

CDC Chronic Fatigue Research Program External Peer Review

5-7 November 2008

Panel of External Reviewers: Matthew Boulton, MD, MPH, Anthony L. Komaroff, MD (Chair), Gudrun Lange, PhD, James Oleske, MD (excused), Peter White, MD

The external review panelists visited the CDC Chronic Fatigue Research Program from November 5 to 7, 2008. The Chronic Fatigue Syndrome (CFS) team is charged both with conducting research and educational programs. The visit included initial and exit briefings with Stephan Monroe, PhD, the Director of the CDC Division of Viral and Rickettsial Diseases in the National Center for Zoonotic, Vector-borne, and Enteric Diseases, William Reeves, MD, the Director of the CDC Chronic Fatigue Research Program, as well as program team leaders. Several opportunities were provided to interact with all program staff through PowerPoint and poster presentations and a facilities tour over the three days of the review.

Executive Summary

Both the research and education teams presented an informative overview of their mission, goals, and accomplishments in an integrated format of presentations and poster presentations. We summarize here our responses to the primary questions posed to the panelists by Dr. Monroe:

1. **“Are the current mission and goals of the program appropriate and consistent with the public health mission of CDC?”** The review panelists felt that the efforts of the CDC have highlighted the public health importance of CFS, through CDC’s documentation of the high prevalence and substantial functional and financial burden imposed by this illness. The panelists felt that the CDC was uniquely positioned to conduct a broadly based research program derived from the population, a large-scale educational outreach program, particularly to healthcare professionals, and to be an expert web based resource for patients, their families and non-healthcare professional bodies. The panelists also believed that the CDC was the best placed institution to lead the establishment of both research and educational networks, both nationally and internationally.
2. **“What should be the specific goals and objectives of the program over the next 3-5 years (i.e., what should be the target(s) that the program is aiming for?”** The review panelists felt that they were better positioned to evaluate the goals and objectives articulated by the leadership of the program than to propose their own goals and objectives. In general, the panelists felt that the accomplishments of the research program thus far have been substantial, and that all of the current research projects address important issues. The panelists’ judgement was that the CDC team currently leads the world in both the breadth and depth of their research into CFS. At the same

time, the panelists felt that a written articulation of a five-year plan for both research and education needed to be created and shared widely.

3. **“Given the recommendations above, what research and programmatic activities should the program be engaged in now and in the coming years in order to be on track to achieve the desired goals and objectives?**
 - a. **Current activities that should be continued or expanded**
 - b. **Current activities that should be reduced or eliminated**
 - c. **New activities that should be initiated: intramural, or via extramural collaboration”**

A compilation of the review panelists’ detailed responses to these questions appears below.

Research Program

Strengths to be further encouraged

1. The review panelists judged that over the past decade, the CDC team has amassed a very important body of research work on CFS. In particular, CDC has led the world in defining the illness, including improving the quantitative precision with which the illness is defined—through development of a standardized case definition. While some have recently criticised the recent standardization of the research criteria for CFS, the panelists believed that the CDC’s work on psychometric operationalization of the existing 1994 case definition should improve the reliability of research.
2. The CDC also has played a key role in elucidating the heterogeneity of CFS, measuring the prevalence of the illness, assessing the cost to society from both lost productivity and from medical care expenses, identifying possible psychosocial underpinnings of the illness, identifying possible genetic polymorphisms that render a patient vulnerable to the illness, and more broadly studying pathophysiology (such as its studies of gene structure and expression in CFS). The panelists believed that CDC had done much to elucidate the pathophysiology of CFS and in particular the links between biological and psychosocial risk markers.
3. An objective marker to assess the impact of the group’s research activities was provided in the form of number of research publications and impact factors. The group has published 115 peer reviewed papers since 2000 and the consequent ISI citations were the highest in the world for a single institution in the area of CFS.
4. Although there is much talk about approaching the study of complex chronic illnesses by using a “biopsychosocial model”, the CDC research team has actually “walked the walk.” CDC has organized a broad array of disciplines in its studies of CFS—including epidemiology, biostatistics, demography, psychology, and molecular diagnostics.

5. Moreover, those efforts have been shared beyond CDC with great success. For example, through the C³ and CAMDA programs, extremely large data sets, containing clinical, demographic, psychological, laboratory, and molecular diagnostic data, have been openly shared with external colleagues, which has resulted in a paradigm shift in how CFS is now regarded. The decision to seek speedy publication in public access electronic journals also results in sharing information with the research community at the earliest possible time. The panelists would encourage further data sharing at the appropriate times.
6. The CDC has taken advantage of its proximity to Emory University to engage talented clinical investigators, particularly in behavioral sciences, neurology, neuroimaging and endocrinology, in the study of patients recruited as part of CDC's studies. It also is working with the University of Miami.
7. The panelists were impressed by the program's scientific and intellectual rigor.
8. The loyalty, commitment, enthusiasm, intellectual rigor and dedication of team members was impressive. Staff meetings occur weekly, lasting two hours, the open nature of communication was obvious, and the importance and emphasis on making consensual decisions was clear. It was similarly clear that when there are differences of opinion, Dr. Reeves does not hesitate to make a final decision.
9. The review panelists were particularly impressed with the group morale, given that there has been a sustained organizational ambivalence about the placement of the CFS program within CDC, which could have been confusing and disheartening to some. Solid backing and commitment by CDC would further enhance group cohesion and productivity.

Potential areas for development

1. **Five year plan:** The panelists were disappointed not to see a carefully articulated 5-year research strategy that integrates current epidemiologic, laboratory, and educational activities of the program. While recognizing that research results and external events almost always cause some alteration in such plans, the panelists strongly felt that such a plan, incorporating contingencies, would bring focus to the effort, and share vision and direction both within the team itself and with external interested parties. It would also help the program leadership to better determine how best to use limited research dollars.
2. **Links to public health:** The reviewers were disappointed with the absence of any research linkages to other public health institutions. For example, the CDC group should consider whether it can collaborate in the use of established databases—such as the Behavior Risk Factor Surveillance System (BRFSS) in which all states participate—to better elucidate risk markers.

3. **EIS officers:** A related concern was the absence of Epidemic Intelligence Service (EIS) officers in the CFS research program for many years now, and the apparent lack of any recent attempts by the program leadership to recruit EIS officers. Team leadership should make a serious effort to recruit an EIS officer through active recruiting practices. An EIS officer would bring additional scientific expertise and would speak to the internal credibility and importance of the program within CDC.
4. **External collaborators:** Although the program has collaborated with medical schools in its research, the reviewers thought that this kind of collaboration could be expanded. In particular, the reviewers suggested that the CDC could galvanize the development of both international and national research (and educational) networks comprising academic researchers, providers, public health practitioners, and community based groups. These networks might be used to consider in particular the creation of registries and/or special surveillance programs.

There is a notable lack of engagement with governmental public health (i.e. state and local public health department) by the program. Epidemiology units in state health departments and state public health laboratories have a long standing tradition of active involvement with the CDC in the conduct of joint applied research. That research collaboration has played a critical role in initiating enhanced surveillance and improved characterization of many emerging diseases and conditions. The program should also consider more active involvement with national public health practice professional organizations such as CSTE, APHL, NACCHO and ASTHO. These organizations have a critical role to play in defining CFS as an important public health issue.

Organizations that face the financial burden of dealing with complex chronic illnesses, such as prepaid group practices and health insurance companies, might also have an interest in supporting the CDC's efforts to prevent and control CFS. CDC should consider discussion with such organizations.

5. **Research networks:** The CDC is ideally placed to organize detailed planning of an international CFS research network—identification of institutions that could be involved, specification of common data definition and data collection techniques. To this end, group leadership might want to consider identifying one or two members of the team who could be delegated to conduct the planning and implementation of these networks.
6. **GWA studies:** Some mention was made of undertaking genome-wide association (GWA) studies of CFS. Such an undertaking requires a very large sample size to be scientifically valid, and should not be considered until there is a national or international network in place that could deliver the required samples.
7. **Gene expression studies:** Gene expression studies, on the other hand, are not so dependent on large sample sizes, and already have led to interesting results. One important new area relating to gene expression has not been pursued—microRNA expression patterns in patients with CFS—and should be considered. Some of the

panelists were also concerned about the variability in the results of gene expression studies by the CDC and other groups, and would encourage the program to work with other investigators to standardize the conduct of these studies.

8. **Pathophysiology and endophenotypes:** While impressed with the scientific discoveries of the pathophysiology associated with CFS, and the goal of identifying “endophenotypes”, the panelists had two concerns:
 - The panelists were not convinced that time series alone would be enough to elucidate whether the abnormalities found were causal or simply the effects of having CFS. The panelists recommend that the CDC program urgently consider intervention studies to help to elucidate the direction of causality in the several pathophysiologies identified by the CDC. This strategy was not articulated clearly. For example, since both cognitive behavior therapy and graded exercise therapies are known to address some of the abnormalities found, and since both these therapies have been shown to be efficacious for CFS, these behavioral interventions should be seriously considered. Collaborations with providers and medical schools practised in randomised controlled trials might provide the best means to achieve this.
 - The group should articulate a clearer strategy for addressing the issue as to how heterogeneity is going to confound the establishment of risk markers and pathophysiology.
9. **Pharmacotherapy:** Some discussions have been had with the pharmaceutical industry, which has a growing interest in medications to treat fatigue. This kind of interest should be fostered and nurtured.

Educational Program

The review panelists were not asked to review the effectiveness of the *public* education program funded by the CDC, and conducted by a contractor. Instead, they focused on CDC’s efforts at *professional* education about CFS and the Web site information it has created to educate the general public.

Strengths to be encouraged

1. The *professional* education program began by attempting to identify professionals in multiple communities who would become trainers of their peers. The CDC concluded that this program did not have sufficient impact. The decision to “cut its losses” and take a new approach was the mark of firm leadership and impressed the panelists.

2. The CFS booth at multiple professional conferences drew over 12,000 visitors. Although no formal assessment could be conducted of the impact of this effort, the level of interest was impressive.
3. The 31 Grand Rounds presentations given by CDC MDs have been attended by over 1,500 physicians and other health professionals, and impressed the panelists. The panelists noted with approval that these contacts had a great potential for establishing extramural collaborations.
4. The online CME programs on CFS have led to nearly 1,000 course completion certificates.
5. The visibility and credibility of CDC as an institution has been an important partner in making CFS a visible illness.
6. A particularly impressive professional education effort has been the DocStyles programs in which a sample of 142,000 physicians assessed their knowledge about and attitudes toward CFS. The ability to conduct a survey that large, with a 60% response rate, is impressive. Moreover, the survey documents an enormous growth in the understanding of CFS by practicing physicians over the past 10-20 years—some of it due to the efforts of the CDC in studying and publicizing the illness.
7. The CDC intends to lead the development of clinical guidelines for the management of CFS for use in the USA, and to disseminate these widely. The review panelists applaud this plan and regard this as an urgent priority for CDC.

Potential areas for development

1. **Public health contacts:** As with the *research* component of the program, the panelists felt that the CDC had not reached out to the public health practitioners in its public and professional education activities. There should be a focus to identify, contact, and collaborate with traditional public health agencies to promote understanding of CFS as a public health issue. For example, the existing network of over 3000 local health departments could be engaged in helping to develop and distribute information sheets about CFS.
2. **Web sites for professionals:** The program's web sites for professionals and for the general public has not had a lot of traffic. The program should systematically assess whether major web sites for health professionals—such as Medscape—include content about CFS, and links to the pertinent pages on the CDC Web site. If not, the CDC would likely be effective in working with these web sites in creating these links.

Web sites for the public: Likewise, the program should systematically assess whether the major health Web sites for the general public—such as WebMD, MSN, AOL.body, EverydayHealth.com, and About.com—contain content about CFS and links to the pertinent pages for the public on the CDC Web site.

A summary of strategic recommendations

1. The CDC should continue to support the CFS program so that it can continue its successful work.
2. Dr. Reeves should create a 5-year strategic action plan with clear milestones and performance measures, focused on how the plan hopes to achieve improved prevention and control. The plan would identify the strengths and risks of each of the current major projects underway, how the results of one project might influence the conduct of another project, and establish the likely route map between current projects and the mission aim of control and prevention of CFS. A progress report that refers to the written plan should be reviewed by an external panel in 2 years, although this might not necessarily require a site visit.
3. The program should establish closer relationships with traditional public health agencies (i.e. state and local health departments) for the purpose of enhancing both research and education collaborations.
4. The program should consider utilizing already existing database resources to further the understanding of CFS in regard to its risk markers and its standing as a significant public health issue.
5. Clinical guidelines on management should be developed for use in the USA, by the CDC team in collaboration with others, and disseminated for CFS.
6. The team needs to consider studies that test the direction of causality of pathophysiology, such as using interventions.

Potential conflicts of interest of panelists

Dr Komaroff, Dr. Lange, and Dr. White have collaborated in research with the CDC program, published research papers with staff members, and attended meetings hosted by CDC. They have never received financial payments from the CDC beyond travel and accommodation expenses.