Registry of Unexplained Fatiguing Illnesses and Chronic Fatigue Syndrome (CFS): A Pilot Study

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Abstract

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Summary

Centers for Disease Control and Prevention (CDC) seeks approval to conduct information collection activities associated with the *Registry of Unexplained Fatiguing Illnesses and Chronic Fatigue Syndrome (CFS): A Pilot Study* (hereafter referred to as the *Registry Pilot Study*).

Using Bibb County, Georgia as a test area, CDC will recruit specific types of physicians and other health care providers, such as chiropractors, physical therapists, and psychologists, who practice in Bibb County and areas within 30 miles of Bibb County and who are likely to see adolescent or adult patients (age 12 to 59 years) with unexplained fatiguing illnesses, including CFS. Providers who are employed solely by the military, nursing homes, prisons or dialysis centers will not be eligible to participate.

During a one-year period, participating providers will initially screen their patients for eligibility in a registry of unexplained fatiguing illness before referring them to this study. Patients whose fatigue can be explained by medical or psychiatric conditions will not be eligible, because the presence of unresolved conditions precludes a classification of CFS. Referred patients will be asked to consent to be contacted for a detailed telephone interview. Consenting parents, as proxy respondents, will consent to be contacted and interviewed about their referred adolescents. The detailed interview will collect information on fatigue and other symptoms, medical and psychiatric conditions, demographics, psychiatric comorbidity, and other psychosocial factors. The telephone survey is similar to the instrument approved by OMB for the baseline *Survey of CFS and Chronic Unwellness in Georgia* (OMB #0920-0638) and currently in review for the *Follow-up Survey of CFS and Chronic Unwellness in Georgia (*also OMB #0920-0638). Following the detailed interview, CDC will evaluate the data to determine each subject's eligibility for the clinical evaluation component.

Eligible subjects will be invited to the CDC clinic in Macon, Georgia. Clinical evaluation protocols and instruments for the *Registry Pilot Study* are similar to the procedures and materials used in

the *Survey of CFS and Chronic Unwellness in Georgia* (OMB #0920-0638). Because clinical studies are exempt from OMB review, the portions of the clinical evaluation are provided to OMB for information only. In this submission, we request OMB approval of these information collections:

- Health care provider recruitment and information collection instruments.
- Referral and consent to contact information.
- Telephone survey data collection.
- Portions of the clinical evaluation that are not exempted from review.

Justification

A.1. Circumstances Making the Collection of Information Necessary

A.1.a. Authorizing Legislation

The authorizing legislation for the *Registry Pilot Study* is contained in the US Code. Section 42 USC 241 of this Code (Attachment 1) authorizes collection this information.

A.1.b. Congressional Support for CFS Research.

Chronic fatigue syndrome (CFS) is a Congressional priority, and CDC is responsible for its prevention and control. Beginning in 1992, Congressional language has stressed legislators' desire for CDC to develop control and prevention measures for CFS. Congressional language has for many years recommended developing a registry for CFS patients and educating health care providers about CFS. As early as 2003, Congress requested a CFS Registry and provider education, as stipulated in the paragraph below.

> "The (Appropriations) Committee further expects that CDC … accelerate its CFS research plan to identify the causes, risk factors, diagnostic markers, natural history and economic impact of CFS; to create a CFS patient registry, and to educate health care providers about the detection, diagnosis and management of CFS." (Congressional Record 2003)

More recent Congressional directives may be found in Attachment 2. This protocol addresses these Congressional concerns.

A.1.c. Need for Data Collection

CFS is a complex medical and public health problem. CFS is characterized by medically and psychiatrically unexplained disabling fatigue that is not relieved by rest and is accompanied by symptoms of prolonged postexertional malaise, unrefreshing sleep, impaired concentration and short-term memory,

muscle and joint pain, headache, sore throat, and tender lymph nodes [Fukuda *et al*., 1994]. At least one million adults in the U.S. suffer from CFS [Reyes *et al*., 2003; Jason *et al*., 1999; Bierl *et al*., 2004]. Their median duration of illness is seven years, a quarter of them are unemployed or receiving disability [Solomon *et al*., 2003], and the average affected family forgoes $20,000 annually in lost earnings and wages (half the median U.S. household income). Overall, CFS costs the U.S. just over $9 billion annually in lost productivity [Reynolds *et al*., 2004].

The *Survey of Chronic Fatigue Syndrome and Chronic Unwellness in Georgia (*hereafter referred to as the *Baseline Survey)* (OMB #0920-0638), conducted between 2004 and 2005, provided baseline information on CFS in metropolitan, urban, and rural regions in Georgia (Atlanta, Macon and Warner Robins, and the counties surrounding Macon, respectively). The *Baseline Survey* evaluated the occurrence of CFS in different racial/ethnic populations, obtained data concerning access to and utilization of health care and economic impact of CFS, and evaluated associated risk factors.

Analyses of *Baseline Survey* data show that 2.54% of the adult population of Georgia suffers from CFS. This figure is 6- to 10-fold higher than previous prevalence estimates and likely reflects improved screening methods and more sensitive and specific diagnostic criteria. CFS prevalence is higher among whites compared to blacks. Overall risk of CFS did not differ between metropolitan, urban, and rural populations. However, this was only true among women ($p = .37$). Among men, CFS prevalence varied significantly among geographic strata; 0.42% of men in the metropolitan area, 1.82% of male urban residents, and 2.89% of men from rural areas suffered CFS. This was reflected in sex-specific risk ratios; in the metropolitan area, the CFS prevalence in women was 11.2 times that in men ($p = .009$), whereas in the urban and rural populations the female-to-male ratios of CFS prevalence were 1.7 and 0.8, respectively, and did not represent statistically significant differences. The other major finding to date is that 48% of persons clinically evaluated because CFS-like illness was identified during telephone interviews had exclusionary medical or psychiatric conditions. Most of these subjects' conditions were amenable to treatment.

The goal of the present study is to implement a one-year pilot study of a Registry of Unexplained Fatiguing Illness and CFS in Bibb County, Georgia. This pilot study will evaluate the efficacy and efficiency of two study designs for identifying, screening, and enrolling a large number of well-characterized patients into a registry for further study, including clinical intervention trials. The two study designs are based on referrals of patients from health care providers: one design is based on physician-based referrals only; the other, on a combination of physician and other health care provider referrals. CDC will also pilot a health care provider education intervention during this one-year period. The Registry will ultimately be longitudinal in design to allow the study of the natural history of CFS and factors associated with remission. In addition, the Registry will serve as the basis for studying health care utilization among CFS patients and the effects of CFS education on health care providers knowledge, attitudes and beliefs about CFS. Finally, the Registry will identify well-characterized CFS patients for consideration in clinical intervention trials. The *Registry Pilot Study* has five specific aims.

Aim 1: Enroll approximately 185 persons with CFS and unexplained fatiguing illnesses and characterize them with respect to illness symptoms, allostatic load, functional impairment and disability, personality diagnosis, presence of depression and anxiety, history of traumatic events and exposure to stressful live events. CDC is conducting population-based studies (OMB #0920-0638) to calculate prevalence and incidence of CFS, evaluate public health aspects of the illness, identify risk factors and laboratory markers, and develop prevention strategies. However, such studies are inadequate to answer some pivotal questions concerning clinical aspects of CFS. For example, subjects with CFS experience waxing and waning symptoms over time, with 57% reporting partial or complete remission over a three-year period and 10% reporting complete remission. Remission is more common in the first two years of illness [Nisenbaum R *et al.*, 2003], but people identified with CFS in the general population of Georgia have been ill for an average of seven years [Maloney EM, unpublished data]. The small number of subjects with recent onset of symptoms precluded the ability to study the complete natural history of CFS. One specific aim of the Registry is to identify large numbers of subjects with recent

onset of symptoms who can be followed to describe the natural history of illness in detail. The use of provider-based referrals and ascertainment of persons with unexplained fatiguing illnesses are mechanisms to enhance enrollment of subjects with CFS within the first year of illness. Registry enrollees will provide the pool of candidates needed for future clinical intervention trials designed to treat fatigue.

Characterization of CFS cases requires not only the classification of persons as having CFS, but also identifying their common comordities, including anxiety and personality disorders, as well as depression. Well-characterized patients should also be assessed for presence of reported risk factors, including early childhood trauma and high allostatic load [Heim *et al*, 2006; Maloney *et al.*, 2006]. Allostatic load is an index based on laboratory and clinical factors that, in total, have been described to represent the cumulative wear and tear on the body and brain due to chronic exposure to stress or an inadequate stress response [McEwen B, et al., 1993].

Aim 2: Implement a health care provider CFS-education component targeting the types of providers expected to participate in the Registry. CDC has developed CFS education materials specific to health care providers. CDC will introduce various educational materials and monitor the impact of the materials on the number of referrals and enrollment. CDC provides learning opportunities (such as, self-study clinical medical education (CME) materials) to participating providers and will invite local health care providers to attend specific education events (public forum "town hall" meetings, hospital grand rounds, inhouse educational seminars) during the course of the Registry Pilot Study enrollment period.

Aim 3: Assess knowledge, attitudes and beliefs (KABs) among participating providers. CDC will test the efficacy of these provider education materials by obtaining baseline measures of provider knowledge, attitudes, and beliefs (KABs) concerning CFS; disseminating provider educational materials as an intervention; and following up one year later with providers to see if their CFS KABs have

changed. CDC will collect KAB data from participating health care providers and from non-participants who attend CDC-led town hall meetings, hospital grand rounds, and practice-level, in-house seminars.

Aim 4: Assess economic impact of CFS and reported health care utilization among persons with CFS and other unexplained fatiguing illnesses. The allocation of public and private health care and disability resources requires accurate information concerning the economic burden of disease. Development and evaluation of public health control and prevention programs demand accurate information concerning the costs and benefits of interventions and information concerning access to and utilization of health care by those who are ill. Congress has directed CDC to accelerate its CFS research plan to identify the economic impact of CFS and to accelerate its educational activities for health care providers. The Registry Pilot Study will evaluate direct and indirect costs of CFS, and access to and utilization of health care by those who suffer from CFS by administering questionnaires that measure these factors. An advantage of the provider-based design of the Registry is that, in addition to analyzing self-reported data, we will be able to objectively measure the types of health care providers accessed by persons with CFS and other fatiguing illnesses and assess referral patterns among different kinds of providers. This pilot study will also measure the average number of referrals from varying types of physicians and other health care providers to add to this growing body of literature.

Aim 5: Assess feasibility of the two study designs for a (1) physician-based Registry and a (2) physician and other health care provider-based Registry. Based on the results of *this Registry Pilot Study*, we will assess whether a physician-based design is all that is needed to identify a large number of persons with unexplained fatiguing illness or CFS, or whether a combined design of physicians and other health care providers results in a substantially higher number of enrollees. Factors to be assessed include the number of subjects enrolled and efficiency of each design at enrolling subjects (i.e., average cost per enrolled subject). We will also assess the relative contribution of the varying provider types to the size of the Registry.

A.2. Purpose and Use of the Information Collected

As noted in Section A.1.c, the purpose of the proposed *Registry Pilot Study* is to identify large numbers of subjects with recent onset of fatigue who can be followed to describe the natural history of fatiguing illness in detail. These registry enrollees will form the pool of candidates needed for future clinical intervention trials.

Using provider-based referrals of persons with unexplained fatiguing illnesses increases the quality of the referrals because referrals will have been pre-screened by the providers to rule out other illnesses. This process is much more efficient than identifying such subjects through probability methods, which would require surveying a very large number of people in order to identify those with the relatively rare condition of CFS.

Importantly, the *Registry Pilot Study* will provide the baseline information for future clinical intervention trials. Enrolled subjects will be well characterized in terms of their duration and severity of illness, comorbid conditions, presence of risk factors (sex, stress history, high allostatic load), all of which will help to identify homogeneous subgroups for selection in intervention trials. Further, follow-up of these enrolled subjects will allow us to assess whether these risk factors for illness are also risk factors for prolonged illness course. In addition, the Registry pilot study provides for the means of evaluating the effects of provider education on the providers' knowledge regarding the diagnosis and management of CFS.

CDC will utilize the data to implement measures that decrease the morbidity of CFS in the general public. Specifically, information on clinical course and knowledge regarding variables related to morbidity of CFS (e.g., stress history and allostatic load) will be incorporated into ongoing provider education and public awareness programs. Data concerning specific aspects of stress history and allostatic load will used to further refine molecular epidemiology laboratory studies directed at defining the pathophysiology of CFS. Information on access to and utilization of health care will be used in planning and evaluating a targeted pilot regional intervention program for the vast majority of persons in

the community with CFS who have not been diagnosed. Data collected from health care providers will be used to enhance provider education materials published by CDC.

A.3. Use of Information Technology and Burden Reduction

CDC will use website and computer-assisted interviewing technology to facilitate data collection and reduce burden.

A secured website will be offered to providers who prefer to use the Internet to make referrals and to patients who prefer the Internet to give consent to be contacted. Providers and their patients will decide which medium is least burdensome as they will also be offered the options of prepaid, business return envelopes and a toll-free line to call.

All telephone interviews will be conducted using computer-assisted telephone interviewing (CATI) technology. CATI is an efficient interviewing mode that reduces respondent burden and improves the quality of the data collected. The CATI system will include logic checks and skip-pattern controls to ensure that respondents receive the appropriate questions and that the interview process goes smoothly. These programmed checks also identify inconsistent responses, allowing the interviewer to resolve discrepancies during the interview.

The sample management portion of the CATI system efficiently handles large samples, as well as samples with numerous strata or clusters. Distribution of telephone numbers to interviewers is very fast. The system allows for flexible scheduling of callbacks to allow respondents to be called at their convenience. It also contains well-tested calling algorithms for delivering records to interviewers based on the outcomes of previous call attempts that maximize the probability of completing interviews and thereby increase response rates.

Another CATI software module allows supervisors to monitor production and quality, including monitoring of interviews as they transpire. Researchers have easy access to survey responses and data

frequencies for each variable. For survey review and preliminary analysis, the CATI system can produce a copy of the questionnaire with survey frequencies posted next to each question.

The CATI system also contains protections against data loss. Completed questionnaire data are stored during the interviewing process; nightly, a full backup of the entire CATI system occurs.

During the clinical evaluation, eight clinical evaluation questionnaires (30%) will be administered using ACASI (audio-enhanced computer-assisted self-administered interviews). Like CATI, ACASI includes logic checks and skip-pattern controls to ensure that respondents receive the appropriate questions and that the interview process goes smoothly. Should a respondent have difficulty reading, the audio portion can be activated and the computer will read questions and answer categories to the subject.

A.4. Efforts to Identify Duplication and Use of Similar Information

CDC is creating this registry to identify early onset of CFS for future intervention studies, and this study of CFS cannot readily be accomplished by other methods. In our Georgia Baseline Survey, which is a population-based study of CFS, only 20-25% of CFS cases were indentified within 2 years of developing their illness (unpublished data). Yet approximately 75% of all CFS cases in that study reported seeing a doctor for their symptoms. We think that identifying potential subjects via referrals from health care providers will allow us to expand the number of CFS cases we diagnose early in the illness process, thus improving upon the population-based survey study as a means to identify new and relatively new cases.

A.5. Impact on Small Businesses or Other Small Entities

This information collection involves health care providers, some of whom are employees or owners of small health care practices. The forms that providers will fill out and the processes for returning the information are designed to minimize burden on these small businesses. By asking the provider to designate a single point person at each office who can take responsibility for following the referral protocol, we will avoid burdening multiple staff employees who may rarely be involved with the provider's patients.

Furthermore, the provider may choose the most convenient medium to transmit referral information. The provider or his/her designee may mail the referral information, call the information into us via a toll free number, or use a secured website to transfer referral data.

A.6. Consequences of Collecting the Information Less Frequently

The proposed data collection takes place over a one-year period. During this time, registry candidates will be interviewed by telephone once and clinically evaluated once.

Participating health care providers will be surveyed twice about the knowledge, attitudes, and beliefs about CFS. Between provider information collections, CDC will disseminate education materials as an intervention. Changes in knowledge, attitudes and beliefs cannot be measured without a post-intervention survey.

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

The *Registry Pilot Study* is in full compliance with the guidelines of 5 CFR 1320.5.

This supporting statement describes reimbursement to participating subjects who are clinically evaluated in Section A.9.

The main goal of this study is to test the best design for identifying large numbers of subjects who have experienced early onset of fatiguing illness and creating a pool of candidates for future intervention trials. Probability sampling of community subjects is not an appropriate design, because few subjects having relatively recent onset of illness will be identified. Therefore, results from this study will not be generalized to the study universe. See Section A.1.c and Section B.1 for further description of the study's design.

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

A.8.a. Federal Register Notice and Public Comment

In accordance with the Paperwork Reduction Act of 1995, the Chronic Viral Diseases Branch published a notice in the Federal Register announcing the agency's intention to request an OMB review of the proposed data collection activities. The notice was published on July 31, 2007 in Volume 72, Number 146, page 41758-41759for a 60-day period for public comment. During the 60-day public comment period, CDC did not receive any comments. The 60-day Federal Registry Notice is attached (Attachment 3).

A.8.b. Consultants

The CDC drew on the expertise of consultants in the development of registry materials. These consultants are listed in Exhibit A.8.1.

Exhibit A.8.1. Consultants

Name	Title	Organization	Telephone	Year(s) in which consultation took place
Dana Brimmer, Ph.D.	Liaison	CFS Provider Education Project	(720) 277-3543	2005-2006
Marjorie Morrissey	Senior Survey Director	Abt Associates Inc.	(312) 867-4061	2005-2007
Scott Royal, Ph.D.	Project Director	Abt Associates Inc.	(301) 634-1717	2005-2007

On December 15, 2005, CDC contractor Abt Associates conducted a focus group with nine health care providers from Bibb County, Georgia to find out about their knowledge, attitudes, and beliefs towards CFS and to understand the constraints providers would face should they be asked to participate in the *Registry Pilot Study.* The feedback we received from the providers has been incorporated into the forms and contacting materials.

A.9. Explanation of Any Payment or Gift to Respondents

Telephone interview respondents will not receive payment for their participation. Subjects who complete the clinical evaluation component will receive $450 for rearranging their work life and private life to take part in an eight- to nine-hour clinical evaluation. Exhibit A.9.1 explains how CDC derived this amount.

Exhibit A.9.1

Mean weekly hourly income in Georgia in 2000 (May 2000)	$16.45[1]	
Assume annual inflation rate	17.5%[2]	
Adjusted mean hourly wage in 2007	$19.33	
Time off from work to participate in this study		
Preparation time (completion of at-home questionnaires and specimen collection)	2.5	
Travel (1.0 hr round trip)	1.0	
Clinic stay @ 8hrs	8.0	
Total time	11.5	
Average reimbursement		$223
Dependent Care Coverage		
$6 per hour @10 hours	$60	
Average reimbursement		$60
Other Expenses		
Assume round trip mileage	30	
Mileage rate	$0.445	
Reimbursement for miles		$14
Parking and Tolls		$25
At-home urine and saliva collection burden		$100
Light meal following clinical evaluation		$20
Average reimbursement		$149
Total Reimbursement		$441
Rounded amount		$450

[1] **SOURCE:** US Department of Labor, Bureau of Labor Statistics: Georgia statewide, all industries, all ownerships, all establishment sizes, average weekly wage in 2000

[2] **SOURCE:** US Department of Labor inflation calculator.

Adolescents and their parents will spend less time at the clinical evaluation. They will be reimbursed $100 and $300, respectively. Exhibit A.9.2 displays the reimbursement schedule for clinic participation.

Health care providers will not be paid. However, because this is a pilot study, CDC plans to run a methodology study to test the effectiveness of a token gift—a two-dollar bill, attached to the first remailed provider recruitment letter. We plan to determine if providers are more likely to respond or to remember the mailing during the non-response telephone prompting effort. A control group will not receive this token gift.

CDC's contractor will also employ non-monetary gifts, such as donuts, note pads or coffee cups during personal visits to providers who have failed to respond to the invitations to participate.

Exhibit A.9.2
Reimbursement Schedule for Clinical Evaluation Participation

Level of Participation	Adult Subject	Parent of Adolescent	Adolescent
Found Ineligible after arriving at clinic, but before consented to participate	$50	$50	$25
Decides not to participate before signing the consent	$50	$50	$25
Voluntarily withdraws any point after signing the consent form	$225	$150	$125
Discharged by staff for any reason prior to completing the evaluation	$450	$300	$100
Completes the clinical evaluation	$450	$300	$100

A.10 Assurance of Confidentiality Provided to Respondents

This submission has been reviewed for Privacy Act applicability and it has been determined that the Privacy Act applies to this study. Regulations for the Protection of Human Subjects also apply. Data for the proposed study will be collected and protected in accordance with Privacy Act system notice 09-20-0136, "Epidemiologic Studies and Surveillance of Disease Problems."

Health care provider data collection will be conducted by two CDC contractors, Abt Associates and Dana Brimmer, Ph.D. Although the first name, last name, address, and telephone information will be collected, CDC will not have access to this information. CDC will receive data labeled only by unique identification (ID) numbers. Abt Associates will maintain the only link between patient-subject name and ID number. Researchers will be able to link providers to their referred patients by ID numbers only.

CDC contractors are extremely conscious of the need to protect the confidentiality of data. Abt Associates staff and Contractor Brimmer will sign Affidavits of Non-Disclosure that are required by CDC. Violation of the signed agreement is grounds for immediate dismissal. If prosecuted and convicted, violators may be fined up to $250,000 and/or imprisoned up to five years.

Because this study conforms to 45 CFS 46 (regulations for protection of human subjects), this study is subject to review and approval by the CDC Institutional Review Board (IRB) and the Abt Associates IRB. Health care providers will be informed of their right to expect confidentiality in provider recruitment materials (Attachment 5a) and CDC website Frequently Asked Questions (FAQs) (Attachment 5b). Subjects will be assured confidentiality in the introductory patient-subject materials (Attachments 8a and 8b), the CATI detailed interview (Attachment 9) and clinical evaluation consent forms (Attachment 21).

A.10.1 Contractor Abt Associates Confidentiality Assurance

All Abt Associates project staff, including data collection staff, are carefully instructed on protecting confidentiality. Such instruction is a key component of Abt Associates' project and corporate training. Instructions are based on CDC's standard procedures and on specifics dictated by Abt Associates' physical facilities. All Abt Associates staff with access to confidential information are required to sign non-disclosure agreements, a standard requirement for all employees and subcontractor staff who have access to confidential data.

Abt Associates has conducted numerous projects involving sensitive information; consequently, facilities and procedures have been developed to maintain this confidentiality. At all sites, building security forces are on duty twenty-four hours, seven days per week. The Cambridge office has a DOD-approved Secret Security Clearance. Access to data processing areas, computer servers, and the computer tape libraries is controlled, with only authorized personnel allowed in. Locked tape files and storage areas are used by all contracts. In addition, individual data banks and files are protected by passwords and other techniques that prohibit access by staff who do not have appropriate clearances. All databases are password protected with only the data administrators having write authority over files.

Each computer platform at Abt Associates Inc. is protected by a log-in system that requires the user to produce both group and individual identification, including personal passwords. This system protects individual files as well as general access to automated hardware and software. Individuals cannot change group affiliation; only a systems administrator can institute such modifications. This system effectively restricts computer access to authorized users.

Auditing programs, in place on each of the platforms, allow system administrators and project directors to monitor the identity and log-in times of all users on the system. Virus scanners are used on all computer networks and PCs to protect against data loss from malicious virus attack.

Data collected at the CDC clinics will be stored temporarily in locked cabinets before being shipped to Abt Associates on a weekly basis.

A.10.2 Contractor Brimmer's Confidentiality Assurance

Contractor Dana Brimmer will assure health care provider confidentiality by signing an Affidavit of Non-Disclosure. In addition, her computer is password-protected. She will store any hard copies of completed questionnaires in a locked file cabinet. At the end of the study, provider questionnaires and attendant forms will be transferred to CDC for long-term storage.

A.11. Justification for Sensitive Questions

There are topics in the telephone interview and in the clinical evaluation that are sensitive and private in nature. Questions that are sensitive in nature are:

- Questions regarding use or abuse of alcohol and other controlled substances
- Questions concerning psychiatric diagnoses
- Questions on gynecological history (including pregnancy)
- Questions concerning stress and trauma

The first two topics noted above are essential to the purpose of the project, because the information they provide is necessary for identifying individuals who meet the CFS case definition. At present, CFS must be identified by excluding other conditions or illnesses that are associated with chronic fatigue. Persons with psychiatric conditions or effects of substance abuse or recent pregnancy may exhibit symptoms similar to the CFS symptom cluster. The questions concerning gynecological history contribute to the complete medical history for women, which is a basic requirement of the diagnostic process. The questions concerning stress and trauma are important for identifying known precipitating factors for CFS and identifying individuals to invite for future studies of CFS.

The CATI detailed interview (Attachment 9) advises respondents when sensitive questions will be asked and reiterates the voluntary nature of participation and the right to refuse any questions. All staff, including clinic staff, receive training on the elements of consent, which includes the right to refuse to answer some or all questions without penalty.

A.12. Estimation of Hour Burden Including Annualized Hourly Costs

For the *Registry Pilot Study*, providers will be asked to complete a Provider Practice form (Attachment 5a) that collects data pertaining to the provider's practice. This is a one-time-only sign-up form. Participating providers will be asked to complete a questionnaire (Attachment 6b) about their CFS knowledge, attitudes, and beliefs (KABs) at the start of one-year registry referral period to collect baseline data. Approximately one year later, a similar questionnaire (also Attachment 6b) will be

administered again to detect changes in provider KABs due to provider-education interventions introduced during the provider education component. The KAB questionnaire will also be handed out during provider education events, such as town halls, grand rounds, and in-house seminars. We expect such events to generate 100 providers, who are not already study participants, to complete this form.

For each referral, participating health care providers will detach and complete the Provider Referral form (Attachment 7). Patients who are interested in participating will be asked to complete the Consent to Contact portion (also Attachment 7) after reviewing introductory materials (Attachment 8a). Referred patients who consent to be contacted become the universe of patient-subjects for this study.

Patient-subjects will then be asked to complete a one-time-only detailed telephone interview. It is anticipated that detailed interviews will be completed with 395 respondents. The estimated average time needed by a respondent to complete the detailed interview is about 25 minutes. The estimated time needed for completing the detailed interview is derived from our experience on the *Baseline Survey*.

Because clinical studies are exempt from OMB review, the portions of the clinical evaluation relating to clinical study are provided to OMB for informational purposes only. They include:

- A medical history for adult subjects (Attachment 10a) and for adolescents (Attachment 10b).
- A gynecological history for adult females (Attachment 11a) and for adolescent females (Attachment 11b)
- Saliva specimen collection instructions (Attachment 12)
- Overnight urine collection instructions (Attachment 13)
- A medication usage history (Attachment 14)
- The physical examination form (Attachment 15)
- A mental health history (Attachment 16), called the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders-IV* (SCID).

The remaining portions of the clinical evaluation that are subject to OMB review appear in the burden estimates in Exhibit A.12.1, below. The hour-burden estimates include the time needed for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and

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. See Attachment 17 for a justification of non-exempt clinical evaluation questionnaires.

Exhibit A.12.1. Summary of Respondent Burden Estimates And Annualized Costs to Respondents

ROW	Form	Number of Respondents	Number of Responses per Respondent	Average Hours per Response	Annual Response Burden (Hours)	Average Hourly Wage	Average Respondent Cost
1	Health Care Provider Provider Verification Form	583	1	17/60	165	$69.59[a]	$11,482
2a	Health Care Provider Questionnaire (Knowledge, Attitudes, and Beliefs) – (Pre-intervention)	466	1	8/60	62	$69.59	$4,315
2b	Health Care Provider Questionnaire (Knowledge, Attitudes, and Beliefs) (Post Intervention)	373	1	8/60	50	$69.59	$3,480
2c	Health Care Provider Knowledge, Attitudes, and Beliefs Questionnaire (at CDC presentations)	100	1	8/60	13	$69.59	$905
3	Health Care Provider Referral/Consent to Contact Form (Providers)	373	2	8/60	99	$69.59	$6,889
4	Referrak/Consent to Contact Form[b] (Patient)	507	1	12/60	101	$16.28[c]	$1,644
5	CATI Detailed Telephone Interview[b]	395	1	25/60	165	$16.28	$2,686
6	Health Care Utilization/Sense of Community (for adults)	196	1	20/60	65	$16.28	$1,058
7	Health Care Utilization[d] (for parent of adolescent)	50	1	20/60	17	$16.28	$277
8	Economic Impact (adult)	196	1	20/60	65	$16.28	$1,058
9	Spielberger State-Trait Anxiety Inventory (for adult subjects)	196	1	20/60	65	$16.28	$1,058
10	Personality Diagnostic	196	1	42/60	137	$16.28	$2,230

ROW	Form	Number of Respondents	Number of Responses per Respondent	Average Hours per Response	Annual Response Burden (Hours)	Average Hourly Wage	Average Respondent Cost
	Questionnaire (for Adult Subjects)						
11	Childhood Trauma Questionnaire (PDQ-4+) (for adult subjects)	196	1	25/60	82	$16.28	$1,335
12	Traumatic Life Events Questionnaire (for adult subjects)	196	1	20/60	65	$16.28	$1,058
13	Life Experiences Survey (for adult subjects)	196	1	20/60	65	$16.28	$1,058
14	Fatigue Status for Adolescents Questionnaire	50	1	8/60	7	$5.15	$36
15	Adolescent Health Questionnaire	50	1	20/60	17	$5.15	$88
16	Symptoms Inventory	246	1	12/60	49	$14.02[e]	$687
17	Medical Outcomes Study Short Form 36	246	1	20/60	82	$14.02	$1,150
18	Multi-dimensional Fatigue Inventory	246	1	12/60	49	$14.02	$687
19	Zung Self-Rating Depression Scale	246	1	20/60	82	$14.02	$1,150
20	Illness Perception Questionnaire	246	1	20/60	82	$14.02	$1,150
21	Davidson Trauma Scale	246	1	12/60	49	$14.02	$687
22	Ironson-Woods Spirituality/ Religiousness Index	246	1	8/60	33	$14.02	$463
23	Illness Management Questionnaire	246	1	20/60	82	$14.02	$1,150
24	Ways of Coping Questionnaire	246	1	33/60	135	$14.02	$1,893
25	Social Support Questionnaire	246	1	20/60	82	$14.02	$1,150
	Totals	6,779			2,077		$50,824

[a] Based on "Physicians and Surgeons—All Other" rate of $66.79, adjusted for inflation. Source: Occupational Employment and Wages, May 2005, Bureau of Labor Statistics, US Department of Labor, adjusted for inflation.

[b] Completed by adults and parents of adolescents

[c] Based on Macon Georgia "All Occupations" rate of $15.62, adjusted for inflation. Source: Occupational Employment and Wages, May 2005, Bureau of Labor Statistics, US Department of Labor.

[d] Completed by parents of adolescents

[e] A weighted, blended rate of adults and adolescent subjects.

A.13. Estimate of Other Total Annual Cost Burden to Respondents or Recordkeepers

There are no capital costs or start-up cost associated with this study and no additional cost burden to respondents.

A.14. Annualized Cost to the Federal Government

The data for the *Registry Pilot Study* will be collected during an approximate fifty-two week period. The estimated contract cost to the government is $329,044 for the provider component; $1,373,755 for the subject component. These costs include the costs of information collection, design, development, printing forms, mailing list compilation and maintenance, mailing, travel, editing, data deliverables, analyses, and publishing results.

A.15. Explanation for Program Changes or Adjustments

This is a new information collection.

A.16. Plans for Tabulation and Publication and Project Time Schedule

A proposed schedule appears in Exhibit A.16.1. Our proposed start date for the study will be four weeks following receipt of OMB clearance; data collection is expected to last approximately twelve months.

Exhibit A.16.1. Proposed Project Schedule

Mail provider recruitment materials	2 weeks after OMB approval
Begin mailing patient recruitment materials	4 weeks after OMB approval
Telephone data collection begins	6 weeks after OMB approval
Clinical evaluations begin	10 weeks after OMB approval
Telephone data collection ends	12 months after telephone information collection begins

Clinical evaluations end	11 months after clinical information collection begins
Cleaning and processing data	3 to 14 months after OMB approval
Data analysis	16 months after OMB approval
Publication	18 months after OMB approval

CDC's CFS Study Group, with assistance from the contractor, will be responsible for all analyses and publications. All studies undertaken by this group have resulted in publications in peer-reviewed journals.

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

The expiration date will be displayed on the paper questionnaires for this study. The expiration date will also be provided for telephone survey respondents upon request.

A.18. Exceptions to Certification for Paperwork Reduction Act Submissions

This submission requests no exceptions to the Certification for Paperwork Reduction Act (5 CFR 1320.9).

B. Collection of Information Employing Statistical Methods

B.1. Respondent Universe and Sampling Methods

The proposed *Registry Pilot Study* health care provider universe comprises health care providers who:

- Practice in or within 30 miles of Bibb County, Georgia
- Have these credentials:

Physicians

General Practitioners	Family Medical Practitioners

Infectious Disease Practitioners	Gastrointestinal Practitioners
Internists	Endocrinologists
Psychiatrists	Neurologists
Rheumatologists	Gynecologists/Obstetricians
Allergists	Pediatricians
Anesthesiologists at Pain Clinics	Immunologists

Non-physicians

Clinical Psychologists	Dentists
Physician Assistants	Physical Therapists
Nurse Practitioners	Doctors of Chiropractic
Registered Massage Therapists	Registered Acupuncturists
Registered Nutritionists	

- Are *not* employed solely by the military, nursing homes, prisons or dialysis centers

Based on data obtained from State of Georgia professional licensing boards, CDC estimates that there are 1,767 of these types of providers in the universe. Given the aim of recruiting large numbers of subjects with early onset of fatiguing illness for future clinical trials (see Section A.1.c), all members of the health care provider universe will be recruited to participate; there will be no sampling. Exhibit B.1.1 illustrates CDC's best estimates of health care provider response rates. At this time CDC expects 583 providers will participate in this study. This is an estimate based on CDC's understanding of how well CFS is received in the medical community; actual data collection may prove otherwise.

Exhibit B.1.1.
Sample Assumptions for *Registry Pilot Study* Health Care Providers

Estimated Universe	1,767
Non-Response (Refusals, Unavailable, Deceased, etc.)(47%)	(831)
Unlocatable or Moved Away (20%)	(353)
Agree to Participate and Make Referrals (33%)	583
Study participants who complete the first (baseline) KAB questionnaire (80%)	466
Study participants who complete the second KAB questionnaire (80%)	373

Non participants who complete the KAB questionnaire during educational events	100

CDC expects participating providers to refer 634 patient subjects over the course of a one-year data collection period. This estimate is based on the *Baseline Survey* participation rates and takes into account the CFS and other fatiguing illnesses rates in Bibb County. Exhibit B.1.2 provides estimated response rates for subjects, which culminates with acceptance into the registry.

Exhibit B.1.2.
Sample Assumptions for *Registry Pilot Study* Patient Subjects

	N
Provider-based Patient Referrals	634
Patient Non-response (20%)	(127)
Patient (or Parent of Patient) Consents To Be Contacted (80%)	507
CATI Detailed Interview	
CATI interview Non-response (22%)	(112)
CATI Interview Completed (78%)	395
Post CATI Data Assessment	
Ineligible based on CATI data (15%)	(59)
Eligible but declines future contact (2%)	(8)
Eligible based on CATI Data and consents to future contact (83%)	328
Clinical Evaluation	
Clinical Evaluation Nonresponse (25%)	(82)
Clinical Evaluations Completed with Adults (60%)	196
Clinical Evaluations Completed with Adolescents (15%)	50
Post Evaluation Data Assessment	
Ineligible based on Clinical Data (25%)	(62)
Enrolled in the Registry (75%)	185

B.2. Procedures for Collection of Information

B.2.a Statistical Methodology for Stratification and Sample Selection

This study will not use statistical methodology for stratification and sample selection. The *Pilot Registry Study* is designed to yield large numbers of subjects with early onset of fatiguing illness for a registry of CFS and other fatiguing illnesses. In the future CDC will use the registry to provide well-characterized subjects for clinical trials designed to treat CFS. Results obtained from this study will not be generalized to the population. Instead, they will be used to assess the feasibility of using physicians and other health care providers to identify eligible candidates for the registry.

B.2.b Estimation Procedure

No statistical weights will be applied to the data because there is no sampling in the design of this study.

B.2.c Level of Accuracy

As its primary objective, the *Registry Pilot Study* aims to produce large numbers of subjects with early onset of CFS and other fatiguing illnesses that may develop into CFS. This study cannot and will not be used to provide population estimates.

B.2.d Use of Periodic Data Collection Cycles To Reduce Burden

Registry Pilot Study health care providers will be asked to complete two questionnaires of their knowledge, attitudes, and beliefs about CFS so that changes can be detected following dissemination of provider education materials. The patients they refer will be asked to complete a single telephone interview and a single clinical evaluation. Use of periodic data collection cycles would have no effect on respondent burden.

B.2.e Data Collection Protocol

Following OMB approval, CDC contractor Abt Associates will mail invitational materials to certain health care providers who participate in or within 30 miles of Bibb County. These materials (Attachment 5a) include an advance letter, frequently asked questions (FAQs), and a customized Provider Practice form that lists all known office addresses for the provider. Providers will also be referred to the CDC website for CFS studies to obtain more information (Attachment 5b). Abt Associates will track response and follow up non-response with up to two re-mails and follow-up telephone calls. If necessary, an Abt Associates representative will attempt to meet with the health care provider in person to explain the study and address concerns.

Providers will complete the Provider Practice form, provide minimal information about his/her practice, and return it to Abt Associates via the mail. If a provider decides not to participate, no further contact will be made with the provider. If the provider is eligible and agrees to participate, he/she will be mailed referral materials (Attachment 6). These include a cover letter and guidelines for making

referrals. Also included are introductory materials (Attachment 8a) to be given to qualified referrals. Providers who refer patients to this study will be asked to complete the referral portion of the Referral/Consent to Contact Form (Attachment 7). They will be able to detach the referral portion and mail it to the contractor, phone the information to the contractor, or use a secured website to make the referral.

Patients may consent to be contacted about the study by completing the Consent to be Contacted portion of the referral form (also Attachment 7). They will also be encouraged to visit the CDC web site to get answers to frequently asked questions (Attachment 8b). Adult patients and parents of adolescents who consent to be contacted about the registry and agree to participate will complete a detailed telephone interview to obtain data on subject[3] health status. The script that the telephone interviewers will use to contact respondents and conduct the interviews is included in the questionnaire (Attachment 9). The telephone survey is similar to the instrument approved by OMB for *Baseline Survey*. The interview will collect information on fatigue and other symptoms, medical and psychiatric conditions, and demographics. As in the *Baseline Survey*, we will also collect from adult subjects psychiatric comorbidity and other psychosocial factors.

Potential respondents who are initially reluctant to cooperate may be sent follow-up letters, emphasizing the importance of their participation in the study and giving them a toll-free telephone number to call to schedule or complete interviews. Two separate follow-up letters were designed for this study. The first letter is directed to respondents whom we have been unable to reach by telephone. The second letter is directed to respondents who are reluctant to complete detailed interviews. These letters are included as Attachment 18.

Following the detailed interview, CDC will evaluate the interview data to determine each subject's eligibility for the clinical evaluation component. Ineligible subjects will be notified by mail (Attachment 19). Scheduling coordinators will call eligible subjects and invite them to the CDC clinic in Macon, Georgia. Participating subjects will be mailed a clinic appointment packet (Attachment 20) that

[3] Parents of adolescents will complete the telephone detailed interview as a proxy respondent for their child.

confirms the appointment, provides directions to the clinic, a checklist of what to bring to clinic, a copy of the appropriate consent form (Attachment 21), and a sample schedule of clinic activities. Participants will be asked to collect and bring saliva specimens and 12-hour (overnight) urine to the clinical evaluation.

Finally, adult subjects will be asked to complete these instruments at home and bring the completed forms to the clinic: Medical History Form (Attachment 10a, exempt from OMB review), a Gynecological History Questionnaire (if appropriate) (Attachment 11a, exempt from OMB review), a health care utilization questionnaire (also Attachment 20), and an economic impact questionnaire (also Attachment 20). Parents of adolescents will be asked to complete the Medical History Form (Attachment 10b, exempt from OMB review) and a health care utilization questionnaire (also Attachment 20) as proxy respondents for their children. At-home questionnaires require subjects to reconstruct health-related events. CDC recognizes that the quality and completeness of historical information improves when subjects can consult records and check with family members.

Upon arrival at the clinic, subjects will review the consent form (or the parental permission form and assent form if the subject is an adolescent). Staff will answer questions and address concerns before written consent is obtained (or parental permission and assent are obtained). Participating subjects will be assessed for eligibility. If eligible, staff will give the saliva and 12-hour urine to staff for processing. Subjects will be asked to provide blood and urine specimens. Following breakfast, the schedule varies. Exhibit B.2.2 illustrates the different types of "paths" that a subject might follow.

Exhibit B.2.2
Clinic Flow for a Typical Clinic Day

<table>
<tr><th></th><th>Subject 1</th><th>Subject 2 (Adolescent)</th><th>Subject 3</th><th>Subject 4</th></tr>
<tr><td>7:30 am</td><td>Informed Consent</td><td>Informed Consent</td><td></td><td></td></tr>
<tr><td>8:00 am</td><td>Blood Draw</td><td>Blood Draw</td><td>Informed Consent</td><td>Informed Consent</td></tr>
<tr><td>8:30 am</td><td>BREAKFAST</td><td>BREAKFAST</td><td>Blood Draw</td><td>Blood Draw</td></tr>
<tr><td>9:00 am</td><td>Medical & Meds Hx</td><td rowspan="2">Gynecological History, Health Questionnaire
Medical & Meds Hx</td><td>BREAKFAST</td><td>BREAKFAST</td></tr>
<tr><td>9:30 am</td><td rowspan="5">SCID</td><td>Questionnaires</td><td rowspan="3">Questionnaires</td></tr>
<tr><td>10:00 am</td><td rowspan="3">Questionnaires</td><td>Medical & Meds Hx</td></tr>
<tr><td>10:30 am</td><td rowspan="4">SCID</td><td>Medical & Meds Hx</td></tr>
<tr><td>11:00am</td><td rowspan="2">Physical Exam and physician’s review of medical history</td></tr>
<tr><td>11:30 am</td><td>Questionnaires</td><td rowspan="2">SCID</td></tr>
<tr><td>12:00pm</td><td rowspan="2">Physical Exam and physician’s review of medical history</td><td>Questionnaires</td></tr>
<tr><td>12:30 pm</td><td>LUNCH</td><td>LUNCH</td><td>LUNCH</td></tr>
<tr><td>1:00 pm</td><td>LUNCH</td><td rowspan="2">Physical Exam and physician’s review of medical history</td><td rowspan="2">Questionnaires</td><td rowspan="4">SCID</td></tr>
<tr><td>1:30 pm</td><td rowspan="4">Questionnaires</td></tr>
<tr><td>2:00pm</td><td>Questionnaires</td><td rowspan="3">Physical Exam and physician’s review of medical history</td></tr>
<tr><td>2:30 pm</td><td></td></tr>
<tr><td>3:00pm</td><td></td><td>Questionnaires</td><td>Questionnaires</td></tr>
</table>

Exhibit B.2.2 **Clinic Flow for a Typical Clinic Day**				
3:30pm				
4:00pm				

Regardless of schedule, subjects will complete a 2-week medication usage history (Attachment 14, exempt from OMB review) with a lab technician, and adolescent females will be asked to complete an adolescent version of the Gynecological history (Attachment 11b, exempt from OMB review), prior to the physical examination. During the physical examination, the physician will review the Medical History (completed at home), the Medication History, and, if appropriate, the Gynecological History with the subject and clarify answers before making a differential diagnosis about the subject's fatigue. The physician findings will be recorded in the Physical Examination Form (Attachment 15, exempt from OMB review).

During the course of the clinical evaluation, the subject will complete a psychiatric history, called the *Structured Clinical Interview for the DSM-IV*,[4] with a trained interviewer who is a clinician (e.g., psychologists and psychiatric social workers) or a non-clinician with experience in psychological assessment. The subject will also be asked to complete self-administered questionnaires that cover symptomology (Attachment 22), other psychiatric assessments (Attachment 23), and stress and coping (Attachment 24). Adult subjects will also complete questionnaires pertaining to early and adult life experiences (Attachment 25). Exhibit B.2.3 lists the instruments to be completed by adults and adolescents. See Attachment 17 for a justification of each clinical evaluation instrument.

The clinical evaluation is expected to last eight hours for adults and seven hours for adolescents. Subjects (and parents of adolescents) will be reimbursed for their time and effort. Adult subjects will receive $450; parents of adolescents will receive $300 for the time and expense of completing the questionnaires at home, managing the saliva and urine collection, arranging time off from work, and

[4] *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; exempt from OMB review.*

dependent care coverage. Adolescents will receive $100. See Section A.9 for an explanation of the reimbursement schedule.

CDC staff will evaluate clinic data to determine if the subject has any medical or psychiatric conditions that would explain the person's fatigue. If the subject has no exclusionary conditions, resulting from a review of the physical examination, laboratory results, and medical and psychiatric findings, the subject will be notified of acceptance into the registry (Attachment 26). If the subject is found to be ineligible, he/she will be notified (Attachment 19), as well.

Exhibit B.2.3

Registry of Unexplained Fatiguing Illnesses and CFS: A Pilot Study

		Sample Type	
Attachment	**Instrument**	**Adult**	**Adolescent**
9	Detailed Interview	✓	✓
	At Home		
10a	Medical History - Adult	✓	
10b	Medical History - Adolescent		✓
11a	Gynecological History-Adult	✓	
20	Health Services Utilization-Adult	✓	
20	Health Services Utilization-Adolescent		✓
20	Economic Impact	✓	
	Physical Examination and Review of Medications		
11b	Gynecological History-Adolescent		✓
14	Two-week Medication History	✓	✓
15	Physical Exam Form	✓	✓
	Symptomatology		
21	Adolescent Subject Fatigue Questionnaire		✓
21	Symptoms Inventory	✓	✓
21	Medical Outcomes Study	✓	✓
21	Multidimensional Fatigue Inventory	✓	✓
	Psychiatric		
22	Structured Clinical Interview for DSM-IV (a mental health history)	✓	✓
22	Personality Diagnostic Questionnaire (PDQ-4+)	✓	
22	Zung Self-Rating Depression Scale	✓	✓
22	Spielberger State-Trait Anxiety Inventory	✓	
22	Davidson Trauma Scale	✓	✓
	Early and Adult Life Experiences		
25	Childhood Trauma Questionnaire	✓	
25	Traumatic Life Events Questionnaire	✓	
25	Life Experiences Survey Questionnaire	✓	
	Stress and Coping		
26	Ironson-Woods Spirituality/Religiousness Index	✓	✓
26	Ways of Coping Questionnaire	✓	✓
26	Illness Management Questionnaire	✓	✓
26	Social Support Questionnaire	✓	✓
26	Adolescent Health Questionnaire		✓
26	Illness Perception Questionnaire	✓	✓

B.2f Quality Control

All telephone interviews will be conducted by professional interviewers with special training in administering these survey instruments.

Quality control measures include monitoring of telephone interviews by supervisory staff using Abt Associates' monitoring system. Abt Associates' Telephone Centers are equipped with separate monitoring rooms that allow unobtrusive monitoring of interviewers. Interviewers will not know when they will be monitored. The monitoring supervisor will listen to the telephone interview while observing the interviewer's data entry on a computer monitor that mirrors the interviewer's screen.

All telephone interviewers will be routinely monitored at selected time intervals. They will be given active coaching and immediate feedback, both positive and negative, on their performance so that success can be rewarded and reinforced, while problems are identified and corrected. The monitoring system is also used to evaluate performance patterns across interviewers to identify any problematic areas or items in the questionnaire. If individual interviewers need to improve, retraining will focus on the specific problems. If these interviewers fail to improve after remedial training, they will be replaced.

As an additional quality control measure, project staff will review questionnaire item frequencies, as well as interview length, numbers of completed interviews, and similar information, to identify any potential for interviewer falsification; correct skip pattern errors; and detect any other anomalies in the data.

Clinic staff will be reviewed periodically to make sure the protocol is being followed. As necessary monitors will observe operations and review procedures with staff. Those who fail to improve after remedial training will be replaced.

B.3. Methods to Maximize Response Rates and Deal with Non-response

The success of any survey in achieving high response rates depends on the strategy that is used to encourage respondents to participate and on the energy with which this strategy is pursued. CDC and Abt Associates have considerable experience conducting data collection efforts using methods and modes

similar to those proposed for the *Registry Pilot Study*. Experience with the *San Francisco Study, Sedgwick County Studies,* the *National Pilot Survey for Chronic Fatigue Syndrome,* and the *Survey of Chronic Fatigue Syndrome and Chronic Unwellness in Georgia* provides insights into the most effective strategies to maximize response rates for both fatigued and non-fatigued individuals.

Procedures that will be used to maximize response rates for the *Registry Pilot Study* reflect best practices in the survey industry.

- Mailing recruitment materials to selected health care providers prior to attempting to contact them by telephone. Advance letters introduce the study to potential participants and increase cooperation.
- Using the CDC logo to get the attention of the health care provider.
- Using different media to decrease the burden of health care participants. Health care providers will be able to refer patients using US mail, the Internet or calling a toll free phone number.
- Remailing packets of materials to health care providers before telephone prompting begins.
- Using a cadre of executive interviewers to prompt health care professionals on the status of their participation.
- Minimizing provider burden by consolidating prompting calls to practices that have more than one health care provider who has been invited to participate.
- Streamlining the referral process for providers, providing clear-cut guidelines for referrals; providing consultations with a CDC physician for unanticipated situations.
- Using professional telephone interviewers who understand the study and who are skilled at gaining cooperation from respondents.
- Conducting telephone interviews primarily during evening and weekend hours, when subjects are most likely to be at home.
- Allowing respondents to schedule telephone interviews at their convenience.
- Employing specially trained refusal conversion interviewers to contact adult subjects who are initially reluctant to participate in the study. Before telephoning the initially reluctant respondents, refusal conversion interviewers review the history of contacts with specific respondents and, if necessary, consult with supervisors to determine the best refusal conversion strategy.

B.3.a Procedures for Dealing with Non-response

Minimizing non-response is part of each step in the *Registry Pilot Study*. Procedures are described below.

- Using a call management system that tracks and manages the sample of telephone numbers so that telephone numbers are called at different times on different days, appointments with respondents are kept, and callbacks are made at the appropriate times.

- Maintaining a sufficient staff of interviewers so that respondents are called in an efficient and timely manner—appointments and callbacks must occur at the correct times even during peak calling hours.

- Training interviewers in refusal aversion techniques to prevent initial refusals.

- Performing on-line monitoring of 5 percent of all calls placed so that action can be taken to correct poor interviewing practices.

- Identifying best interviewing practices and sharing them with the entire interviewing staff through regular project meetings, interviewer debriefings, and refresher trainings.

- Arranging ongoing training for interviewers and supervisors to improve their skills and alert them to protocol changes and revisions.

- Assigning clinic-eligible subjects to scheduling coordinators who will have exclusive contact with the subject that includes:

    - Introducing the clinical component.

    - Scheduling/rescheduling appointments.

    - Explaining the contents of the appointment packet mailing on a form-by-form basis.

    - Making clinic appointment reminder calls.

    - Following up with a post-appointment thank-you call.

- Using professional medical staff at the clinic—physicians to give physical examinations; phlebotomists to draw blood samples, lab technicians to process blood, urine, and saliva specimens and prepare them for shipment to laboratories.

- Reimbursing subjects for participating in the clinical evaluation. Adult subjects who complete the evaluation will receive $450; parent of adolescents, $300; and adolescents, $100.

B.3.b Response Rates

Two of the *Registry Pilot Study* aims are to assess the feasibility of building a registry of fatiguing illness and CFS in Georgia and to identify large numbers of individuals with early onset of CFS or other fatiguing illnesses. By design, this is not a statistical survey. Nevertheless, response rates are important and will be reported to OMB should the registry be extended.

B.3.c. Analysis of Non-response

Although a variety of methods will be used to maximize response, some degree of non-response is inevitable. CDC plans to monitor the point at which respondents elect to withdraw from participation. For providers, we will monitor non-response by specialty.

Because we will ask providers to give basic demographic information, such as sex, race, ethnicity, and year of birth for each patient referral they make, we will be able to detect which types of patients did not give consent to be contacted for a telephone interview. Should an analysis reveal that certain groups of people are systematically failing to consent, the contractor and CDC will examine ways to make the recruitment materials more inclusive and will submit changes to the Institutional Review Boards (IRBs) of CDC and Abt Associates. CDC will also monitor non-response during telephone interviewing, as well as eligible subjects who decline to participate in the clinical evaluation to see if there are significant differences in participation by sex, race, ethnicity, or age.

B.4. Tests of Procedures or Methods to be Undertaken

The instrument and procedures for the proposed *Follow-up Study* have been used in four CDC CFS public health research program studies previously approved by OMB: the *San Francisco Study* (OMB #0920-0336); the *Sedgwick County Studies* (OMB #0920-0401); the *National Pilot Survey for Chronic Fatigue Syndrome* (OMB #0920-0498); and, most recently, the *Survey of Chronic Fatigue Syndrome and Chronic Unwellness in Georgia* (OMB #0920-0638).

On December 15, 2005, a focus group of nine health care providers was convened to understand how providers regard CFS as well as the benefits and barriers to participating in a registry. Their responses informed the design of recruitment materials for providers and referral procedures.

For this study, CDC plans to test a simple incentive, attaching a two-dollar bill to the first re-mailed packet sent to non-responding health care providers. This strategy has been used in other studies [Olmsted *et al*., 2005] to get the attention of health care providers. The novelty of the two-dollar bill will allow the provider to differentiate this study from the many that vie for the provider's attention. Should the provider fail to respond, mentioning the two-dollar bill to the provider or his/her assistant during telephone prompting is likely to jog the person's memory. Although the value of this test is minor, based on research, we believe that this incentive will shorten the provider's response time.

B.5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

This is not a statistical survey. Individuals were not consulted on statistical aspects of the study. Abt Associates and Dana Brimmer, Ph.D. have worked closely with CDC staff to develop the survey and instrument designs and will collect all data and participate in some data analysis. The project director, Scott Royal, oversees Abt Associates' staff. The names, roles, and telephone numbers for Abt staff are included in Exhibit B.5.1 below.

Exhibit B.5.1. Names, Roles and Telephone Numbers for Abt Associates Staff

Activity	Abt Staff Member	Telephone Number
Provider Knowledge, Attitudes, and Beliefs	Dana Brimmer, PhD	(720) 277-3543
Survey and Instrument Design	Marjorie Morrissey Rebecca Devlin	(312) 867-4061 (312) 867-4037
Data Collection	Scott Royal, PhD	(301) 634-1717

Two CDC personnel are responsible for receiving and approving materials prepared by Abt Associates. Elizabeth Maloney, DrPH., is CDC's principal investigator and can be contacted at (404) 639-2349. Joann House is CDC's project officer and can be reached at (404) 639-3748.

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