Follow-up Study
of Chronic Fatigue Syndrome in Georgia

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A. Justification

1. Circumstances Making the Collection of Information Necessary

a. Authorizing Legislation

The authorizing legislation for the *Follow-up Study of Chronic Fatigue Syndrome in Georgia* (hereafter referred to as the *Follow-up Study*) is contained in the US Code. Section 42 USC 241 of this Code authorizes collection this information (Attachment 1).

b. Congressional Support for CFS Research.

Chronic fatigue syndrome (CFS) is a Congressional priority. Beginning in 1992, Congressional language has stressed legislators' desire for CDC to develop control and prevention measures for CFS. Recent Congressional language (2003-2006) has encouraged CDC to use advanced surveillance methodologies to describe risk factors and clinical parameters of the illness and to search for diagnostic markers. Congressional language has stressed that this information be used to educate health care providers about the diagnosis and treatment of CFS and to better inform the public about the illness (Attachment 2). This protocol addresses these Congressional concerns.

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 post-exertional 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 7 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 (Baseline Survey)* (OMB #0920-0638, expiration date: August 2005), conducted between 2004 and 2005, provided baseline information on CFS in metropolitan, urban, and rural regions of 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 of metropolitan, urban, and rural Georgia, 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, suggesting that the incidence will be higher among whites, as well. 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 were amenable to treatment if appropriately recognized as having CFS. The *Follow-up Study* has four specific aims.

Aim 1. Clinical, Psychosocial and Environmental Variables that Characterize the Clinical Course of CFS. We designed the *Follow-up Study* to evaluate changes in clinical parameters of CFS over the interval since the *Baseline Survey*. Clinical evaluation of fatigued study participants and randomly selected well controls assesses functional impairment by using the Medical Outcomes Survey 36-item Short Form or SF-36 [Ware & Sherbourne, 1992], fatigue measured by the Multi-dimensional Fatigue Inventory or MFI [Smets *et al*., 1995], and the occurrence and severity of symptoms as measured by the CDC Symptom Inventory [Wagner *et al*., 2005].

The findings that acute stress often precedes and exacerbates CFS in adults, combined with the strong association of childhood stress with CFS, support a stress-diathesis model, in which genetic liabilities interact with stressful experiences in determining individual vulnerability to disease, including CFS. We hypothesize that CFS patients with a lifetime history of stressful experiences will be less likely to recover or improve compared to CFS patients who do not have a lifetime history of stressful experiences. We collected data on stress history during the *Baseline Survey* with the purpose of confirming this association in the *Follow-up Study*.

Aim 2 – Physiologic Markers that Characterize CFS. Clinical, psychosocial and environmental factors evaluated in Specific Aim-1 are also reflected physiologically as allostatic load. Allostatic load was first described by McEwen and Stellar [McEwen & Stellar, 1993] as the cumulative wear and tear on the body and brain resulting from chronic over-activity or inactivity of the HPA axis in adaptation to environmental challenge, such as acute disease, physical and emotional trauma (i.e., stress). The allostatic load index includes laboratory measurements of metabolic, cardiovascular, inflammatory and HPA-axis factors. We hypothesize that high allostatic load will be significantly associated with worsening clinical course of CFS. We are particularly interested in whether allostatic load index predicts clinical outcome in the acute versus gradual onset cases and whether the illness contributes to the allostatic load index.

Aim 3 - Economic Impact of CFS — Access to/Utilization of Health Care. Congress has directed CDC to accelerate its CFS research plan to identify the economic impact of CFS and accelerate its educational activities for health care providers. The *Follow-up Study* will evaluate direct and indirect costs of CFS, compare access to/utilization of health care by those who suffer from CFS with well and unwell controls, and measure changes in health care utilization and economic impact over time. Clinical follow-up of subjects with CFS will also allow us to examine the relationship between provision of health care and recovery. Information concerning economic impact of CFS will be used to tailor an intensive regional provider education project, develop public health strategies, and evaluate cost effectiveness of different therapeutic modalities.

Aim 4 – Incidence of CFS in Different Racial/Ethnic Populations of Metropolitan, Urban, and Rural Georgia. An understanding of the occurrence of new incidents of CFS is fundamental to focusing etiologic research, targeting health-care and educational programs, and developing prevention strategies. This will be the first follow-up in a study of five-year CFS incidence. The objective is to estimate the incidence of CFS among those categorized as unwell and well in the *Baseline Survey*.

2. Purpose and Use of the Information Collected

As noted in Section A.1.b, the purpose of the proposed *Follow-up Study* is to evaluate for a second time subjects who participated in the *Baseline Survey* and at that time indicated their willingness to be recontacted. We will utilize the data to implement measures that decrease the morbidity (burden) 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 84% of people with CFS who have not been diagnosed and treated. Finally, this is the first of four additional studies to estimate the incidence of CFS.

The *Follow-up Study* uses methodology developed for the *Baseline Survey* (OMB #0920-0638). Like the *Baseline Survey*, the follow-up study entails a detailed telephone interview to obtain data on participant health status during the last twelve-month period. The 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 baseline data collection. See Attachment 3 for a copy of the survey instrument. Eligible subjects will be asked to participate in clinical evaluations. Clinical protocols and instruments for this follow-up are similar to the procedures and materials used in the baseline study (OMB #0920-0638). Please see Attachment 4 for the full study protocol. Because clinical studies are exempt from OMB review, the clinical portion of this study is provided to the Office of Management and Budget for information only. In this submission, we request only a review of the telephone survey data collection.

3. Use of Information Technology and Burden Reduction

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 cases 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.

4. Efforts to Identify Duplication and Use of Similar Information

We are aware of no studies to define the clinical course of CFS and identify associated risk factors in representative US metropolitan, urban, and rural communities. Because medical evaluation is necessary to confirm a classification of CFS, this survey of CFS cannot readily be combined with other studies in defined metropolitan, urban, and rural communities. 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

No small businesses are involved in this study

6. Consequences of Collecting the Information Less Frequently

The proposed data collection is a follow-up to the *Baseline Survey*. The collection of longitudinal data is required to obtain information regarding clinical course, access to and

utilization of health care, economic impact and incidence of CFS in metropolitan, urban, and rural communities of Georgia.

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

There are no special circumstances for this information collection. The *Follow-up Study* is in full compliance with the guidelines of 5 CFR 1320.5.

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

a. Federal Register Notice and Public Comment

In accordance with the Paperwork Reduction Act of 1995, the Division of Viral and Rickettsial Diseases 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 October 25, 2006 in Volume 71, Number 206, pages 62473 to 62474 and provided a 60-day period for public comment. A copy of this notice is provided in Attachment 5. No public comments were received.

b. Other Consultants

As noted earlier, the methodology and instrumentation for the *Follow-up Study* are the same as the materials used for the *Baseline Survey*. The CDC drew on the expertise of a group of consultants from Abt Associates Inc. for their development. These consultants are listed in Exhibit A.8.1.

Exhibit A.8.1. Consultants from Abt Associates Inc.

Name	Title	Address	Telephone	Year(s) in which consultation

				took place
Scott Royal, Ph.D.[a]	Project Director	Abt Associates Inc. 4550 Montgomery Avenue Suite 800 North Bethesda, MD 20814 scott_royal@abtassoc.com	(703) 919-0189	2006-2007
David Hoaglin, Ph.D.	Principal Scientist	Abt Associates Inc. 55 Wheeler Street Cambridge, MA 02138 dave_hoaglin@abtassoc.com	(617) 349-2814	2003-2007
Johnny Blair	Survey Methodologist	Abt Associates Inc. 4550 Montgomery Avenue Suite 800 North Bethesda, MD 20814 johnny_blair@abtassoc.com	(301) 634-1825	2003, 2006

9. Explanation of Any Payment or Gift to Respondents

Telephone interview respondents will not receive payment for their participation.

10. Assurance of Confidentiality Provided to Respondents

The CDC Privacy Act Officer has reviewed this OMB application and has determined that the Privacy Act is applicable. Participants will be asked sensitive questions regarding: (1) pregnancy history, (2) use or abuse of alcohol and other controlled substances, (3) psychiatric diagnoses, and (4) stress and trauma. While data will be filed by identification number, because the data can be linked to respondent names by the contractor and sensitive information is being collected, the Privacy Act applies.

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." Data collection will be conducted by Abt Associates, the contractor hired by CDC for this project. Although the first and last names and addresses of all respondents will be collected during interviews to contact respondents for the clinical portion of the study and for follow-up studies of CFS, CDC will not have access to this information. CDC will receive data labeled only by identification (ID) numbers. Abt Associates will maintain the only link between name and ID number. Survey data are maintained at Abt Associates until the electronic data are verified and there is no longer need for reference to hard-copy documents (approximately six months after the end of data collection). At that time, the data will be moved to Abt Associates' off-site storage facility. At the conclusion of the study, the survey data will be destroyed in accordance with the terms of the contract between CDC and Abt Associates.

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 Affidavits of Non-Disclosure, a standard requirement for all employees and subcontractor staff who have access to confidential data. These staff will also 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. Prior to each period of data collection, confidentiality requirements are reviewed with all staff.

Abt Associates Inc. is extremely conscious of the need to protect the confidentiality of data. For over forty years, the company 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. In all company offices, access to data processing areas is controlled, with only authorized personnel allowed in the computer rooms and the computer tape libraries. 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. Access to areas where confidential data are maintained is restricted to authorized personnel. 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.

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 include:

- A question on pregnancy history.
- Questions regarding use or abuse of alcohol and other controlled substances.
- Questions concerning psychiatric diagnoses.
- Questions concerning stress and trauma.

The first three 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 exclusion. A primary criterion to be classified as a CFS case is the absence of preexisting clinical conditions that may produce a similar syndrome. Psychiatric conditions and effects of substance abuse and recent pregnancy may exhibit symptoms similar to the CFS symptom cluster. For example, a confirmed CFS classification requires that certain specific psychiatric disorders have not previously occurred. The questions concerning stress and trauma are important for identifying precipitating factors for fatiguing illness as well as for identifying individuals to invite for future studies of CFS.

In interviews conducted for the *Baseline Survey*, participants willingly answered questions on these topics. No adverse events associated with these questions were reported.

12. Estimation of Hour Burden Including Annualized Hourly Costs

The proposed Follow-up Study entails follow-up interviews by telephone with subjects who participated in the Baseline Survey in three segments of the Georgia population: metropolitan (represented by DeKalb and Fulton Counties), urban (represented by Bibb County, which contains the city of Macon, and the nearby city of Warner Robins, in Houston County), and rural (represented by counties surrounding Macon). For the *Follow-up Study*, respondents will be asked to complete a one-time-only detailed telephone interview. It is anticipated that detailed interviews will be completed with 2,870 respondents who completed baseline interviews and agreed to be contacted for follow-up. The estimated average time needed by a respondent to

complete the detailed interview is about 18 minutes. The estimated time needed for completing the detailed interview is derived from our experience on the *Baseline Survey*.

A summary of the respondent burden estimates is included 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. Respondents to this study will be interviewed by telephone, so the majority of their time will be spent answering the survey questions. Respondents will spend almost no time reviewing instructions or gathering, maintaining, or reviewing data. Annualized costs associated with the hour burdens for the collection of information are also included in the table below.

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

Form	No. of Respondents	No. Responses per Respondent	Average burden per Response (in hours)	Total Burden Hours	Hourly Wage Rate	Total Respondent Costs
Follow-up Study Detailed Interview	2,870	1	18/60 [b]	861	$18.70[a]	$16,100

[a] Based on preliminary data for all occupations in Georgia, Quarter 3 2005. Source: Quarterly Census of Employment and Wages, Bureau of Labor Statistics, US Department of Labor.

[b] The 60-day federal register notice listed the estimated average burden response as 30/60 hours. Since publication of the notice, the questionnaire has been shortened so that it is estimated to take about 18 minutes to complete.

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

There are no capital costs, operating costs, or maintenance costs to report.

14. Annualized Cost to the Federal Government

The data for the *Follow-up Study* will be collected during an approximate forty-week period. The estimated contract cost to the government is $320,000 for the telephone survey.

15. Explanation for Program Changes or Adjustments

This is a reinstatement with change of a previously approved collection.

The goal of the Follow-up Study is to build on the Baseline Survey and identify risk factors for and biomarkers of CFS morbidity by evaluating changes in clinical parameters of CFS over the interval since the Baseline Survey.

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 two weeks following receipt of OMB clearance; data collection is expected to last approximately ten months.

Exhibit A.16.1. Proposed Project Schedule

Mail advance letters	2 weeks after OMB approval
Telephone data collection begins	4 weeks after OMB approval
Clinical evaluations begin	10 weeks after OMB approval
Telephone data collection ends	6 months after OMB approval
Clinical evaluations end	9 months after OMB approval
Cleaning and processing data	3 – 10 months after OMB approval
Data analysis	9 – 16 months after OMB approval
Publication	16 months after OMB approval

Section B of this submission describes in detail our plans for weighting and estimating incidence of CFS and other fatiguing illnesses. The Congress has directed CDC to complete such analyses. Our specific hypotheses are described in Section A.1 above. 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.

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.

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).