allows the underlying biology to be discovered.

- **Methods to be used to collect:**

The study has been conducted in multiple stages and includes four study protocols. The first two protocols (one for adults and one for adolescents/children) used clinical epidemiologic longitudinal studies with retrospective and prospective rolling cohort study design. The third and fourth protocols used standardized approaches to collect the data of cognition and exercise testing and Natural Killer (NK) cell function on a subset of participants from the first longitudinal study protocol on adults. Data have been collected via medical record abstraction and self-administered questionnaires/instruments along with standardized tests for exercise and cognition.

- **The subpopulation to be studied:**

The study sample includes patients from ME/CFS specialty clinics and other physician networks in the United States. The second study protocol enrolled patients aged 10-17 years while the other three protocols enrolled adult patients aged 18-70 years.

- **How data will be analyzed:** Conventional analytical methods such as general linear models and generalized linear models (e.g. logistic regression models) will be used to examine differences across sites and study group comparisons. Computational and algorithm-based analysis approaches will be used to identify subgroups or clusters and examine potential biomarkers in ME/CFS.

1. Circumstances Making the Collection of Information Necessary

The purpose of this submission is to request OMB authorization for an existing collection in use without an OMB control number. We are requesting three years to complete the information/data collection.

This project was not previously understood to be applicable to the paperwork reduction act (PRA), but upon routine review of the contracts, it was determined that PRA is, in fact, applicable. We are pursuing OMB clearance at this time to bring the project into compliance for the remaining duration of the study.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a disabling and complex illness. People with ME/CFS are often not able to complete their usual activities and quality of life is greatly impacted by the illness. At times, ME/CFS may confine them to bed. People with ME/CFS have overwhelming fatigue that is not improved by rest. ME/CFS may get worse after any activity, whether

it's physical or mental. This symptom is known as post-exertional malaise (PEM). Other symptoms can include problems with sleep, thinking and concentrating, pain, and dizziness.

ME/CFS is most common in people between 40 and 60 years old, and the illness affects children, adolescents, and adults of all ages. Among adults, women are affected more often than men. While Whites are diagnosed more than other races and ethnicities, people of all racial and ethnic groups are equally as susceptible to the illness. Many people with ME/CFS have not been diagnosed, especially minority groups. About 836,000 to 2.5 million Americans suffer from ME/CFS, yet about 90 percent of people with ME/CFS have not been properly diagnosed. Overall, ME/CFS costs the U.S. economy about \$17 to \$24 billion annually in medical bills and lost incomes.

Although several biologic abnormalities have been found in groups of people with ME/CFS, to date, none is sufficiently unique or characteristic to be considered diagnostic. A number of case definitions have been used in research and for diagnosis, and although the case definitions share many features, they differ in number and type of required symptoms. Because studies of ME/CFS use one or more case definitions as entry criteria for their study enrollment, developing a data-driven case definition has been challenging.

Physicians worldwide recognize an illness with similar features, yet there remains a marked heterogeneity in patients. While additional disease stratification was recommended in the 1994 International Research Case Definition, few measures beyond acute and chronic onset of illness have been widely used. In order to refine a definition, it is crucial to use a standardized approach to collect data on key dimensions of the illness from a large number of ME/CFS patients recruited from multiple clinical practices. Such standardized data on all domains of ME/CFS illness will inform further discussions of case definitions and provide information on potential ME/CFS sub-groups that could be evaluated for linkage to specific biologic measures.

There is also a significant need to improve the quality of care available to ME/CFS patients. To help contribute to this effort, we are looking at ways to standardize approaches to physical examination, neuropsychological testing, exercise testing, and lab assays for use in future clinical studies in ME/CFS.

Authorizing legislation comes from Section 301 of the Public Health Service Act (42 U.S.C. 241) (Attachment 1).

2. Purpose and Use of Information Collection

In this supporting statement, CDC is requesting OMB review of the Multi-site Clinical Assessment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (MCAM) study. The study has been conducted in multiple stages and includes four study protocols.

CDC provides generic protocols and the collaborating clinics modify them as appropriate to obtain their local IRB approval. The first two protocols are to conduct clinical epidemiologic longitudinal studies with retrospective and prospective rolling cohort study design. These studies were designed not only to retrospectively abstract participants' medical records before their study enrollment but also to prospectively collect detailed clinical and epidemiologic data. Follow-up is conducted annually (10–14

months) to coincide with return clinic appointments. The number of follow-up visits for each participant will vary depending on the stage at first enrollment. Persons enrolled at the first stage would have a maximum of five follow-up visits. The third and fourth protocols use standardized approaches to collect cognition and exercise testing and Natural Killer (NK) cell function data on a subset of participants from the first longitudinal study protocol on adults. The specific objectives of each component of this study are discussed in more detail below.

- I. Protocol #1 – MCAM in Adults (Attachment 3 for forms/tests administered to patients). The goal of this protocol is to examine the heterogeneity of adults with ME/CFS as diagnosed in the clinical practices of clinicians experienced with identification and management of CFS or ME. The specific objectives are:
 - a. To use standardized questionnaires to measure illness domains of ME/CFS and to evaluate patient heterogeneity overall and between clinics;
 - b. To describe the course of illness, identify the measures that best correlate with meaningful clinical differences, and assess the performances of questionnaires as patient/person-reported outcome measures;
 - c. To describe prescribed medications, orders for laboratory and other tests, and management tools used by expert clinicians to care for persons with ME/CFS;
 - d. To collect biospecimens for future hypothesis testing and for evaluation of morning cortisol profiles; and
 - e. To identify measures that best distinguish persons with ME/CFS from those in the comparison groups and detect subgroups of persons with ME/CFS who may have different underlying illness triggers.
- II. Protocol #2 – MCAM in Children and Adolescents (Attachment 4 for forms/tests administered to patients). The goal of this protocol is to examine the heterogeneity of children and adolescents (aged 10-17) with ME/CFS as diagnosed in the clinical practices of clinicians experienced with identification and management of CFS or ME. The specific objectives are:
 - a. To use standardized questionnaires to measure illness domains of ME/CFS and to evaluate patient heterogeneity overall and between clinics;
 - b. To use a standardized approach for data collection to reduce measurement errors due to different data collection instruments;
 - c. To inform the ME/CFS case definition in children and adolescents using evidence-based data collected from various clinical practices; and
 - d. To improve measures of illness domains (questionnaires and biologic) and allow patients identified by case definitions used in the clinical practices to be phenotypically sub-grouped in a way that allows the underlying biology to be discovered.
- III. Protocol #3 – MCAM: Cognition and Exercise Testing (Attachment 5 for forms/tests administered to patients). The goal of this protocol is to measure cognitive function and exercise capacity in adult ME/CFS patients as well as to measure post-exertional changes in cognition and symptoms as a correlate of post-exertion malaise (PEM). Standardized testing will be used to capture cognitive function and exercise capacity and self-reported questionnaires will be used to measure symptoms. The specific objectives are:

- a. To identify a brief, valid neuropsychological screening battery that can reliably and repeatedly identify whether patients may have deficits in cognitive function. Traditional neuropsychological testing is lengthy and costly, and it is often not feasible to pursue in clinical practice. In this study component, we aim to examine whether CogState can be a cost-effective tool to assess deficits in cognitive function in patients with ME/CFS.
- b. To identify a standardized method to determine exercise capacity (aerobic fitness) in patients with ME/CFS.
- c. To assess post-exertional changes in cognitive function and exercise capacity as a correlate of PEM.

IV. Protocol #4 – MCAM: Natural Killer Cell Testing (No form was administered to patients). The goal of this protocol is to measure the Natural Killer (NK) cell function in patients with ME/CFS. The specific objectives are:

- a. To identify a method of assays that can provide valid and reproducible NK cell functional data within the context of geographically separated clinic sites shipping specimens to a central laboratory for testing.
- b. To use the identified and verified method from Objective (a) for blood collection and assay platform to measure NK function on the cohort of the first study protocol.

This study occurs in a clinical setting, with some self-administered questionnaires or instruments to be completed at home prior to the clinic visit, and includes data collection to evaluate overall health, ME/CFS-related symptoms, illness domains including PEM, fatigue, sleep, cognition, pain, autonomic symptoms, immunity, and infection. To minimize the burden of the study on participants, authorized study personnel reviewed participant medical records to abstract information on medical/family history, infection and immunization history, medications, laboratory and test results at the first and most recent visits to the clinic. For self-administered questionnaires/instruments, participants can respond to the questions via a web-based system (OpenMedNet, Open Medicine Institute) or a paper form before or at the next clinic visit. Collections of the information at the appropriate time points is necessary for accomplishing the objectives of the study.

3. Use of Improved Information Technology and Burden Reduction

CDC uses website, computer-assisted, and web-based data collection forms to facilitate data collection and to reduce burden.

To minimize the burden of the study on participants, we have authorized study personnel abstracting information on medical/family history, infection and immunization history, medications, laboratory and test results. For the instruments self-administered by participants, about 75% of participants will fill out via a web-based system (OpenMedNet - <https://www.openmednet.org/>, Open Medicine Institute). Some instruments are rotated to use in each follow-up and not administered at all follow-up visits. Skip-pattern design and controls are used to ensure that participants receive the appropriate questions and that the administration process goes smoothly. Additionally, instruments have been adapted for fewer questions to reduce burden on severely ill patients and healthy controls. Furthermore, the clinics collaborating in this study can convert their hard copies of medical records to searchable scanned PDF files or electronic analyzable format via standardized data abstraction forms from this study.

For cognition testing, we use a computer-administered cognitive test battery (CogState Brief Battery (CBB), <https://cogstate.com/featured-batteries/cogstate-brief-battery/>) rather than traditional neuropsychological testing that could be lengthy and costly. CogState Brief Battery can be accessible via laptop or web-based system. This will enable participants completing multiple sessions of CogState tests to assess the impact of exercise challenge on post-exertional malaise. A secure FTP site was set up for each site for temporary storage and to submit data including electronic data files and PDF files of scanned data collection forms/instruments.

4. Efforts to Identify Duplication and Use of Similar Information

We are not aware of the availability of any similar information using a standardized approach to collect longitudinal data on key dimensions of the illness from a large number of ME/CFS patients recruited from multiple clinical practices in the United States. Because of the nature of the information that must be collected, it would not be feasible to combine this with other population studies conducted by CDC.

5. Impact on Small Businesses or Other Small Entities

This information collection involves ME/CFS specialty clinics, which are clinician-owned small healthcare practices or employees of a non-profit organization. The information data collection coincides with patients' clinical appointments but does not interrupt routine healthcare. Clinicians perform their routine physical examinations and record the information on the web-based form or hard-copy form that will be entered by their clinic staff later. The contract award for this information collection also included additional personnel costs to clinics such as study and data coordination and lab supplies.

6. Consequences of Collecting the Information Less Frequently

The study includes baseline and follow-up visits. Follow-up occurs annually (10–14 months) to coincide with return clinic appointments. The number of follow-up visits for each participant will vary depending on the stage at first enrollment. Persons enrolled at the first stage would have a maximum of five follow-up visits. In the United States, most ME/CFS studies with samples from clinical settings are cross-sectional and the sample size is often small. Therefore, it is critical to collect longitudinal data in this study.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

This request fully complies with the regulation 5 CFR 1320.5.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

A. A 60-day Federal Register Notice was published in the *Federal Register* on August 03, 2020, vol. 85, No. 149, pp. 46633 (Attachment 2). CDC did/did not receive public comments related to this notice.

B. [Describe efforts to consult outside the agency OR state “No consultations outside of CDC occurred.”]

The CDC drew on the expertise of several groups of consultants to develop the design and methods, and select questionnaires for the MCAM study. The subject matter experts that we consulted are listed in the following table.

Name	Title	Telephone
Lucinda Bateman, MD	Adjunct Assistant Professor, Department Of Anesthesiology Founder & Medical Director Bateman Horne Center, Salt Lake City, UT	801-359-7400
Dane Cook, PhD	Professor of Kinesiology Co-Director of the Exercise Psychology laboratory University of Wisconsin– Madison, Madison, WI	608-262-0259
Patricia DeLaMora, MD	Associate Professor of Clinical Pediatrics, Weill Cornell Medical College Weill Cornell Medicine, NY, NY	646-962-6845
Nancy Klimas, MD	Chair of Clinical Immunology Director, Institute for Neuro- Immune Medicine Nova Southern University,	954-262-2850
Andy Kogelnik, MD, PhD	Physician, Open Medicine Clinic Director, Open Medicine Institute, Mountain View, CA	650-691-8633
Gudrun Lange, PhD	Clinical Neuropsychologist Mount Sinai Beth Israel, NY, NY	201-281-6118
Charles Lapp, MD	Medical Director, Hunter- Hopkins Center, Charlotte, NC	704-543-9692
Benjamin Natelson, MD	Professor, Neurology Director, Pain & Fatigue Study Center Mount Sinai Beth Israel, NY, NY	212-844-8930
Daniel Peterson, MD	Member of Simmaron’s Scientific Advisory Board	775-832-0989

	President, Sierra Internal Medicine, Incline Village, NV	
Richard Podell, MD	Internist, Richard Podell Medical Practice, Summit, NJ	908-273-7770

9. Explanation of Any Payment or Gift to Respondents

Participants would be compensated based on the number of the study components that they complete across four IRB-approved study protocols (Protocol #1: \$50, Protocol #2: \$50, Protocol #3: \$100, Protocol #4: \$50). Protocol #3 involves a combined test for cognition and exercise and takes about 2-hours to complete the tests during patients’ office visit. Additionally, participants will need to take few more sessions of CogState tests online for cognition in the following consecutive days from home. Due to the complexity of 3-day data collection, participants will be compensated more for the time that spend on this particular study protocol. Payment of up to \$250 has been offered to participants as a token of appreciation for extra time spent in this study in addition to their regular office visit. The payment varies based on the number of study components that participants complete, e.g. participation in all four protocols or some of them.

10. Protection of the Privacy and Confidentiality of Information Provided by Respondents

CDC’s Privacy Review Office has reviewed this request and in accordance with guidance provided by the Privacy Office, Information Collection Requests (ICRs) that DO NOT entail the collection of Personally Identifiable Information (PII) or Information in Identifiable Form (IIF) NO LONGER REQUIRE submission of a Privacy Impact Assessment (PIA) to the Privacy Office. Privacy Review was not needed since no PII is sent to CDC.

11. Institutional Review Board (IRB) and Justification for Sensitive Questions

Institutional Review Board (IRB)

NCEZID’s Human Subjects Advisor determined that information collection is research involving human subjects. IRB approval is required. The generic protocol and informed consent templates were developed by the CDC based on the feedback from the contract kick-off meeting with the individual site principal investigators as well as the leadership in the CDC team. The CDC defers to OMI’s IRB approval for this protocol. That is because the majority of the patients come through the OMI group and the CDC only receives the coded data from the collaborating clinics via secured data transfer system. Each collaborating site is responsible for submitting the locally amended protocol, informed consents, data collection forms/instruments to their local/institutional ethics committee. Local ethics board approval were obtained before the start of the study, and the study must be kept current and in good standing with the local IRB until the end of the clinical enrollment, or as required by the local IRB.

All four study protocols have been approved by CDC IRB. See Attachment 6 for IRB approval letters. Currently, only OMI is still enrolling and conducting the MCAM study. Both MSBI and Nova Southern University submitted 4 protocols as one IRB package and their latest IRB approval letters are attached

for your reference as well. HRPO has changed their policies and they are no longer requiring formal continuation requests when we rely. In Attachment 6, you will also find the updated memo from the Human Studies Team for the status of reliance protocols.

Justification for Sensitive Questions

There are topics in the data abstraction forms and instruments that are sensitive and private in nature. Questions that are sensitive in nature are:

- Questions concerning psychiatric diagnoses (including depression and anxiety)
- Questions on gynecological history (including pregnancy)

Persons with psychiatric conditions or recent pregnancy may exhibit symptoms similar to the ME/CFS symptom cluster. The questions concerning gynecological history contribute to the complete medical history for women, which is a basic requirement of the medical evaluation process.

12. Estimates of Annualized Burden Hours and Costs

The study has been conducted in multiple stages and includes four study protocols. The first two protocols are to conduct clinical epidemiologic longitudinal studies with retrospective and prospective rolling cohort study design. The third and fourth protocols use standardized approaches to collect the data of cognition and exercise testing and Natural Killer (NK) cell function on a subset of participants from the first longitudinal study protocol on adults. There are no direct costs to the participants /respondents themselves. Indirect costs to participants/respondents, however, may be calculated in terms of the costs of their time spent in responding to the data collection forms/instruments.

For the *Protocol #1 – MCAM in Adults*, study participants (patients enrolled for the study) were asked to complete the prospective data collection on Appendix 11a – Appendix 22 (Attachment 3) that collects data pertaining to health, quality of life, ME/CFS-related symptoms on fatigue, cognition, pain, sleep, orthostatic and autonomic symptoms, depression, anxiety, and illness impact. The information collection is completed by three contractors: Open Medicine Institute (OMI) Consortium, Mount Sinai Beth Israel (MSBI), and Institute for Neuro-Immune Medicine (INIM). This part of the MCAM study was planned in September 2011 and has been conducted since 2012. It was estimated to be completed by September, 2023. This part of the information has been collected via web-based forms (OpenMedNet) for patients enrolled at OMI consortium clinics and via hard-copied forms for patients enrolled at MSBI and INIM clinics.

The hour-burden estimates include the time needed for reviewing instructions, completing and reviewing the collection of information. Annual response burden hours were calculated by computing the product of number of participants/respondents, number of responses per participant/respondent, and average burden per response in hours. Multiplying annual response burden hours by the corresponding mean hourly wage provides annual total participant costs. Annualized costs associated with the hour burdens for the collection of information are also included in the table below.

A. Estimated Annualized Burden Hours

Exhibit 12.A. Summary of Estimated Annualized Burden Hours

Form Name	No. of Participants	No. of Responses per Participant	Average Burden per Response (in hrs.)	Total Burden (in hrs.)
Adult patients: administered by web-based forms (online via OpenMedNet); See Attachment 3 for the forms				
CDC Symptom Inventory (CDC-SI)/Form A	45	1	12/60	9
CDC Symptom Inventory (CDC-SI)/Form B	20	1	10/60	3
CDC Symptom Inventory (CDC-SI)	20	1	8/60	3
Short Form CDC-SI/Checklist	85	1	10/60	14
Medical Outcomes Study Short Form 36	85	1	7/60	10
Multidimensional Fatigue Inventory (MFI-20)	85	1	5/60	7
DePaul Symptom Questionnaire (DSQ)	45	1	24/60	18
DSQ, 26 selected questions	65	1	12/60	13
DSQ, 18 selected questions	85	1	6/60	9
PROMIS Short Form (PROMIS SF - Fatigue, SD, SRI, PB, PI) & Sleep Data Collection Form	85	1	5/60	7
PROMIS SF - Fatigue, SD, SRI, PB, PI	85	1	4/60	6
Brief Pain Inventory (BPI)	85	1	13/60	18
Patient Health Questionnaire (PHQ-8), Generalized Anxiety Disorder (GAD-7), CDC Health-Related Quality of Life (HRQoL-4)	85	1	10/60	14
CDC HRQoL-4	85	1	3/60	4
CDC HRQoL-4 with activity limitation questions	85	1	4/60	6
Self-Rating Depression Scale (SDS)	45	1	7/60	5
Illness Impact Questionnaire	85	1	3/60	4
Saliva Data Collection Sheet	85	1	5/60	7
Orthostatic Grading Scale (OGS)	85	1	3/60	4
COMPOSITE Autonomic Symptom Score 31 (COMPASS-31)	85	1	5/60	7
Adult patients: administered by hard-copied forms; See Attachment 3 for the forms				
CDC Symptom Inventory (CDC-SI)/Form A	24	1	42/60	17
CDC Symptom Inventory (CDC-SI)/Form B	30	1	20/60	10
CDC Symptom Inventory (CDC-SI)	15	1	10/60	3
Short Form CDC-SI/Checklist	69	1	20/60	23
Medical Outcomes Study Short Form 36	69	1	17/60	20
Multidimensional Fatigue Inventory (MFI-20)	69	1	10/60	12
DePaul Symptom Questionnaire (DSQ)	24	1	36/60	14

DSQ, 26 selected questions	45	1	18/60	14
DSQ, 18 selected questions	69	1	20/60	23
PROMIS Short Form (PROMIS SF - Fatigue, SD, SRI, PB, PI) & Sleep Data Collection Form	24	1	6/60	2
PROMIS SF - Fatigue, SD, SRI, PB, PI	69	1	5/60	6
Brief Pain Inventory (BPI)	24	1	13/60	5
Patient Health Questionnaire (PHQ-8), Generalized Anxiety Disorder (GAD-7), CDC Health-Related Quality of Life (HRQoL-4)	24	1	10/60	4
CDC HRQoL-4	69	1	4/60	5
CDC HRQoL-4 with activity limitation questions	69	1	7/60	8
Self-Rating Depression Scale (SDS)	24	1	7/60	3
Illness Impact Questionnaire	69	1	3/60	3
Saliva Data Collection Sheet	69	1	5/60	6
Orthostatic Grading Scale (OGS)	69	1	5/60	6
COMPOSITE Autonomic Symptom Score 31 (COMPASS-31)	69	1	7/60	8
Pediatric patients (aged 10-17 years): administered by web-based forms (online via OpenMedNet); See Attachment 4 for the forms				
CDC Symptom Inventory: For Baseline Subjects Pediatrics	36	1	8/60	5
CDC Symptom Inventory: For the Follow-Up Subjects Pediatrics	29	1	6/60	3
SF-36 Health Survey	64	1	5/60	5
Multidimensional Fatigue Inventory (MFI-20)	64	1	2/60	2
Selected Questions from DePaul Pediatric Health Questionnaire (DPHQ), 19 Questions	64	1	5/60	5
PROMIS Pediatric Instruments (Fatigue & Pain)	64	1	2/60	2
Pediatric Pain Questionnaire (PPQ)	64	1	7/60	8
Visual Analogue Scale	64	1	6/60	6
Hospital Anxiety and Depression Scale	64	1	5/60	5
Pediatric Daytime Sleepiness Scale	64	1	2/60	2
Social Participation Form Pediatric	64	1	7/60	8
Sociability Form	64	1	3/60	3
Saliva Collection Form	64	1	5/60	5
Pediatric patients (aged 10-17 years): administered by hard-copied forms; See Attachment 4 for the forms				
CDC Symptom Inventory: For Baseline Subjects Pediatrics	3	1	20/60	1
CDC Symptom Inventory: For the Follow-Up Subjects Pediatrics	3	1	9/60	0
SF-36 Health Survey	3	1	9/60	0

Multidimensional Fatigue Inventory (MFI-20)	3	1	7/60	0
Selected Questions from DePaul Pediatric Health Questionnaire (DPHQ), 19 Questions	3	1	10/60	0
PROMIS Pediatric Instruments (Fatigue & Pain)	3	1	3/60	0
Pediatric Pain Questionnaire (PPQ)	3	1	15/60	1
Visual Analogue Scale	3	1	8/60	0
Hospital Anxiety and Depression Scale	3	1	7/60	0
Pediatric Daytime Sleepiness Scale	3	1	3/60	0
Social Participation Form Pediatric	3	1	10/60	0
Sociability Form	3	1	5/60	0
Saliva Collection Form	3	1	5/60	0
Adult patients: administered by web-based forms (online via OpenMedNet and CogState); See Attachment 5 for the forms				
CogState Practice Section	109	1	17/60	31
CogState Baseline Section	109	1	27/60	49
WAIS IV DS F+B, TOPF	109	1	10/60	18
Exercise (Bike) Testing	64	1	30/60	32
CogState Time 1 Section	109	1	22/60	40
CogState Time 2 Section	109	1	12/60	22
CogState Time 3 Section	109	1	12/60	22
CogState Time 4 Section	109	1	12/60	22
Visual Analogue Scale for CFS Symptoms	60	1	8/60	8
EQ-5D-Y Health Questionnaire	60	1	6/60	6
PROMIS SF v1 – Physical Function	60	1	5/60	5
Physical Fitness and Exercise Activity Levels of Scale	60	1	2/60	2
International Physical Activity Questionnaire (Self-Administered Long Form)	60	1	5/60	5
Physical Activity Readiness Questionnaire	60	1	5/60	5
Adult patients: administered by hard-copied forms; See Attachment 5 for the forms				
Visual Analogue Scale for CFS Symptoms	49	1	8/60	6
EQ-5D-Y Health Questionnaire	49	1	6/60	5
PROMIS SF v1 – Physical Function	49	1	5/60	4
Physical Fitness and Exercise Activity Levels of Scale	49	1	2/60	2
International Physical Activity Questionnaire (Self-Administered Long Form)	49	1	5/60	4
Physical Activity Readiness Questionnaire	49	1	5/60	4
Total				711

B. Estimated Annualized Burden Costs

Exhibit 12.B. Summary of Estimated Annualized Burden Costs

Form Name	Total Burden Hours	Hourly Wage Rate*	Total Participant Costs
Adult patients: administered by web-based forms (online via OpenMedNet); See Attachment 3 for the forms			
CDC Symptom Inventory (CDC-SI)/Form A	9	\$23.86	\$214.74
CDC Symptom Inventory (CDC-SI)/Form B	3	\$23.86	\$79.53
CDC Symptom Inventory (CDC-SI)	3	\$23.86	\$63.63
Short Form CDC-SI/Checklist	14	\$23.86	\$338.02
Medical Outcomes Study Short Form 36	10	\$23.86	\$236.61
Multidimensional Fatigue Inventory (MFI-20)	7	\$23.86	\$169.01
DePaul Symptom Questionnaire (DSQ)	18	\$23.86	\$429.48
DSQ, 26 selected questions	13	\$23.86	\$310.18
DSQ, 18 selected questions	9	\$23.86	\$202.81
PROMIS Short Form (PROMIS SF - Fatigue, SD, SRI, PB, PI) & Sleep Data Collection Form	7	\$23.86	\$169.01
PROMIS SF - Fatigue, SD, SRI, PB, PI	6	\$23.86	\$135.21
Brief Pain Inventory (BPI)	18	\$23.86	\$439.42
Patient Health Questionnaire (PHQ-8), Generalized Anxiety Disorder (GAD-7), CDC Health-Related Quality of Life (HRQoL-4)	14	\$23.86	\$338.02
CDC HRQoL-4	4	\$23.86	\$101.41
CDC HRQoL-4 with activity limitation questions	6	\$23.86	\$135.21
Self-Rating Depression Scale (SDS)	5	\$23.86	\$125.27
Illness Impact Questionnaire	4	\$23.86	\$101.41
Saliva Data Collection Sheet	7	\$23.86	\$169.01
Orthostatic Grading Scale (OGS)	4	\$23.86	\$101.41
COMPOSITE Autonomic Symptom Score 31 (COMPASS-31)	7	\$23.86	\$169.01
Adult patients: administered by hard-copied forms; See Attachment 3 for the forms			
CDC Symptom Inventory (CDC-SI)/Form A	17	\$23.86	\$400.85
CDC Symptom Inventory (CDC-SI)/Form B	10	\$23.86	\$238.60
CDC Symptom Inventory (CDC-SI)	3	\$23.86	\$59.65
Short Form CDC-SI/Checklist	23	\$23.86	\$548.78
Medical Outcomes Study Short Form 36	20	\$23.86	\$466.46
Multidimensional Fatigue Inventory (MFI-20)	12	\$23.86	\$274.39
DePaul Symptom Questionnaire (DSQ)	14	\$23.86	\$343.58
DSQ, 26 selected questions	14	\$23.86	\$322.11
DSQ, 18 selected questions	23	\$23.86	\$548.78
PROMIS Short Form (PROMIS SF - Fatigue, SD, SRI, PB, PI) & Sleep Data	2	\$23.86	\$57.26

Collection Form			
PROMIS SF - Fatigue, SD, SRI, PB, PI	6	\$23.86	\$137.20
Brief Pain Inventory (BPI)	5	\$23.86	\$124.07
Patient Health Questionnaire (PHQ-8), Generalized Anxiety Disorder (GAD-7), CDC Health-Related Quality of Life (HRQoL-4)	4	\$23.86	\$95.44
CDC HRQoL-4	5	\$23.86	\$109.76
CDC HRQoL-4 with activity limitation questions	8	\$23.86	\$192.07
Self-Rating Depression Scale (SDS)	3	\$23.86	\$66.81
Illness Impact Questionnaire	3	\$23.86	\$82.32
Saliva Data Collection Sheet	6	\$23.86	\$137.20
Orthostatic Grading Scale (OGS)	6	\$23.86	\$137.20
COMPOSITE Autonomic Symptom Score 31 (COMPASS-31)	8	\$23.86	\$192.07
Pediatric patients (aged 10-17 years): administered by web-based forms (online via OpenMedNet); See Attachment 4 for the forms			
CDC Symptom Inventory: For Baseline Subjects Pediatrics	5	\$11.93	\$56.81
CDC Symptom Inventory: For the Follow- Up Subjects Pediatrics	3	\$11.93	\$34.09
SF-36 Health Survey	5	\$11.93	\$63.91
Multidimensional Fatigue Inventory (MFI- 20)	2	\$11.93	\$25.56
Selected Questions from DePaul Pediatric Health Questionnaire (DPHQ), 19 Questions	5	\$11.93	\$63.91
PROMIS Pediatric Instruments (Fatigue & Pain)	2	\$11.93	\$25.56
Pediatric Pain Questionnaire (PPQ)	8	\$11.93	\$89.48
Visual Analogue Scale	6	\$11.93	\$76.69
Hospital Anxiety and Depression Scale	5	\$11.93	\$63.91
Pediatric Daytime Sleepiness Scale	2	\$11.93	\$25.56
Social Participation Form Pediatric	8	\$11.93	\$89.48
Sociability Form	3	\$11.93	\$38.35
Saliva Collection Form	5	\$11.93	\$63.91
Pediatric patients (aged 10-17 years): administered by hard-copied forms; See Attachment 4 for the forms			
CDC Symptom Inventory: For Baseline Subjects Pediatrics	1	\$11.93	\$11.36
CDC Symptom Inventory: For the Follow- Up Subjects Pediatrics	0	\$11.93	\$5.11
SF-36 Health Survey	0	\$11.93	\$5.11
Multidimensional Fatigue Inventory (MFI- 20)	0	\$11.93	\$3.98
Selected Questions from DePaul Pediatric Health Questionnaire (DPHQ), 19 Questions	0	\$11.93	\$5.68

PROMIS Pediatric Instruments (Fatigue & Pain)	0	\$11.93	\$1.70
Pediatric Pain Questionnaire (PPQ)	1	\$11.93	\$8.52
Visual Analogue Scale	0	\$11.93	\$4.54
Hospital Anxiety and Depression Scale	0	\$11.93	\$3.98
Pediatric Daytime Sleepiness Scale	0	\$11.93	\$1.70
Social Participation Form Pediatric	0	\$11.93	\$5.68
Sociability Form	0	\$11.93	\$2.84
Saliva Collection Form	0	\$11.93	\$2.84
Adult patients: administered by web-based forms (online via CogState and OpenMedNet); See Attachment 5 for the forms			
CogState Practice Section	31	\$23.86	\$733.98
CogState Baseline Section	49	\$23.86	\$1,165.73
WAIS IV DS F+B, TOPF	18	\$23.86	\$431.75
Exercise (Bike) Testing	32	\$23.86	\$766.93
CogState Time 1 Section	40	\$23.86	\$949.86
CogState Time 2 Section	22	\$23.86	\$518.10
CogState Time 3 Section	22	\$23.86	\$518.10
CogState Time 4 Section	22	\$23.86	\$518.10
Visual Analogue Scale for CFS Symptoms	8	\$23.86	\$190.88
EQ-5D-Y Health Questionnaire	6	\$23.86	\$143.16
PROMIS SF v1 – Physical Function	5	\$23.86	\$119.30
Physical Fitness and Exercise Activity Levels of Scale	2	\$23.86	\$47.72
International Physical Activity Questionnaire (Self-Administered Long Form)	5	\$23.86	\$119.30
Physical Activity Readiness Questionnaire	5	\$23.86	\$119.30
Adult patients: administered by hard-copied forms; See Attachment 5 for the forms			
Visual Analogue Scale for CFS Symptoms	6	\$23.86	\$154.52
EQ-5D-Y Health Questionnaire	5	\$23.86	\$115.89
PROMIS SF v1 – Physical Function	4	\$23.86	\$96.58
Physical Fitness and Exercise Activity Levels of Scale	2	\$23.86	\$38.63
International Physical Activity Questionnaire (Self-Administered Long Form)	4	\$23.86	\$96.58
Physical Activity Readiness Questionnaire	4	\$23.86	\$96.58
Total			\$16,284

*Based on “All Occupations” mean hourly wage of \$23.86 for adult patients and for younger children and adolescents, we used a weighted and blended rate of early adolescents and late adolescents: a figure of \$11.93 per hour. Source: Occupational Employment and Wages, May 2016, Bureau of Labor Statistics, US Department of Labor, https://www.bls.gov/oes/current/oes_nat.htm

Exhibit 12.1.2. Summary of Respondent Burden Estimates and Annualized Costs to Respondents – administered by hard-copied forms

*Based on “All Occupations” mean hourly wage of \$23.86. Source: Occupational Employment and Wages, May 2016, Bureau of Labor Statistics, US Department of Labor.

https://www.bls.gov/oes/current/oes_nat.htm

For the *Protocol #2 – MCAM in Children Adolescents*, study participants (patients aged 10-17 and enrolled for the study) will be asked to complete the prospective data collection on Appendix 11a – Appendix 22 (Attachment 4) that collects data pertaining health, quality of life, ME/CFS-related symptoms on fatigue, cognition, pain, sleep, orthostatic and autonomic symptoms, depression, anxiety, and illness impact. The information collection will be completed by two contractors: Open Medicine Institute (OMI) Consortium and Institute for Neuro-Immune Medicine (INIM). This part of the MCAM study was planned in September 2012 and has been conducted since 2013. It was estimated to complete by September, 2023 This part of the information has been collected using web-based forms (OpenMedNet) for patients enrolled at OMI consortium clinics and via hard-copied forms for patients enrolled at INIM clinics.

The hour-burden estimates include the time needed for reviewing instructions, completing and reviewing the collection of information. Annualized costs associated with the hour burdens for the collection of information are also included in the table below.

Exhibit 12.2.1. Summary of Respondent Burden Estimates and Annualized Costs to Respondents – administered by web-based forms (OpenMedNet)

*To estimate an hourly rate for younger children and adolescents, we used a weighted and blended rate of early adolescents and late adolescents: a figure of \$11.93 per hour, derived from the U.S. Department of Labor, Bureau of Labor Statistics, Occupational earnings tables.

Exhibit 12.2.2. Summary of Respondent Burden Estimates and Annualized Costs to Respondents – administered by hard-copied forms

*To estimate an hourly rate for younger children and adolescents, we used a weighted and blended rate of early adolescents and late adolescents: a figure of \$11.93 per hour, derived from the U.S. Department of Labor, Bureau of Labor Statistics, Occupational earnings tables.

The third and fourth protocols use standardized approaches to collect cognition and exercise testing and Natural Killer (NK) cell function data on a subset of participants from the first longitudinal study protocol on adults, *Protocol #1 – MCAM in Adults*. The *Protocol #4 – MCAM: Natural Killer Cell Testing only obtains* extra tubes from participants and do not ask them to fill out any instrument for data collection.

Exhibit 12.3.1. Summary of Respondent Burden Estimates and Annualized Costs to Respondents – administered online (OpenMedNet and CogState)

*Based on “All Occupations” mean hourly wage of \$23.86. Source: Occupational Employment and Wages, May 2016, Bureau of Labor Statistics, US Department of Labor.

Exhibit 12.3.2. Summary of Respondent Burden Estimates and Annualized Costs to Respondents – administered hard-copied forms

*Based on “All Occupations” mean hourly wage of \$23.86. Source: Occupational Employment and Wages, May 2016, Bureau of Labor Statistics, US Department of Labor.

Across all four protocols of the MCAM study, the annual reporting burden to respondents/participants is as follows: the burden hours estimated at 715 and the burden costs estimated at \$16,284.

13. Estimates of Other Total Annual Cost Burden to Respondents or Record Keepers

There are no costs to the study participants other than their time to participate.

14. Annualized Cost to the Government

The data collection activities described in this submission have been conducted by three contractors: Open Medicine Institute (OMI) Consortium, Mount Sinai Beth Israel, and Institute for Neuro-Immune Medicine. The MCAM study was planned in September 2011 and has been conducted since 2012. It is anticipated to complete by September 2023. The estimated contract cost to the federal government is \$12.2 million for all four protocols of this MCAM study over a 10-year period. The total annualized cost to the government is about \$1.22 million. These costs include the costs of information collection, design, development, printing forms, travel, meetings, and data deliverables.

15. Explanation for Program Changes or Adjustments

This is a new information collection request for ongoing information collection in use without an OMB number.

16. Plans for Tabulation and Publication and Project Time Schedule

The study is conducted in eight stages following 4 IRB-approved study protocols. It includes baseline and follow-up visits. Not all participants would be enrolled in the same stage, and therefore, baseline data could come from any stage. Follow-up is planned annually (10–14 months) to coincide with return clinic appointments. The number of follow-up visits for each participant will vary depending on the stage at first enrollment. Additional clinics were added at Stage-7 (approximately 2019-2021) to enroll Baseline pediatric patients and will be followed up at Stage-8 (approximately 2021-2023). These additional pediatric participants will be followed up at least once. Except for the enrollment of this cohort, data collection of all other parts of has been completed. The proposed project schedule is summarized in Exhibit 16.

Exhibit 16. Proposed Project Schedule

Project Time Schedule	
Activity	Time Schedule
New information collection begins	4 weeks after OMB approval
Information collection (See Exhibit 16.1):	

- Baseline Information Collection	January, 2012 – July, 2021*
- 1 st Follow-Up Information Collection	August, 2013 – September, 2023*
- 2 nd Follow-Up Information Collection	April, 2014 – September, 2023*
- 3 rd Follow-Up Information Collection	July, 2016 – December, 2019
- 4 th Follow-Up Information Collection	June, 2017 – December, 2019
- 5 th Follow-Up Information Collection	January, 2018 – December, 2019
Cleaning and Processing Data:	
- ME/CFS Baseline Data	6-months after completing the collection (~December, 2013)
- Interim Baseline Data (ME/CFS, Healthy Controls)	December, 2017
- Baseline Data (All Study Groups)	6-months after completing the collection
- 1 st Follow-Up Data	6-months after completing the collection
- 2 nd Follow-Up Data	6-months after completing the collection
- 3 rd Follow-Up Data	6-months after completing the collection
- 4 th Follow-Up Data	6-months after completing the collection
- 5 th Follow-Up Data	6-months after completing the collection
Technical Reports:	
- IOM Report on ME/CFS: using ME/CFS baseline Data	August, 2014
- FDA Clinical Outcome Assessment Qualification: using baseline data of ME/CFS patients and healthy controls	July, 2017 – June, 2019
Publications:	
- Paper on the study method	2017
- Papers using baseline data	One year after completing the collection (~2019)
- Papers using longitudinal data	One year after completing the collection (~2020)

*indicates those additional pediatric participants enrolled at Stage-7 and the follow-ups will be through September 2023.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

The display of the OMB Expiration date is inappropriate. The expiration date will not be displayed on the online or hard-copied forms, but it will be provided upon request.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.

Attachments

1. Appropriation Language
2. 60-Day FRN
3. Appendices_Protocol #1_MCMA_Adults
4. Appendices_Protocol #2_MCAM_Pediatric
5. Appendices_Protocol #3_MCAM_CE

6. IRB Approval Letters