Evidence Report/Technology Assessment
Number 66

Systematic Review of the Current Literature Related to Disability and Chronic Fatigue Syndrome

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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Structured Abstract

Objective. The objective of this evidence report was to perform a systematic review of the published literature to provide the Social Security Administration (SSA) with the best available evidence and most current medical knowledge regarding disability in persons with Chronic Fatigue Syndrome (CFS).

Search Strategy. English language and adult population published literature from 1988 to November 2001 was searched using MEDLINE, Current Contents, Cochrane Library, and PsychINFO databases and supplemented by a manual review of bibliographies of all accepted papers.

Selection Criteria. Interventional or observational studies of at least two adult patients reporting CFS according to either the CDC 1988, CDC 1994, Oxford 1991, or Australia 1990 criteria were accepted. Studies were required to report disability (evidence of a medically determinable physical or mental impairment) and data regarding employment or work.

Data Collection and Analysis. Data on patients, interventions, and outcomes were extracted from accepted studies. Studies were scored for quality and level of evidence. Data were summarized for study, patient, and treatment level characteristics as well as outcomes of interest. A panel of diverse technical experts and peer reviewers provided review and commentary on the draft report.

Main Results. Of 3,840 citations identified, 53 studies describing 4,558 patients with CFS met all eligibility criteria. Twenty-two of these studies described comparator groups of healthy controls totaling 775 patients. The majority of CFS patients represented in the 37 studies reporting employment status were unemployed. The evidence suggests that some individuals with CFS have cognitive or affective impairments on neuropsychological tests, but results are not consistent. Depression of greater severity is associated with unemployment, but no other impairment appeared to be consistently associated with disability or work outcomes. No specific interventions have been proven to be effective in restoring the ability to work. No specific patient characteristics have been identified as best predictors of positive employment outcomes in CFS patients. The patient's level of functioning at the time of diagnosis should be compared to functioning prior to the onset of illness especially as it relates to work, school, social and home activities.

The major limitations of this review are related to the weaknesses inherent in the current medical and scientific published literature regarding CFS. Study designs were not sufficiently homogeneous to allow quantitative synthesis of individual study results, and external validity was low. While some studies reported test and scale results, this was highly variable with relatively sparse and inconsistent reporting of both baseline and outcome data. No studies specifically measured the impact of baseline impairment data or treatment interventions on work function or employment outcomes.

Conclusions. While relationships between various impairment measures and work/disability status might be explored in some cases, the best available evidence from the literature did not allow for determination of causality. The limitations inherent in the current literature review are noted and the research community is urged to conduct methodologically rigorous, longitudinal, interventional studies to determine what baseline characteristics are associated with inability to work, and what interventions are effective in restoring the ability to work in the CFS population.

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Agency for Healthcare Research and Quality

Evidence Report/Technology Assessment

Number 66

Systematic Review of the Current Literature Related to Disability and Chronic Fatigue Syndrome

Summary

Overview

The purpose of this project, nominated by the Social Security Administration (SSA), and contracted through the Agency for Healthcare Research and Quality (AHRQ) was to develop an evidence base that would provide SSA with the most current medical and scientific knowledge for evaluating disability as defined by the SSA in persons with Chronic Fatigue Syndrome (CFS). This review will also serve to highlight gaps in the current literature and areas ripe for future research.

This database of best available evidence was established through a systematic review of the CFS literature pertinent to diagnosis, measurement, and treatment of disability resulting from any medically determinable physical or mental impairment.

Reporting the Evidence

Several key questions guided this review. Questions were originally posed by SSA and refined in collaboration with expert panel members and representatives from SSA and AHRQ to focus on the issues of disability and impairment in CFS. The revised key questions are as follows:

1. What is the evidence that some individuals with CFS have discrete impairments that are associated with disability? (Note that impairments include both physical and mental impairments.)
2. What is the evidence that in the CFS population, current neuropsychological tests reliably detect cognitive or affective impairments associated with decreased ability to work?
3. What is the evidence that in individuals with CFS treatments are effective in restoring the ability to work?
4. What patient characteristics best define improvement in functioning or positive outcomes in the CFS population? Where it occurs, how is improvement in functioning related to the ability to engage in work activity?

Methodology

A multidisciplinary panel of professionals with a broad range of clinical expertise in CFS was assembled early on to provide guidance and direction regarding:

- Establishing a working definition of CFS for purposes of this task order.
- Refining the original key questions as posed by SSA.
- Making recommendations regarding the breadth of the literature to be reviewed, analyses that should be performed, and sources of data to be accessed to ensure an evidence report that would be responsive to SSA's concerns.

Members of the panel served throughout the course of the project as the Technical Expert Panel (TEP), responded to questions during the review, and commented on the draft evidence report. The systematic review followed a prospective protocol that was developed *a priori* and shared with the nominating partner (SSA), the TEP, and the Task Order Officer at AHRQ. The protocol outlined literature search methods, study eligibility criteria, data elements for extraction, and methodological

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strategies to minimize bias and maximize precision during the process of data collection, extraction, and synthesis.

The published literature was searched from January 1, 1988 to November 15, 2001, using Medline®, Current Contents®, Cochrane Library, and PsychINFO databases. In addition, the bibliographies of all accepted studies and review articles from the past 2 years were searched for potentially relevant citations. The retrieval cut-off date was March 15, 2002.

English language published literature from 1988 to 2001 was sought, utilizing the following search strategy:

fatigue syndrome, chronic [MeSH] or *chronic fatigue* [*syndrome*].

Limits: English language, human subjects.

All citations and abstracts were printed and screened at MetaWorks. Full papers were obtained for all abstracts that mentioned CFS and disability. The electronic searches noted above were supplemented by a manual search of the reference lists of all accepted studies and relevant review articles. To be included in the review, studies were required to report CFS as diagnosed according to one of the four accepted CFS definitions, evidence of a medically determinable physical or mental impairment, and data regarding employment or work in at least two adult patients.

Data from each accepted study was extracted by one investigator and reviewed by a second. Key data elements sought for extraction from each study included study, patient, and intervention characteristics, as well as outcomes of interest. All eligible papers were evaluated and scored for both internal and external validity, with possible scores ranging from 2 to 8.

No quantitative analyses were performed beyond descriptive statistics to summarize findings. Eleven peer reviewers, drawn from clinicians with expertise in CFS and professional organizations, along with eight TEP members reviewed and provided comments on the draft evidence report. Feedback was incorporated into the final report as appropriate.

Findings

Of all 3,840 citations identified, 53 studies met all eligibility criteria. The majority of studies were conducted in the United States or Western Europe. There were 17 interventional and 36 observational studies, covering 4,558 primarily female adult patients with CFS. Twenty-two of these studies described comparator groups of healthy controls totaling 775 patients.

No quantitative syntheses were possible because of insufficient and/or inconsistent reporting or results. The evidence supports the following conclusions:

- Some individuals with CFS have discrete cognitive or affective impairments on neuropsychological tests, but these results are not consistent, nor can any causality associated with decreased rates of employment be inferred due to the cross-sectional design of most of the studies.
- Depression of greater severity is associated with unemployment, but no other impairment appeared to be consistently associated with disability or work outcomes.
- No specific interventions have proven to be effective in restoring the ability to work, and interventional trials describing both baseline and outcome data were sparse. The most commonly reported interventions included drug therapy and cognitive behavioral therapy; the latter lending a possible association between improvement in the ability to work and an increase in the number of patients employed.
- No specific patient characteristics have been defined that serve as best predictors of positive employment outcomes in CFS patients.
- It is important to compare the patient's level of functioning at the time of diagnosis to his/her level of functioning prior to the onset of illness especially as it relates to work, school, social, and home activities.
- The major limitations of this review are related to the weaknesses inherent in the current medical and scientific published literature related to CFS. Study designs were not sufficiently homogeneous to allow quantitative synthesis of individual study results, and external validity was low. While some studies reported test and scale results, this was highly variable with relatively sparse and inconsistent reporting of both baseline and outcome data. Longitudinal studies which would allow for assessment of effect of baseline characteristics on long-term work outcomes were extremely rare.

Future Research

It is clear from this review of the literature addressing work status in patients with CFS that more studies are needed to enable researchers to better assess and evaluate disability in this population. Following are priorities for future research:

- Longitudinal, interventional studies are mandatory in order to determine what baseline characteristics are associated with inability to work and which interventions are effective in restoring the ability to work.
- Authors should report more detailed information about impairment and work status at baseline and after intervention, preferably stratified by patient characteristics.
- Future studies of employment status should clarify if employment means full or part time, prior work or new work, and also provide information on duration of return to work.
- Further research is needed to determine the impact of cognitive behavior therapy, graded exercise, and other interventions on the issue of disability.
- The literature would be enhanced if standardized measurements of impairment were developed, defined, and used to evaluate the impact of all interventions, and if

some assessment was made regarding the impact of impairment on employability in this specific patient population.

- Further research is needed to determine validity and reliability of self-reported instruments in assessment of impairment and disability in CFS patients who are often formerly high functioning individuals, unlike chronic mentally ill patients or low functioning patients with physical impairments. Validity and reliability of these instruments should be determined in patients with concurrent or prior neuropsychological diagnoses, given the high lifetime incidence of same, and particularly in patients who may have different motivations for determining disability. Instruments should also be validated in compensation settings.
- Further research is needed to determine whether and which validated neuropsychological non-self-reported assessment tools yield sufficient evidence to evaluate functionality as it relates to ability to work.
- Further research in needed to determine whether there are characteristics of care providers or prior work experiences that relate to ongoing CFS disability.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by MetaWorks Inc. Evidence-based Practice Center (EPC), Medford, MA, under Contract No. 290-97-0016. It is expected to be available in the winter 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 66, *Systematic Review of the Current Literature Related to Disability and Chronic Fatigue Syndrome*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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Evidence Report

Chapter 1. Introduction

Purpose of Review

In 2001, the Agency for Healthcare Research and Quality (AHRQ) commissioned the San Antonio Evidence-based Practice Center to conduct a systematic literature review entitled "Defining and Managing Chronic Fatigue Syndrome (CFS)".[1] This earlier report focused on diagnosis and management of CFS and established a foundation for the current report, the objective of which is to evaluate the best available evidence on detecting and managing disability in persons with CFS. We seek to add to the groundwork laid by the earlier Evidence Report, without repeating the same information.

This topic was nominated by the Social Security Administration (SSA), which defines disability as "the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment (or combination of impairments) which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months".[2] Patients must have a severe impairment that makes them "unable to do (their) previous work or any other substantial gainful activity".[2] The impairment "must result from anatomical, physiological, or psychological abnormalities which can be shown by medically acceptable clinical and laboratory diagnostic techniques. A physical or mental impairment must be established by medical evidence consisting of signs, symptoms, and laboratory findings, not only by a statement of symptoms".[2]

While these requirements may be easily documented for some illnesses, assessing disability for CFS, a condition for which there is no accepted diagnostic test or widely effective treatment,[1] presents a greater challenge. The goal of this evidence review is to ensure that the SSA is using the most current medical knowledge for evaluating disability in persons with CFS.

Prevalence and Diagnostic Criteria

The prevalence of CFS is difficult to quantify, due to the lack of validated diagnostic tests and the heterogeneity of the CFS population.[3] It is estimated that CFS affects approximately 0.2 to 0.7 percent of adults in the United States and the United Kingdom,[4-6] and that women are affected more often than men.[7] CFS occurs in all ethnic groups and in people of every socioeconomic status.[4, 7, 8] The societal implications of CFS constitute a significant public health problem.[4]

Fatigue is frequently reported in primary care settings, but the vast majority of patients who complain of fatigue do not suffer from CFS, which is defined by specific diagnostic criteria.[9] Several operational case definitions of CFS have been developed by consensus groups in the United States, United Kingdom, and Australia .[10-13] The Centers for Disease Control (CDC) first developed diagnostic criteria for CFS in 1988,[11] with the most recent revision in 1994.[10] CFS is defined by the CDC as a syndrome of severe, disabling physical and mental fatigue lasting for at least six months, exacerbated by minimal exertion, and unexplained by a conventional medical diagnosis. CFS represents a diagnosis of exclusion. The differential diagnosis of CFS includes symptoms of depression, somatization disorder, anxiety disorder, hypochondriasis, activity-induced chronic fatigue, fibromyalgia, hypothyroidism, Lyme disease, and multiple sclerosis.

While people with CFS may report a variety of symptoms in many organ systems, extensive research has not revealed any serious underlying pathology.[14]

The diagnostic work-up for CFS recommended by the CDC includes a history and physical examination, including mental status examination, and laboratory tests including complete blood count (CBC) with differential, erythrocyte sedimentation rate (ESR), liver function tests, total protein, albumin, calcium, phosphorus, glucose, blood urea nitrogen, creatinine, electrolytes, thyroid function tests, and urinalysis.[10] None of these tests are diagnostic for CFS, but they may point the clinician toward an alternative diagnosis. No causal agent and no diagnostic laboratory tests or biological markers have been verified for CFS. Earlier reports suggested a role for Epstein-Barr Virus (EBV) in the pathogenesis of CFS.[15] Some physicians persist in ordering serial EBV titers to diagnose and follow patients with CFS; however, available evidence indicates that EBV serology has no role in standard laboratory evaluation of persons with CFS.[4] The diagnosis of CFS remains one of exclusion, since a diagnostic laboratory marker or pathognomonic biopsy specimen has not been identified.[4]

Treatment of CFS

No treatment for CFS has proved to be effective. A systematic review of interventions for treating CFS showed mixed results of effectiveness for all treatments, with promising results with cognitive behavioral therapy (CBT) and graded exercise therapy.[1, 16] Numerous pharmacologic approaches have been tested, including antidepressants,[17] corticosteroids,[18, 19] mineralocorticoids,[20] anti-viral medications, anti-fungal agents, and immunotherapy. Many alternative treatments have also been tried, unsuccessfully.[21] In addition to CBT[22] and graded exercise,[23] a myriad of other non-pharmacological approaches have also been tested, including massage therapy, prolonged bedrest, biofeedback, stress management, anti-allergy and anti-yeast diets.[21]

Challenges in Determining Disability

Determining levels of disability, as a manifestation or consequence of fatigue, presents an important research challenge. Evaluating disability in CFS patients is hampered by the difficulties in defining and diagnosing CFS, the unknown etiology, and the heterogeneity of the population. The core complaint, fatigue, is entirely subjective, and does not readily fit the SSA definition of "anatomical, physiological, or psychological abnormalities"[2] that can be demonstrated by objective testing. Impairment is also variably defined and measured. Interpretation of the clinical significance of specific impairment measurements is limited by the many different impairment scales used, the different health domains measured, and the relatively small numbers of patients studied. As a result, studies of impairment and disability in CFS often cannot be readily compared, even in study cohorts with homogenous case definitions.
There are thus numerous unanswered questions regarding CFS disability. This review of the current medical and scientific research related to CFS disability was nominated by the SSA, and a Task Order was commissioned by the AHRQ to assist in answering several key questions related to assessment and management of disability in people with CFS. This research will assist

the SSA in ensuring that it is using the most current medical knowledge for evaluating disability in persons with CFS.

Chapter 2. Methodology

All work included in this Task Order was carried out by MetaWorks investigators, using systematic review methods derived from the science of review research.[24, 25] These methods were generally applied according to standard operating procedures at MetaWorks and are shown in Figure 1.

The SSA submitted to AHRQ a list of questions pertinent to disability and CFS. AHRQ developed a Task Order, and presented it to MetaWorks. After MetaWorks investigators conducted a preliminary review of the literature, an Expert Panel meeting was held in Washington, DC, on November 15, 2001. The purposes of this meeting were to:

1. Establish working definition of CFS for purposes of this task order.
2. Refine key questions.
3. Get recommendations regarding breadth of literature to be reviewed, analyses to be performed, and sources of data that should be accessed to ensure the evidence report is responsive to SSA's concerns.

Key Questions

The SSA initially suggested a comprehensive list of questions to be addressed by this review. During the Expert Panel meeting, the original key questions were modified to focus more specifically on the issues of disability and impairment in CFS. The following revised questions were reviewed by the Expert Panel and representatives from SSA, and were approved by the AHRQ Task Order Officer (TOO).

1. What is the evidence that some individuals with CFS have discrete impairments that are associated with disability? (Note that impairments include both physical and mental impairments).

2. What is the evidence that in the CFS population, current neuropsychological tests reliably detect cognitive or affective impairments associated with decreased ability to work?

3. What is the evidence that in individuals with CFS, treatments are effective in restoring the ability to work?

4. What patient characteristics best define improvement in functioning or positive outcomes in the CFS population? Where it occurs, how is improvement in functioning related to the ability to engage in work activity?

Based on the Task Order, MetaWorks researchers developed a Work Plan (Appendix A) which outlined the methods to be followed for the literature search, study eligibility criteria, data elements for extraction, and methodological strategies to minimize bias and maximize precision during the process of data extraction and synthesis. The Work Plan also incorporated decisions made at the expert panel meeting held on November 15, 2001 (Appendix B), regarding the

revised key questions, CFS diagnostic criteria to be used, and recommended changes to the preliminary literature searches. The Work Plan was subsequently reviewed and accepted by AHRQ and SSA.

Causal Pathway

Based on the results of a preliminary literature review, a causal pathway was developed (Appendix A, page A-23). All of the events described in this pathway take place within the CFS universe; i.e., only patients already diagnosed with CFS are included. Patients with fibromyalgia, Gulf War Syndrome, and other related conditions are not included. To diagnose disability in the CFS universe, patients must have a medically determinable condition (defined by clinical signs and symptoms, laboratory abnormalities, or other abnormalities), leading to physical or mental impairment, that results in disability, as defined by the SSA. This causal pathway was presented at the Experts Meeting described above.

The causal pathway was not designed to function as a clinical practice guideline or algorithm for decisions regarding patient care. It was developed solely to provide guidance throughout all phases of the systematic review process specific to the project.

Literature Search

The published literature was searched from January 1, 1988 to November 15, 2001, using Medline, Current Contents®, Cochrane Library, and PsychINFO databases. In addition, the bibliographies of all accepted studies and review articles from the past two years were searched for potentially relevant citations. The retrieval cut-off date was March 15, 2002.

English language and adult population published literature only from 1988 to 2001 was sought, utilizing the following search strategy:

fatigue syndrome, chronic [MeSH] or *chronic fatigue* [*syndrome*].
limits: English language, human subjects.

The preliminary search included studies published from 1990 to 2001. Based on recommendations proposed during the expert meeting, a decision was made to extend the search window back to 1988, the year of the first operational definition of CFS published by the CDC. It was believed that many important studies may have been published immediately after publication of this definition and needed to be included. It was also recommended that the *Journal of Chronic Fatigue Syndrome*, which is not indexed by Medline, but is indexed by PsychINFO, be searched for additional relevant citations. The search was expanded to include PsychINFO database.

Exclusion Criteria

All citations and abstracts were printed and screened at MetaWorks for any mention of diagnosis and/or treatment of CFS disability or impairment (Level I screening) and reviewed for the following exclusion criteria:

- Review, meta-analysis, abstracts, letters, case reports, editorials, commentaries, and unpublished study reports.
- Studies published prior to 1988.
- Studies written in languages other than English.
- Pharmacokinetic and pharmacodynamic studies.
- Animal or *in vitro* or tissue level studies.
- Studies not *related to* or not *specific to* CFS disability or impairment.
- Studies containing < 2 patients as total sample size.
- Pediatric patient population.
- No information related to disability or impairment.
- Outcomes not extractable.
- Mixed population (unable to separate CFS from other populations).
- Studies focused on pathophysiology of CFS (lab findings/lab techniques).
- Studies not conducted in the United States, Canada, Australia or Western Europe.

The geographic limitation was imposed because the purpose of this report was to inform policy pertaining to CFS patients in the United States, and it was believed that studies pertaining to disability in CFS patients in non-Western countries would not be generalizable to CFS patients in the United States.

When it was not possible to determine the eligibility of the study from the abstract alone, full studies of abstracts lacking obvious exclusion criteria were retrieved for Level II screening, during which both inclusion and exclusion criteria were applied. Level II screening forms are shown in Appendix C.

Inclusion Criteria

The following study designs were accepted: observational (prospective, retrospective, and cross sectional), or interventional [randomized controlled trials (RCTs), non-randomized controlled trials (nRCTs), uncontrolled case series (UCS)].
Studies were required to report:

- CFS diagnosed according to one of the four accepted CFS definitions.
- CDC 1988[11] or CDC 1994[10]
- Oxford 1991[12]
- Australia 1990[13]
- Adult patients with CFS *and* disability.

- Medically determinable physical or mental impairment in CFS patients (measures of symptom severity, functional or cognitive impairment, physical activity, exercise testing, general health, or psychiatric impairment).
- At least one objective measure related to disability, per SSA guidelines.

Upon completion of Level II screening, all accepted articles were eligible for data extraction. Due to the abundance of different scales reported in each of the studies, an additional screen was performed, in which each study was reviewed. Outcomes and scales reported in each study were then extracted. From this screening process, studies that specifically reported work outcomes were selected, and pertinent data were extracted from each study.

Linked Studies

After the accepted studies were determined, linked studies were identified. These were studies in which the same patient population was reported in more than one study. Studies which contained primary data were assigned "parent" study status. "Child" studies contained supplemental information, such as follow-up data or additional analyses. Data elements were extracted from the parent studies, and supplemented by information presented in linked ("child") studies, when appropriate.

Rating the Evidence

All eligible studies were evaluated for both internal and external validity at the time of data extraction (Appendix D). One method was developed specifically for this project. Papers received 1 point for each of the following:

1. CFS is defined according to acceptable criteria, and all patients met these criteria,

2. Tests for medically determinable physical and/or mental impairment are specified and reported,

3. Control group, if present, was similar in clinically important demographic factors at the start of the study,

4. All subjects enrolled were accounted for in followup,

5. Confidence intervals or p-values were reported for numerical results,

6. Work activity or disability status was reported.

Thus, papers could receive a maximum of six points for internal validity. All studies were awarded at least two points for internal validity, because they were required to fulfill the first two criteria in order to be accepted into the database. External validity had a scale of 0-2, with zero

points awarded for a study in which the patient sample was self-selected from the CFS population, and two points if the patient sample was a random sample or all patients from a CFS cohort. Thus, the possible range of scores for each study was 2-8.

Study quality was also evaluated using a scale that graded studies based on study design (prospective longitudinal vs. cross-sectional), sufficient patient number, well-matched groups, and well-validated measurement instruments.[38] In addition, RCTs were evaluated based on a validated quality score in which points were awarded for reporting method of randomization, blinding, and withdrawals.[39]

Data Extraction

Data Extraction Forms (DEFs) were designed specifically for this project (see Appendix C), and pilot tested on a small sample of eligible studies. The pilot test allowed for necessary edits to the DEF to be made prior to implementation on all studies. Key data from each eligible study were extracted by a researcher recording data from published articles onto a DEF, and reviewed by a second researcher, checking all DEF fields against the published report. Differences were resolved prior to data entry. In all cases, at least one physician reviewed each study. Dual review of all data served to reduce error and bias in the data extraction process. The data were then entered into MetaWorks' relational database of clinical studies, MetaHub™.

Key data elements sought for extraction from each study included:

Study Characteristics:

- Citation, publication date
- Location
- Study duration, design
- Single time point or longitudinal study
- Industry sponsorship (sponsor name or not reported)
- Validity Score (see Appendix D)
- Quality Score (see Appendix D)
- Total number of patients enrolled
- CFS patients
- Healthy Controls
- Geographic location
- Institution

Treatment Arm Characteristics:

- Number of patients enrolled or randomized
- Number of patients evaluated for efficacy and safety
- Age: years (mean, median, and range)
- Gender distribution

- Duration of CFS symptoms
- Education (years)
- Employment status
- Number of patients working full-time
- Number of patients working part-time
- Number of patients unemployed
- Number of patients receiving disability benefits
- Number of patients with work limitations due to illness
- Number of patients with other medical or psychiatric diagnoses

Interventions:

- Behavioral therapy
- Psychiatric therapy
- Drug therapy
- Exercise therapy

Outcomes:

- Number of patients evaluated at followup
- Employment status
- Number of patients working full-time (including full-time students or "housewives")
- Number of patients working part-time
- Number of patients unemployed
- Number of patients receiving disability benefits
- Number of patients with work limitations due to illness
- Number of patients improved, unchanged, or worse
- Scales, by domain: baseline, outcome, or change in each score
- Cognitive
- Disease or symptom severity
- Exercise testing
- Functional
- General health
- Mental (psychiatric or affective)
- Physical Activity
- Work

The investigators categorized each scale according to one of the above domains. Some scales, such as the Checklist of Individual Strength (CIS),[26] the Sickness Impact Profile (SIP),[27] and the Medical Outcomes Study – Short Form 36 (MOS SF-36),[28] had subscales in multiple domains. Scales in the cognitive domain included the Wechsler Adult Intelligence Scale (WAIS),[29] the Hopkins Verbal Learning Scale,[30] the Everyday Attention Questionnaire (EAQ),[31] and the concentration subscales of the CIS and SIP. Scales in the disease or symptom severity domain included the Chalder Fatigue Scale,[32] and the Profile of Mood States (POMS) subscales

for fatigue, vigor, and activity.[33] The exercise testing domain included treadmill endurance tests and measures of maximum oxygen output capacity (VO_2 max). The functional domain included the total SIP scale. The general health domain included the MOS SF-36 and the Karnofsky Performance Scale (KPS).[34] The mental (psychiatric or affective) domain included the Beck Depression Inventory (BDI)[35] and the Symptom Checklist 90R (SCL 90R) subscale for depression.[36] The physical activity domain included the POMS, MOS SF-36, and SIP subscales for activity. The work domain was mainly captured as number of patients working; however the SIP work subscale was also included. This is not a complete list of scales encountered in the literature, but it encompasses the major categories. As many papers used different scales, organizing them by domain was a necessary and important first step in considering combining data from different studies. Citations for scales extracted from accepted studies are listed in Appendix E.

For each study, results from a maximum of three scales in each of the domains available were extracted. Other results available were noted as "other outcomes." Where more than three scales in a given domain of interest were reported for the same study, decisions on which scales to extract were made using the following criteria, applied sequentially:

1. Scales with a higher number of patients evaluated were extracted preferentially over those with fewer patients evaluated.

2. Scales with group means reported were preferentially extracted over those reported as group medians.

3. Scales with measures of dispersion (standard deviation or standard error) were preferentially extracted over scales where the mean or median for the group was reported, but no measure of dispersion was available.

4. Named scales, for example MOS SF-36, BDI, or Chalder fatigue scale, were preferentially extracted over study-specific or unidentified scales, on the assumption that these scales might be more amenable to pooling across studies.

5. Where, in a single domain, both total and component scale results were reported, the total was extracted preferentially.

After data extraction of all studies, decisions on which scales to analyze were based upon frequency of use.

Database Development

Data were entered from the DEFs into a relational database of clinical trials. When data entry was complete, 100 percent of the data entries were checked back against the original DEFs. In addition, a 20 percent random sample of data in the completed database was checked against the DEFs. An error rate in excess of 2 percent of this sample would have triggered a 100 percent recheck of all data elements entered into the database.

Statistical Methods

Data listings and summary data were prepared for study, patient, and treatment level characteristics, and for outcomes of interest. After the database was complete, verified, and locked, data were entered into table shells. In general, study and patient characteristics and outcomes variables were summarized using standard descriptive statistics weighted by study sample size. Given the heterogeneity of the parameters measured in different studies, the sparse reporting of common impairment measures along with similar work data, and the frequent lack of information about ranges and distributions of the instruments used, pooling of impairment scale results across studies was not possible.

Role of Consultants

The eight participants from academic and community settings who attended the multidisciplinary meeting on November 15, 2001 served as our technical expert panel (TEP), and are listed in Appendix F. All TEP members received copies of the minutes from the meeting, causal pathway, and draft report. Additionally, during the course of the project, periodic conference calls were held with the topic nominator (SSA), the Task Order Officer from AHRQ, and the external co-investigator, Dr. Nelson Gantz. During these conference calls, project updates were provided and issues of concern were addressed.

Peer Review

A group of eleven peer reviewers (Appendix F) was assembled to review a draft version of this report. The panel was composed of experts in CFS, disability, occupational medicine, family practice, and psychiatry. All reviewers were asked to complete the peer review form relative to the content of the report (Appendix G), and were encouraged to provide additional written comments as well. All responses from the TEP and peer reviewers were reviewed and, where appropriate, are incorporated into this final report.

Chapter 3. Results

In the following results, “k” refers to the number of studies, "t" refers to the number of treatment arms, and “n” refers to the number of patients.

Searches

The numbers of abstracts obtained from all searches are displayed in Figure 2. The primary search in Medline (search window: 1988-2001) yielded 3200 citations and the primary search in Current Contents (search window: 1988-2001) yielded 154 additional citations. PsychINFO was also searched and yielded an additional 398 citations, and 88 citations were identified by manual bibliography checks of accepted studies and recent review articles.

A total of 3,840 abstracts identified from electronic searches and bibliography checks were screened against protocol-defined exclusion criteria. After screening of abstracts for exclusion criteria (Level I screening), 420 were accepted and these full-text papers were retrieved for more in-depth screening (Level II). During Level II screening of full-text papers, 346 were rejected, resulting in a total of 53 accepted studies and 21 kin studies meeting all criteria. The bibliography of accepted studies may be found in Appendix H. Appendix I contains full citations for rejected studies, organized by rejection reason. The most common reason for rejection was lack of data on work or disability status (k=124).

Studies

Evidence Table 1 summarizes the main study-level characteristics of the 53 studies accepted for data extraction, which described a total of 4,558 patients with CFS. In addition, 22 of these studies described healthy controls (n=775). Information on other comparator groups, such as groups of patients with multiple sclerosis or fibromyalgia, was not extracted.

Most studies were conducted in North America (k=30; n=1,942). Twenty were performed in Western Europe (n=1,807), and two in Australia or New Zealand (n=65). One study was multicontinental (n=744).[37]

Studies of all designs were accepted. Of the 53 accepted studies, 36 were observational (n=3,210) and 17 were interventional (n=1,348). Thirty-one studies were cross-sectional; i.e., reported results at just one timepoint (n=2,664). One study was a retrospective case series (n=94), and there were 21 prospective studies, which included ten RCTs (n=1,042), eight UCSs (n=366), two case control studies (n=321), and one nRCT (n=71).

For acceptance into the database, studies were required to use at least one of the four accepted diagnostic criteria for CFS. Many studies used more than one definition. Twenty-three studies required patients to fulfill the 1988 CDC criteria for CFS, 20 required that patients fulfill the 1994 CDC diagnostic criteria, and 18 studies required that patients meet the Oxford 1991 diagnostic criteria. Only one study used the Australian criteria, but it used the other three criteria as well.[37]

Study Quality and Validity

Two distinct methods of study quality assessment were performed, and results are displayed in Table 2. In quality scoring, studies were divided into longitudinal vs. cross-sectional design,[38] and demonstrated a great deal of variation in quality within each stratum. Many studies did not receive high scores due to lack of sufficient sample size or lack of well-validated measurement instruments. Using the validity assessment tool defined specifically for this project, studies scored well overall for internal validity, but poorly for external validity, suggesting that the results of this sample of studies may not be generalizable to the entire population of patients with CFS. The mean quality score for the ten RCTs was 3.3, on a scale of 0-5, where 5 represents the most robust evidence.[39]

Patients

Evidence Table 3 shows baseline patient characteristics of all accepted studies. The majority of patients (76 percent) were female. Mean age was reported in 48 studies (n=4,372), and ranged from 24.7 to 46.1 years, with a mean of 38.4 years. Mean duration of CFS in all studies that reported this parameter (k=40, n=3,976) was 5.5 years, and ranged from 1.9 to 8.5 years. Years of education were reported in 14 studies (n=1,310), and ranged from 11.8 to 16.0 years, with a mean of 14.1 years. As shown in Evidence Table 3, the demographic information of the healthy controls was similar to that of the patients with CFS.

To be accepted into the database, studies were required to report data pertaining to employment, but their methods of reporting this parameter varied greatly. Evidence Table 3 summarizes disability information in all of the studies in the database. The total number of employed CFS patients was reported in 35 studies (n=2,652; 42 percent employed). The number of unemployed patients was reported in 37 studies (n=2,720; 54 percent unemployed). The number of studies reporting percent unemployed exceeds the number of studies reporting percent of patients employed by two because one study reported the number of CFS participants not working, and stated that the remainder were either working or not reporting their employment status.[40] Another study reported the percent of patients disabled, and presumed to not be working, but did not give any information pertaining to the percentage of non-disabled patients who were working.[41] Nine of these studies also reported the total number of healthy controls who were employed and unemployed (n=340; 90 percent employed, 9 percent unemployed). These results do not total to 100 percent due to incomplete reporting in some studies.

Some studies divided employment into full-time vs. part-time, and in these studies, an even greater difference was seen between CFS patients and controls. In 16 studies reporting this measure, only 19 percent of 967 CFS patients worked full-time, while in two of these studies, 75 percent of 53 controls worked full-time.

Ten studies (n=511) reported the number of patients who were on disability or temporary sick leave (55 percent), compared with 1 percent of healthy controls (k=2, n=89).

Twenty studies (n=1,919) reported the number of patients who had work limitations due to illness (64 percent), compared with 0 percent of 38 controls in the single study that reported this measure for healthy controls (n=38).

Impairment Domains

Twenty-seven studies reported data in the cognitive domain (including POMS and WAIS), 39 in the disease or symptom severity domain (including POMS and CIS), 12 in exercise testing, nine in the functional domain (including SIP), 15 in the general health domain (including MOS SF-36), 32 in the mental (psychiatric or affective) domain (including BDI and MOS SF-36), and 14 in the physical activity domain (including MOS SF-36 and actometer results).

Key Question 1: Disability and Impairment in CFS Patients

What is the evidence that some individuals with CFS have discrete impairments that are associated with disability? (Note that impairments include both physical and mental impairments).

As summarized in Table 3, 17 studies (n=1,830) reported the incidence of current psychiatric diagnoses in their patients (39 percent). Twelve studies reported the lifetime incidence of psychiatric diagnoses in their CFS patients (65 percent). The most common psychiatric diagnosis was depression. In contrast, four studies (n=200) reported the lifetime incidence of psychiatric diagnosis in their healthy controls (12 percent). While this does not prove an association, it does suggest that patients with CFS have a higher lifetime incidence of psychiatric diagnoses than healthy controls. However, the small sample size prevents drawing any definitive conclusions, and no relationship of psychiatric diagnoses to disability may be established.

Few studies reported the incidence of medical diagnoses in CFS patients. Substance abuse was reported in four studies,[19, 42-44] in a total of 24 of 250 patients (9.6 percent). Fibromyalgia was reported in four studies,[45-48] in a total of 245 of 806 patients (30 percent). One study reported the presence of allergies, in 66 percent of 47 patients; and irritable bowel syndrome, in nine percent of 47 patients.[48] Mitral valve prolapse was reported in a single study, and occurred in three of 18 patients.[49] The same study reported hyperlipidemia, in one of 18 patients. Sparse reporting of medical conditions suggests that CFS patients in these studies either do not have concurrent medical diagnoses, or their medical diagnoses are not reported. This may also relate to the fact that certain medical conditions are exclusionary factors in the consideration of CFS.

Evidence Table 4 shows studies that reported both employment status and impairment scales. This table was compiled to see if associations could be demonstrated between employment status and impairment domains in CFS patients. Figures 3 through 6 show scatter plots exploring possible relationships between employment status and scores on various impairment scales, organized by domain. Each scale was standardized to a 0-100 range. For the disease severity scale, high scores corresponded to increased severity. For general health and physical activity, high scores corresponded to improved health or activity. Figure 3 shows the percentage of patients unemployed vs. disease severity, as measured on POMS fatigue and several fatigue severity scales. Figure 4 shows percentage of patients with work limitations vs. disease severity, as measured on POMS fatigue and several fatigue severity scales. Figure 5 shows percentage of patients unemployed vs. scores on general health, as measured on MOS SF-36, self-rating wellness score, and perceived health score. Figure 6 shows percentage of patients unemployed vs. scores on physical activity scales (MOS SF-36, basic Activities of Daily Living, and

actometer). All of these figures display absence of an apparent association between work status and any self-reported impairment domain.

Evidence Table 5 shows the eight studies that reported both impairment in physical domains (physical activity, general health, disease severity, or exercise testing) and percentage of subjects employed, in both CFS patients and healthy controls.[30, 41, 42, 47, 50-53] Employment data were reported in other studies, but did not include both CFS patients and healthy controls. Significant differences were found between CFS patients and healthy controls on several scales in the physical domain: the MOS SF-36 physical function,[47, 52] general health,[47] health perception,[52] the POMS for fatigue and vigor,[41, 42, 50] the Profile of Fatigue-Related Symptoms (PFRS) for fatigue and somatic symptoms,[51] SIP for mobility and walking,[53] and the CIS for activity.[53] The mean scores are shown in Table 5, along with *p* values, when reported. Measures of dispersion were frequently reported in papers, but were omitted from the table because the authors believed that including these extra values would add minimal interpretive value to the table and would do little to enhance the readability of the text. Although CFS patients had significantly different scores from healthy controls in these studies, it should be remembered that all of these scales may be abnormal in patients who are fatigued for any reason. All but three of these eight studies represent estimates of physical impairment based only on self-reported scales by the patient. Only two of the eight studies describe formal objective exercise testing. No significant differences were found between CFS patients and healthy controls in VO_2 max[30] or maximal voluntary contraction (MVC) during hand grip exercises.[50] The percentage of CFS patients who were employed ranged from 13 to 49 percent in these studies, while the percentage of healthy controls employed ranged from 71 to 100 percent. Most of these employment rates include both full-time and part-time work, but the lowest values, for both CFS patients and healthy controls, were from one study that only reported full-time work.[51] No statistical pooling is possible, due to widely divergent study designs and outcomes measured, but the table does suggest that a lower percentage of CFS patients with abnormalities on physical function and fatigue scales are employed compared to healthy controls with normal scores on these scales.

In two studies,[47, 52] the MOS SF-36 physical function scores showed similar differences between CFS patients and controls. In three studies,[41, 42, 50] the POMS fatigue scores were also similar in CFS patients. These two measures of physical impairment represent the best available evidence of physical impairment in CFS patients at this time.

In summary, the evidence suggests that some individuals with CFS have self-reported discrete physical and mental impairments, and some individuals with CFS have decreased ability to work. It is not possible, however, to correlate impairments with disability based on the published literature.

Key Question 2: Neuropsychological Tests Associated With Impairment in CFS Patients

What is the evidence that in the CFS population, current neuropsychological tests reliably detect cognitive or affective impairments associated with decreased ability to work?

Evidence Table 6 lists the nine studies that reported both neuropsychological impairment scales and work data in both CFS patients and healthy controls.[30, 41, 42, 47, 50-53] Significant differences were found between CFS patients and healthy controls on MOS SF-36 mental

health,[47, 52] POMS confusion and depression,[41, 42, 50] EAQ and PFRS for emotional distress and cognitive difficulty,[51] SCL 90R depression,[52] and SIP and CIS concentration.[53] POMS for anger/hostility and tension/anxiety were significantly different in CFS patients vs. healthy controls in one study,[41] but not in another.[42] Cognitive function was significantly different in CFS patients vs. healthy controls in the WAIS digit span forward in one study,[54] but not in another, in the Hopkins verbal learning.[30] One study reported that the POMS tension/anxiety and anger/hostility scores were not significantly different between CFS patients and healthy controls.[42] The percentage of CFS patients who were employed ranged from 13 to 49 percent in these studies, while the percentage of healthy controls employed ranged from 71 to 100 percent. No statistical pooling is possible, due to widely divergent study designs and outcomes measured, but the table does suggest that CFS patients have a higher frequency of abnormalities on confusion, depression, and concentration scales and lower levels of employment compared to healthy controls.

In two studies,[47, 52] MOS SF-36 mental health scores revealed similar differences between CFS and healthy controls. In three other studies,[41, 42, 50] POMS confusion scores and differences with healthy controls are also of similar magnitude. POMS depression is comparable in only two of these same three studies.[41, 42] This best available evidence suggests that MOS SF-36 mental health and POMS confusion may be the most promising measures of neuropsychiatric status in CFS patients, and may relate to employment status. Individual patient data would be needed to further research this hypothesis.

Figure 7 shows a scatter plot of the percent of patients unemployed vs. the mean depression score, as measured on the BDI, POMS depression, and MOS SF-36 – mental health. The depression scores were standardized to 0 to 100, and lower scores correspond to greater depression. Most of the studies in Evidence Table 6 are represented in this figure, in addition to studies that reported scales in the cognitive or mental domain for CFS patients but not for healthy controls. This figure suggests an association between greater degree of depression and greater percentage of unemployment. It is not possible, however, to determine whether there is a causal linkage between depression and unemployment.

In summary, the evidence suggests that some individuals with CFS have self-reported discrete cognitive or affective mental impairments, and some individuals with CFS also report decreased ability to work. We found no reports examining the relationship (if any) between the patient's perception of potential consequences (e.g., financial gain) and the results of these self-reported impairment instruments.

Key Question 3: Treatments Effective in Restoring Ability To Work in CFS Patients

What is the evidence that in individuals with CFS, treatments are effective in restoring the ability to work?

Evidence Table 7 shows the interventional trials in the database, organized by type of intervention and impairment scale domains. This table was compiled to see if a sufficient number of studies were available to permit study of any associations between intervention and work or impairment domains. However, in no cell of the matrix was there a sufficient number of studies to allow any assessment of association. The most commonly reported scales were in the domains

of disease severity and symptoms (e.g., POMS and CIS) and mental impairment (e.g., BDI and SCL 90R). The most commonly reported interventions were drug therapy (e.g., corticosteroids, mineralocorticoids, and antidepressants) and behavioral therapy. Even for cells in this matrix with three or more studies, there were no apparent consistent associations between domains measured and interventions studied.

Two British studies of CBT[55, 56] reported work scale data before and after an intervention. In one study,[55] in which 32 patients received CBT and a tricyclic antidepressant (dothiepin), the mean baseline ability to work score ± SD (scale range 0-8; decrease = improvement) was 6.31 ± 1.96, and the mean followup score, six weeks later, was 2.72 ± 2.44. The number of patients employed at baseline and followup was not reported, but it is possible (although not explicitly demonstrated), that improvement in the ability to work score would be associated with an increase in the number of patients employed.

In the other study,[56] which was an RCT comparing CBT to relaxation, the Work and Social Adjustment score was reported at baseline and followup, six months later. Again, the scale range was 0-8, with lower scores corresponding to improvement. In the CBT group, the baseline ± SD was 6.0 ± 1.2, and the followup score was 3.3 ± 2.2, while in the relaxation group, the scores were 6.1 ± 1.3 and 5.4 ± 1.8, respectively. The improvement in the CBT work score was significantly greater than that in the relaxation group work score ($p<.001$). Again, it is likely that improvement in the ability to work score would be associated with an increase in the number of patients employed, although this was not demonstrated.

Only six longitudinal studies reported percentage employment at baseline and followup, as shown in Evidence Table 8.[26, 57-61] Percentage of CFS patients employed at baseline ranged from zero to 39 percent, and at followup (three to 42 months after baseline), employment ranged from 23 to 53 percent. Interventions associated with increased percentage of employment at outcome included individualized rehabilitation programs,[57, 58, 60] CBT,[57] and exercise therapy.[59] The studies are not comparable, however, due to differences in study design, duration of followup, and types of intervention. Furthermore, up to 29 percent of patients were lost to followup.

Only one study[57] with a substantial number of patients (n=51) and a high validity score (6) showed a substantial increase in percentage of patients working after an intervention, in this case, CBT. We also note that the two observational studies (no specific therapeutic interventions) reporting work outcomes showed a decrease over time in the proportion of CFS patients employed. These two studies, however, had a large percentage of drop-outs at the followup assessment.

In summary, some CFS patients who underwent a variety of interventions ranging from no treatment to individualized rehabilitation programs were able to return to work, but the sample sizes are too small and the study designs too disparate to allow comparisons of different treatments in their association with returning CFS patients to work.

Key Question 4: Characteristics Associated With Improvement in CFS Patients

What patient characteristics best define improvement in functioning or positive outcomes in the CFS population? Where it occurs, how is improvement in functioning related to the ability to engage in work activity?

Evidence Table 9 describes the nine studies that reported the number of CFS patients who were reported by investigators to be improved over time. The table details the interventions used, and compares the baseline characteristics of the patients who improved to those who did not improve.[26, 43, 45, 49, 55, 56, 61-63] Specific characteristics of interest were mean age, gender, mean duration of CFS symptoms, mean number of years of education, and incidence of depression. Studies did not show any consistent trend with regard to these baseline parameters.

Shorter duration of disease was associated with improvement in two studies,[26, 49] but not in three others.[55, 61, 62] Gender was associated with improvement in two studies,[49, 62,] but not in two others.[55, 61] Age was associated with improvement in one study,[26] but not in two others.[61, 62] Education was not associated with improvement in two studies[61, 62,] and marital status was not associated with improvement in one study.[62]

In four studies, work status was discussed with regard to patient characteristics. These studies were examined to seek characteristics associated with positive work outcomes in the CFS population (Evidence Table 10). In one US study,[45] 226 CFS patients were contacted 1.5 years after their initial evaluation, and asked to fill out a questionnaire pertaining to their working and level of functioning. None of the baseline demographic, clinical, or psychiatric characteristics were predictive of returning to work. In another US study,[64] 32 CFS patients were evaluated to identify traits associated with working. Working patients with CFS were more likely to be male, younger, never married, had less severe muscle and joint pain, higher activity levels, and better physical functioning than non-working patients. In the third study, from New Zealand,[65] 53 CFS patients were questioned regarding their perceptions of health, illness attributions, self esteem, and coping skills, and were followed for six months. Work dysfunction was associated with increased CFS-related symptoms. In a multinational study,[37] 744 CFS patients filled out questionnaires that included questions on functional impairment and ability to work. Greater severity of symptoms was associated with inability to work, but depression was not.

In summary, no patient characteristics in any impairment domain have been consistently identified that best define or predict improvement or positive work or functional outcomes in the CFS population.

Chapter 4. Conclusions

Summary of Answers to Key Questions

1. *What is the evidence that some individuals with CFS have discrete impairments that are associated with disability? (Note that impairments include both physical and mental impairments).*

CFS patients represented in the database have measurable physical and mental impairments; however this is based primarily on a variety of "self-report" instruments, most of which have been validated. These instruments; however, although "validated," have not been validated in a "compensation setting," have not been validated as measures of disability, and have not been validated in CFS patients who are often formerly high functioning individuals, unlike chronic mentally ill patients or low functioning patients with physical impairments. The majority of the CFS patients represented in the 37 studies reporting employment status are unemployed. However, due to the heterogeneity of CFS, small study size, and wide variations in reporting the data, it is not possible to determine whether those CFS patients with discrete impairments and/or measurable disability are those who are unemployed. We could not compare employment status of healthy controls with impairment, as the healthy controls in these studies did not have measurable impairments. No particular measure of impairment appears superior to others in CFS patients, and no measure of disability appears as objective and reproducible as work status.

2. *What is the evidence that in the CFS population, current neuropsychological tests reliably detect cognitive or affective impairments associated with decreased ability to work?*

The evidence suggests that some individuals with CFS have self-reported discrete cognitive or affective mental impairments, as measured on validated tests in the mental or cognitive domain. The majority of CFS patients in studies reporting work outcomes have decreased ability to work. CFS patients with a greater degree of depression are unemployed more often than those with mild or no depression, although no cause and effect relationship can be claimed.

3. *What is the evidence that in individuals with CFS, treatments are effective in restoring the ability to work?*

Some CFS patients who underwent a variety of interventions ranging from individualized rehabilitation programs to CBT demonstrated improvement in functioning and were able to return to work; however, the sample sizes are too small and the study designs too disparate to enable comparisons of different treatments in their association with returning CFS patients to work. Furthermore, a substantial number of CFS patients with no treatment returned to work with the passage of time. So, while some treatment interventions may provide symptom relief,[1] no evidence for efficacy as defined by work outcomes is available.

4. *What are the patient characteristics that best define improvement or positive outcomes in the CFS population such that they experience improvement in functioning? Where it occurs, how is this improvement in functioning related to the ability to engage in work activity?*

No specific demographic, clinical, or psychiatric traits have been shown to be consistently predictive of CFS patients' ability to return to work.

Strengths and Limitations of the Evidence Base

The strengths of this review include the clear definition of the research questions, adherence to an explicit research protocol developed prior to the analysis, the comprehensive nature of the data search (employing both computer databases and manual bibliography searches, resulting in the inclusion of all relevant published materials), consensus between two reviewers of all data elements prior to entry into the database, and a quality control review of every element of this report.

Another primary strength of this evidence base derives from the collaboration of multidisciplinary researchers who participated in its development. The expert panel meeting held early in the project enabled the researchers to focus their attention on areas which the experts believed to be relevant. The report was compiled by investigators who are skilled in employing highly systematic and unbiased methods to collect, review and synthesize data from published clinical literature. Throughout the course of this project, the team received frequent input from the co-investigator (a clinical content expert) representatives from SSA, and the AHRQ Task Order Officer. In addition, the draft report was evaluated by a panel of nine peer reviewers as well as the TEP, and their comments are incorporated as appropriate into this final version of the Evidence Report.

There are many limitations to this review. CFS is a heterogeneous disorder, even within the strict operational definitions used, and it may not be possible to make any generalizations about disability associated with this condition.

The major limitations of this review are those related to weaknesses of the available current medical and scientific published literature related to CFS disability. It should also be noted that cultural differences may exist within this international database. Data summaries do not account for any cultural variances. As with any qualitative analysis, our coding system was inherently subjective, despite developing the quality scale *a priori*, and using two independent researchers to grade each study. However, given the limitations of the grading systems used, study designs were poor and external validity was low. Due to the variety of study designs, scales used, and outcomes reported, results from different studies could not be combined in meaningful ways. Study designs were not sufficiently homogeneous to allow quantitative synthesis of individual study results.

Fundamental gaps exist that hamper an objective assessment of CFS and disability. This stems from the fact that CFS is an illness without clear biological concomitants and therefore relies on a non-objective and often inadequate self-reporting of symptoms and functional limitations as a means of determining the actual extent of impairment and work capacity.

Another limitation of the literature was that it lacked a clear stratification of subjects' employment status according to the onset of illness (acute, gradual or insidious), duration of illness, medical and/or psychiatric comorbid conditions, or quantifiable fatigue scores.

Findings showed an insufficient use of standardized measurements which could be compared across studies and which had the ability to detect (or not) any exaggeration/inadequacy of effort. Numerous patient outcomes were reported, and although we attempted to assign each measurement to a specific domain, it was clear that the different instruments/scales may not have measured precisely the same phenomenon. These instruments although "validated," have not been validated in a "compensation setting," have not been validated as measures of disability, and have not been validated in CFS patients who are often formerly high functioning individuals, unlike chronic mentally ill patients or low functioning patients with physical impairments. While some studies reported test and scale results, the results were reported in a wide variety of formats, with relatively sparse reporting of both baseline and outcome data. Many otherwise eligible studies we reviewed did not report the employment or disability status of CFS patients. Even more rare were studies reporting work data for patients over time, e.g. at baseline and followup for an interventional trial. These missing data mean that, while relationships between various impairment measures and work/disability status might be explored in some cases, causality could not be determined.

Conclusions

This systematic review of the current published research related to CFS disability identified 53 primary studies published between 1988 and 2001 that met prospectively determined inclusion criteria.

The evidence suggests that some individuals with CFS have self-reported cognitive or affective impairments on neuropsychological tests, but these results are not consistent. And while people with CFS may frequently have co-morbid psychiatric conditions, it is unclear whether the neuropsychological test results are due to CFS, or to coexisting psychiatric disorders. Patient's scores on an instrument used to measure depression, indicates that depression of greater severity is associated with unemployment, but no other impairment appeared to be consistently associated with disability or work outcomes. No specific interventions have been proven to be effective in restoring the ability to work. No specific patient characteristics have been defined that best predict positive employment outcomes in CFS patients.

"Whatever one presumes chronic fatigue syndrome (CFS) to be, people suffer with it and because of it."[66] While the diagnosis of CFS is based on patient self-reports and exclusion of other causes of the complaints, a group of patients meeting the case definitions for CFS can be identified. Some of these patients have severe symptoms, and are disabled, according to the SSA definition. In practice, a functional capacity evaluation has been useful in defining what a patient can or cannot do. It is important to evaluate how a patient's current activities compare to activities prior to the onset of illness, and compare their functioning in terms of work, school, social, and home activities.

Chapter 5. Future Research

The following recommendations would enable researchers to generate useful data to support answers for the questions posed in this report.

- Longitudinal, interventional studies are mandatory in order to determine what baseline characteristics are associated with inability to work, and which interventions are effective in restoring the ability to work.

- Authors should report more detailed information about impairment and work status at baseline and after intervention, preferably stratified by patient characteristics.

- Future studies of employment status should clarify if employment means full or part time, prior work or new work, and also provide information on duration of return to work.

- Further research is needed to determine the impact of CBT, graded exercise, and other interventions on the issue of disability.

- The literature would be enhanced if standardized measurements of impairment were developed, defined, and used to evaluate the impact of all interventions, and if some assessment was made regarding the impact of impairment on employability in this specific patient population.

- Further research is needed to determine validity and reliability of self-reported instruments in assessment of impairment and disability in CFS patients who are often formerly high functioning individuals, unlike chronic mentally ill patients or low functioning patients with physical impairments. Validity and reliability of these instruments should be determined in patients with concurrent or prior neuropsychological diagnoses, given the high lifetime incidence of same, and particularly in patients who may have different motivations about disability determinations. Instruments should also be validated in "compensation settings.

- Further research is needed to determine whether and which validated neuropsychological non self reported assessment tools might be considered sufficient evidence to evaluate functionality as it relates do one's ability to work.

- Further research in needed to determine whether there are characteristics of care providers or prior work experiences that relate to ongoing CFS disability.

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Evidence Table 1. Study characteristics

	k	n
Total	**53**	**4,558**
Publication Year		
1988 - 1994	**11**	**1,030**
1995 - 2001	**42**	**3,528**
Accrual Years Reported	**13**	**1,226**
Study Location		
USA	**28**	**1,869**
Canada	**2**	**73**
Western Europe	**20**	**1,807**
Australia/New Zealand	**2**	**65**
Multicontinental	**1**	**744**
Study Design		
Prospective	**21**	**1,800**
RCT	**10**	**1,042**
nRCT	**1**	**71**
Case control	**2**	**321**
UCS	**8**	**366**
Retrospective	**1**	**94**
Case series	**1**	**94**
Cross-sectional	**31**	**2,664**
Interventional - all	**17**	**1,348**
Observational - all	**36**	**3,210**
CFS Diagnostic Criteria Used*		
CDC 1988	**23**	**2,267**
CDC 1994	**20**	**1,912**
Oxford 1991	**18**	**2,173**
Australia 1990	**1**	**744**

k = number of studies
n = number of patients with CFS

RCT = randomized controlled trial
nRCT = non-randomized controlled trial
UCS = uncontrolled case series
CDC = Centers for Disease Control

*** Numbers sum to greater than the total number of studies, as some studies used more than one of these criteria.**

Evidence Table 2. Study quality and validity

	k	n
MacMahon Quality Criteria - Longitudinal		
I a	**10**	**1,312**
I b	**3**	**140**
III a	**3**	**300**
III b	**6**	**142**
MacMahon Quality Criteria - Cross-sectional		
II a	**4**	**520**
II b	**14**	**409**
IV a	**9**	**1,639**
IV b	**4**	**96**
MetaWorks Internal Validity Score (2-6 points)		
2	**2**	**136**
3	**5**	**424**
4	**15**	**1,779**
5	**21**	**950**
6	**10**	**1,269**
MetaWorks External Validity Score (0-2 points)		
0	**35**	**1,737**
1	**3**	**403**
2	**15**	**2,418**
MetaWorks Total Validity Score (mean) (range 2-8)	**5.2**	**4,558**
Jadad Quality Score - RCT only (mean) (range 0-5)	**3.3**	**1,042**

k = number of studies
n = number of patients with CFS

Jadad Quality Scores (0-5): Higher numbers = best quality
MacMahon Quality Criteria (Ia - IVb): Lower numbers = best quality
MetaWorks Total Validity Score (2-8): Higher numbers = best validity

Evidence Table 3. Patient demographics, history, and employment status

Demographics	CFS			Healthy Controls		
	% of patients or mean *	k	n	% of patients or mean *	k	n
Total patients (enrolled/randomized)	100	53	4,507	100	22	775
Percent female	76	49	4,378	73	19	605
Mean age (years)	38.4	48	4,372	37.7	19	596
Mean CFS or symptom duration (years)	5.5	40	3,976	NA	--	--
Mean total education, years	14.1	14	1,310	14.4	6	212
Comorbid conditions						
Patients with any current psychiatric diagnosis	39	17	1,830	6	4	200
Patients with any current psychiatric diagnosis	65	12	930	12	4	200
Patients with depression or dysthymia **	45	13	1,718	12	2	65
Employment Status						
Total employed[1]	42	35	2,652	90	9	340
Employed full time	19	16	967	75	2	53
Unemployed[2]	54	37	2,720	9	9	340
Disability benefits	51	6	364	4	1	47
Disability or temporary sick leave	55	10	511	1	2	89
Work limitations due to illness	64	20	1,919	0	1	38

*** For those studies where the value is known**

**** All patients with reported history of depression or dysthymia diagnoses.**

k = number of studies contributing data

n = number of patients in studies contributing data (less than the total number of patients enrolled at the study level, because some studies did not account for, or present demographic information for all patients

[1] Employed includes working or in school

[2] Unemployed includes retired, not working, or unable to continue schooling

Employed + unemployed does not sum to 100% of patients because complete employment data could not be extracted for all patients.

Number of studies reporting number of patients employed does not equal number of studies reporting number of patients unemployed because 2 studies only reported number unemployed, and the remainder of the patients were either employed or unaccounted for.

Evidence Table 4. Employment status and impairment domains

	Domain Totals by Work Data Reported *													
	Cognitive		Disease Severity/Symptoms		Exercise Testing		Functional		General Health		Mental (Psych/Affective)		Physical Activity	
Employment Status	k	n	k	n	k	n	k	n	k	n	k	n	k	n
Employed	6	478	18	1634	6	183	4	455	10	659	20	1572	11	1246
Full time	4	363	6	717	3	35	3	288	3	122	8	632	4	517
Part time	2	310	5	574	3	35	2	169	3	122	6	579	3	398
Unemployed	7	519	19	1675	6	183	4	455	11	700	21	1613	12	1287
Disability benefit	0	0	3	240	1	2	0	0	1	51	2	208	2	208
Disability benefit or temporary sick leave	4	165	4	202	1	2	0	0	4	202	6	336	4	252
Work limitations due to illness	6	181	9	694	3	150	3	264	4	184	12	702	4	237
Other work data														
Work scales	5	449	5	491	0	0	1	32	4	148	7	524	5	474
Mean hours worked per week	1	51	1	270	1	2	1	270	1	270	1	270	1	51

* At baseline/single time point or at outcome, all study designs

k = number of studies contributing data

n = number of patients in studies contributing data

Evidence Table 5. Employment and physical impairments

Author	Year	Validity Score	# CFS patients	% CFS patients employed	# Healthy controls	% Healthy controls employed	Significant differences: CFS vs. healthy controls	No significant differences: CFS vs. healthy controls
Buchwald	1996	7	185	46	99	91	MOS SF-36 - physical function: 40 vs. 96 (p <=.001) MOS SF-36 - general health: 32 vs. 81 (p <=.001)	
Claypoole	2001	5	22	41	22	86		VO2 max: 18.9 vs. 20.5 ml/kg/min
Garcia-Borrequero	1998	5	42	27*	41	100	POMS - fatigue: 19.9 vs. 6.3 (p <.0001) POMS - vigor/activity: 8.0 vs. 19.0 (p <.0001)	
Lloyd	1994	5	12	42	13	100	POMS - fatigue: 18.1 vs. 2.2 (p <.05)	MVC (% decline after exercise): 61.8 vs. 63.8
Natelson	1995	6	41	18**	36	100	POMS - vigor: 6 vs. 21 POMS - fatigue: 21 vs. 2	
Ray	1993	5	24	13***	24	71***	PFRS - fatigue: 4.0 vs. 0.7 (p <.001) PFRS - somatic symptoms: 2.6 vs. 0.4 (p <.001)	
Schmaling	1998	4	15	13	11	91	MOS SF-36 - health perception: 23.3 vs. 95.8 (p <.001) MOS SF-36 - physical functioning: 37.0 vs. 95.8 (p <.001)	
Vercoulen	1997	7	51	49	53	89	Actometer: 23.3 vs. 35.5 (p <.05) SIP - mobility: 26.2 vs. 33.5 (p <.05) SIP - walking: 31.6 vs. 40.8 (p <.05)	

Measures of dispersion are not included in this table, p values are listed when reported.

MOS SF-36 = Medical Outcomes Study Short-Form General Health Survey
POMS = Profile of Mood States
MVC = Maximal Voluntary Contraction
PFRS = Profile of Fatigue-Related Symptoms
SIP = Sickness Impact Profile
CIS = Checklist Individual Strength

* This study reported the number of patients with vocational disability. It was assumed that the remainder of patients were employed. For controls, vocational disability was reported as N/A, and 100% employment was assumed.

** This study reported the number of patients disabled, and it was assumed that the remainder of patients were employed.

*** This study reported only the number of patients employed full-time.

Evidence Table 6. Neuropsychological tests and work status for CFS patients vs. healthy controls (Key Question 2)

Author	Year	Validity Score	# CFS patients	% CFS patients employed	# Healthy controls	% Healthy controls employed	Significant differences: CFS vs. healthy controls	No significant differences: CFS vs. healthy controls
Buchwald	1996	7	185	46	99	91	MOS SF-36 - mental health: 57 vs. 83 (p<.001)	
Claypoole	2001	5	22	52	22	86		Hopkins verbal learning: 26.1 vs. 27.4
Garcia-Borrequero	1998	5	42	27*	41	100	POMS - confusion: 12.0 vs. 5.9 (p<.0001) POMS - depression: 9.2 vs. 5.4 (*p* <.05)	POMS - tension/anxiety (scores not reported) POMS - anger/hostility (scores not
Lloyd	1994	5	12	42	13	100	POMS - confusion: 14.8 vs. 2.4 (*p* <.1) POMS - depression: 21.5 vs. 0.6 (*p* <.001)	
Michiels	1996	5	35	26	33	100	WAIS digit span forward: 45.3 vs. 52.6 (*p* <.0005)	
Natelson	1995	6	41	18**	6	100	POMS - depression/dejection: 10 vs. 3 POMS - confusion: 14 vs. 2	
Ray	1993	5	24	13***	24	71***	EAQ: 35.6 vs. 49.3 (*p* <.001) PFRS - emotional distress: 3.5 vs. 1.2 (*p* <.001) PFRS - cognitive difficulty: 3.8 vs. 1.0 (*p* <.001)	
Schmaling	1998	4	15	13	11	91	SCL 90-R - depression: 59.3 vs. 25.8 (*p* <.001) MOS SF-36 - mental health: 69.1 vs. 85.5 (*p* <.001)	
Vercoulen	1997	7	51	49	53	89	SIP - concentration: 35.0 vs. 2.2 (*p* =.0001) CIS - concentration: 5.2 vs. 1.9 (*p* =.0001)	

Measures of dispersion are not included in this table. *p* values are listed when reported.

MOS SF-36 = Medical Outcomes Study Short-Form General Health Survey
POMS = Profile of Mood States
EAQ = Everyday Attention Questionnaire
PFRS = Profile of Fatigue-Related Symptoms
SCL 90-R = Symptom Checklist 90 - Revised
SIP = Sickness Impact Profile
CIS = Checklist Individual Strength

* This study reported the number of patients with vocational disability. It was assumed that the remainder of patients were employed. For controls, vocational disability was reported as N/A, and 100% employment was assumed.

** This study reported the number of patients disabled, and it was assumed that the remainder of patients were employed.
*** This study reported only the number of patients employed full-time.

Evidence Table 7. Interventions and work or impairment domains (Key Question 3)

	Domain Totals at Follow-up, post-intervention																	
	Total		Work *		Cognitive		Disease (Severity/ Symptoms)		Exercise Testing		Functional		General Health		Mental (Psych/ Affective)		Physical Activity	
Interventions	k	n	k	n	k	n	k	n	k	n	k	n	k	n	k	n	k	n
Behavioral	4	143	2	62	1	32	3	92	1	30	2	62	2	83	3	92	1	30
Psychiatric	2	94	1	30	0	0	2	94	0	0	0	0	0	0	1	30	1	30
Drug Therapy	5	218	0	0	0	0	4	165	1	35	1	18	2	85	4	165	2	85
Physical/Exercise Therapy	2	148	0	0	0	0	2	148	1	34	0	0	0	0	2	148	1	114
Dietary Therapy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Placebo	6	247	0	0	0	0	6	247	2	64	1	30	2	85	6	247	2	85
Mixed	4	92	0	0	1	23	3	90	2	35	1	23	0	0	3	90	1	34
All Interventional Studies	14	907	2	92	2	55	11	741	3	168	4	133	2	94	10	772	4	378

*** Includes work function scales reported at follow-up, post intervention.**

k = number of studies

n = number of patients

Evidence Table 8. Restoring ability to work in CFS patients (Key Question 3)

Author	Year	Validity Score	Intervention	Time of Followup Assessment (months)	# CFS patients enrolled	% Dropouts	% CFS patients employed at baseline	% CFS patients employed at followup*
Akagi	2001	6	Cognitive behavioral therapy	6	51	0	29	53
Dyck	1996	3	Rehabilitation program	3	2	0	0	50
Fulcher	1997	5	Exercise therapy	15	66	29	39	47
Marlin	1998	2	Individualized programs	6	71	28	0	44
Tiersky	2001	4	None	42	47	26	32	23
Vercoulen	1994	7	None	18	298	17	31	24

*** % of patients employed at follow-up = # patients employed at followup/ # patients enrolled**

Evidence Table 9. Baseline characteristics for CFS patients Reported as improved (Key Question 4)

Author	Year	Validity Score	Intervention	Time of Outcome Assessment (months)	# CFS patients enrolled in study	# CFS patients evaluated for improvement	% CFS patients improved	Baseline Characteristics of Improved vs. Unimproved patients
Bombardier	1995	4	none	18	226	226	61	Absence of dysthymia (r= -.15, *p* <.03)
Butler	1991	5	CBT	1.5	32	27	85	Absence of treatment-resistant affective disorder (BDI: 8.3 vs. 11.7) Same gender, disease severity, disease duration (numbers not reported).
Deale	1997	6	CBT	6	60	27	70	No significant difference on any pretreatment characteristic (numbers not reported).
Kruesi	1989	4	Acyclovir or placebo	6	28	24	88	No significant difference on clinical, chemical, immunologic, or serologic features (numbers not reported).
Lerner	1997	4	Ganciclovir	6	38	18	72	Male gender (3 men in study, all improved), Shorter mean duration of symptoms (1.6 vs. 2.8 yrs)
Peterson	1991	6	none	onset of illness	177	177	12	Female: 61.9% vs 80.1% (*p* =.09) Employed at presentation: 66.7% vs. 49.4% (*p* =.06) Physical functioning scores: 68.5 vs.58.9 (*p* =.01) Social functioning scores: 3.2 vs.42.8 (*p* =.02) SCL-90 anxiety scores: 0.43 vs. 0.66 (*p* =.01) SCL-90 Obsessive/compulsive sco
Saltzstein	1998	4	none	24	15	15	12	Perception that physician's prognosis was positive, social support (numbers not reported).
Tiersky	2001	4	none	42	47	35	57	Higher anxiety: median score 38 vs. 27 (*p* =.02), Ability to perform light duty. No significant differences in age, education, illness severity or duration, employment status, gender, level of depression (all *p* >.05).
Vercoulen	1994	7	none	18	298	246	20	Self-reported improvement was related to younger age, shorter disease duration, less symptom severity, less functional impairment, more sense of control over symptoms (numbers not reported). "Demographic variables were not predictive for

Measures of dispersion are not included in this table. *p* values are listed when reported.

CBT = Cognitive Behavior Therapy BDI = Beck Depression Inventory SCL 90 = Symptom Checklist 90

Table 10. Studies reporting work status correlations

Study ID	Author	Year	Validity Score	n	Relationship Investigated	Finding
701825	Bombardier	1995	4	226	Demographic (age, gender, education), clinical (duration of fatigue), and psychiatric (lifetime psychiatric diagnoses) variables at initial evaluation vs. return to work at follow-up (median 1.5 years later).	Among CFS patients, none of the initial demographic, clinical, or psychiatric variables were predictive of return to work.
699067	Jason	1999	5	32	Demographic (age, gender, marital status), clinical (symptom severity, activity level, physical function) and psychiatric (COPE scales) measures by work status, at single time point.	Working patients with CFS were more likely to be male, younger, never married, had less severe muscle and joint pain, higher activity levels, and better physical functioning than non-working patients.
698360	Moss-Morris	2001	5	53	Cognitive-behavioral factors at initial evaluation vs. SIP Work subscale at 6 month follow-up.	Somatic illness identity (extent of symptoms associated with illness) and limiting coping (extent to which patients limited stress, exercise, and activity) were significant predictors of work dysfunction.
698505	Wilson	2001	6	744	Symptom severity self-report and history of major depressive episode vs. ability to work, at single time point.	Severe functional impairment correlated with inability to work. Presence of major depression was not associated with ability to work.

n = number of CFS patients in study

SIP = Sickness Impact Profile

Appendix A

Appendix A. Work Plan and Causal Pathway

Review of the Current Medical and Scientific Research Related to Disability and Chronic Fatigue Syndrome

Contract # 290-97-0016
December 11, 2001

1. Objective

To conduct a systematic review of the literature and develop an evidence report that will assist the Social Security Administration (SSA) in ensuring that it is using the most current medical knowledge for evaluating disability in persons with Chronic Fatigue Syndrome (CFS). The evidence report will also serve to augment SSA's knowledge base concerning new scientific or medical developments in the diagnosis and treatment of persons with CFS.
Seven key questions were posed to guide the systematic review:

1. What is the evidence that individuals with CFS have a ***discrete physical impairment****?* What is the evidence that individuals with CFS have a ***coexisting mental impairment****?* For example, what is the evidence that comorbid psychiatric/neurologic conditions frequently reported in CFS are present and, if present, are a result of CFS or are an integral part of the CFS disease process?

2. What is the evidence that there are specific clinical tests that can be used to reliably diagnose CFS, for example, are there specific anatomical, psychological, physiological, or medical imaging indices that are diagnostic for CFS?

3. When cognitive deficits are alleged, what is the evidence that individuals with CFS have such deficits and what is the evidence that these potential deficits contribute to ***functional limitations or inability to do work activity****?*

4. Do current neuropsychological tests reliably detect ***cognitive or mental impairments*** in the CFS population? Are there certain tests that are preferred in terms of reliability and validity? Are there certain tests or diagnostic tools that contain reliable correlations between test result(s) and either ***ability or inability to perform designated work-related functions*** (e.g., ability to relate to coworkers and supervision appropriately, ability to maintain concentration or pace, suitable memory capacity for work activities, etc.).

5. What treatments have been shown to be most effective for CFS in terms of restoring an individual's ***ability to do work activity****?*
6. What are the patient characteristics that best define improvement or positive outcomes in the CFS population such that they experience ***improvement in functioning***? Where it occurs, how is this improvement in functioning related to the ***ability to engage in work activity****?*

7. What evidence is available from related fields (e.g., sleep medicine, autonomic nervous system abnormalities, endocrinology, gastrointestinal illness, neurocognitive therapy) that would be applicable to the assessment, ***functional evaluation***, and treatment for CFS?

2. Background

The topic "Review of the Current Medical and Scientific Research Related to Disability and CFS" was nominated by SSA to assist in answering several key questions of diagnosis and management of disability in persons with CFS. This research will assist SSA in ensuring that it is using the most current medical knowledge for evaluating disability in persons with CFS.

Disability is defined by the SSA as the inability to engage in any substantial gainful activity by reason of any medically determinable (by clinical signs, symptoms, and laboratory findings) physical or mental impairment. Disability is thus the crux of this Task Order, and it should be possible to focus the review on CFS literature addressing diagnosis, measurement, and treatment of disability resulting from medically determinable physical and mental impairment in persons with CFS, even though the etiology, diagnosis, and treatment of CFS itself remain elusive.

3. Methods

MetaWorks will apply the latest and established best methods in the evolving science of review research.
A flow diagram outlining the systematic review process is located in Appendix A.
The following tasks will proceed sequentially.

Expert Panel Meeting

In consultation with the Task Order Officer (TOO), through networking with our nominating partner, our co-principal investigator, professional organizations, and purchasers of health care, a panel of experts with a broad range of clinical expertise in CFS was convened in Washington, DC, on November 30, 2001. This meeting had three primary purposes:

1. To establish a working definition of CFS for purposes of this task order.
2. To refine the key questions.
3. To receive the experts' recommendations regarding the breadth of the literature to be reviewed, analyses that should be performed, sources of data that should be accessed, etc., to ensure an evidence report that is responsive to SSA concerns.

A preliminary review of the literature was performed prior to the meeting and the results were shared with the attendees at the meeting. This included the preliminary search strategy and databases used, criteria for determining eligibility for inclusion in evidence synthesis, and results of Level I and Level II screening.

For purposes of guiding the literature review, a draft causal pathway was also developed prior to the meeting and shared with attendees who were asked to provide feedback.
Experts who attended the meeting have been asked to form the Technical Expert Panel (TEP). They will be asked to respond to questions during the process of the literature review, and will be asked to review the draft Evidence Report.

Results of expert meeting

The full report describing the expert meeting has been submitted to AHRQ. The following summarizes the decisions reached at the meeting:

Definition of CFS

It was agreed that four diagnostic criteria for CFS would be accepted for the purpose of this task order:

- 1988 CDC criteria
- 1994 CDC revised criteria
- 1991 Oxford criteria
- 1990 Australia criteria

The details of these criteria are outlined in Appendix B.

Definition of Disability

As defined in the task order and refined and agreed upon by the expert panel, this review will focus on disability in persons with CFS. Disability, per SSA guidelines, is defined based on inability to engage in any substantial gainful activity by reason of any medically determinable (by clinical signs, symptoms, and laboratory findings) physical or mental impairment. Disabled persons cannot do work that they did previously, and cannot adjust to other work. Disability must be expected to last for at least one year. Therefore, treatment and diagnosis will be considered only as they relate to disability in CFS.

Revised Key Questions

1. What is the evidence that some individuals with CFS have discrete impairments that are associated with disability? (Note that impairments include both physical and mental impairments).

2. What is the evidence that in the CFS population, current neuropsychological tests reliably detect cognitive or affective impairments associated with decreased ability to work?

3. What is the evidence that in individuals with CFS, treatments are effective in restoring the ability to work?

4. What patient characteristics best define improvement in functioning or positive outcomes in the CFS population? Where it occurs, how is improvement in functioning related to the ability to engage in work activity?

The previous question 2 was removed, as it was agreed that this question was not directly pertinent to disability. Questions 1 and 3 were combined into Question 1. Question 7 has been removed, as it was agreed that this question falls outside of the scope of this project.
No additional questions were recommended by the expert panel.

Breadth of Literature

It was agreed that the literature search should go back to 1988, when the first case definition of CFS was published. It was also agreed that searching Medline, Current Contents™, Cochrane, Psychlit, and bibliographies of accepted articles and recent review articles should be sufficient to identify the majority of articles that address the key questions.
The inclusion and exclusion criteria were reviewed. It was agreed that English language literature from the United States, Canada, Western Europe, and Australia would be sufficient.
The expert panel did not recommend searching additional databases.

Literature Screening

This task involves identifying and retrieving all potentially relevant literature on the current medical and scientific research related to CFS disability, categorizing by study design, and other key study, patient, and intervention level details for each of the five key questions. Studies which meet the eligibility criteria (see below) will undergo data extraction and data entry.

The published literature, English language and adult population only will be searched from 1988 to 2001, utilizing the following search strategy:
fatigue syndrome, chronic [MeSH] or *chronic fatigue [syndrome*]. Limits: English language, human subjects.

In addition to the MedLine search described above, MetaWorks will search other suitable electronic databases, including Current Contents®, Cochrane Controlled Trials Register (CCTR), and PsychLit, as well as a manual search of accepted study references and review articles published within the past two years. The Cochrane Library and the National Guidelines Clearinghouse will also be searched for additional information on these topics. In addition, pertinent Internet sites will be checked for potential leads to additional studies.

The search cut-off date will be November 15, 2001 and the retrieval cut-off date will be determined after all abstracts have been screened.

All citations and abstracts will be printed and screened at MetaWorks for any mention of diagnosis and/or treatment of CFS disability or impairment (Level 1 screening) and reviewed for the following exclusion criteria:

Exclusion Criteria

Abstracts demonstrating any of the following characteristics will be rejected:

- Review, meta-analysis, abstracts, letters, case reports, editorials, and commentaries.
- Unpublished study reports and abstracts.
- Studies published prior to 1988.
- Studies written in languages other than English.
- Studies not conducted in the US, Canada, Australia or Western Europe.
- Pharmacokinetic and pharmacodynamic studies.
- Animal or *in vitro* or tissue level studies.
- Studies not *related to* or not *specific to* CFS disability or impairment.
- Studies containing < 2 patients as total sample size.
- Pediatric patient population.
- No information related to disability or impairment.
- Outcomes not extractable.
- Mixed population (unable to separate CFS from other populations).
- Studies focused on pathophysiology of CFS (lab findings/lab technique).

In some cases, it may not be possible from the abstract alone to determine the eligibility of the study. Full studies of abstracts lacking obvious exclusion criteria will be retrieved for Level 2 screening, where inclusion and exclusion criteria will be applied.

Inclusion Criteria

The following study designs will be accepted: observational [prospective, retrospective, and cross sectional (XS)], or interventional [randomized controlled trials (RCTs), non-randomized controlled trials (nRCTs), uncontrolled case series (UCS)].

- Adult patients with CFS *and* disability.
- Studies focusing on diagnosis and/or management of a medically determinable physical or mental impairment in CFS.
- Medically determinable impairment must be demonstrated by clinical finding, lab or other test result:
- physical findings, lab tests, imaging tests
- assessment of cognitive or mental impairments
- Studies reporting at least one objective measure related to disability or impairment as measured by:
    - Physical function
    - Work endurance
    - Work or school absenteeism
    - Sick leave

- Days lost
- Light duty
- Productivity
- Activities of Daily Living (ADL)
- Quality of Life (QoL)
- Hospitalizations or admissions to chronic care facilities
- Emergency room or clinic visits
- oxygen capacity (VO_2)
- neuropsychological or QoL measures of functioning that are derived from validated instruments.
- Other
-

Upon completion of Level 2 screening, all accepted articles will be eligible for data extraction.

Causal Pathway

Based on the results of a preliminary literature review, a Causal Pathway was developed (Appendix C). All of the events described in this pathway take place within the CFS universe; i.e., only patients already diagnosed with CFS are included. Patients with fibromyalgia, Gulf War Syndrome, and other related conditions are not included. To diagnose disability in the CFS universe, patients must have a medically determinable condition (defined by clinical signs and symptoms, laboratory abnormalities, or other abnormalities), leading to physical or mental impairment, that results in disability, as defined by the SSA. This Causal Pathway was presented at the Experts Meeting described above.

Assessment of Quality in Primary Studies

All studies will be appraised according to a previously published Level of Evidence (Appendix D). An additional assessment of external and internal validity will be developed.

Data Extraction

Data extraction forms (DEFs) will be created specifically for this project. Data will be extracted onto the DEF independently by one reviewer and the completed DEF will be 100% checked against the original articles by a second reviewer. Any differences will be resolved by consensus; thus, two reviewers must agree on all data. In all cases, at least one physician reviews all data elements. The data will then be entered in MetaWorks' relational database, MetaHub™. At this time, it is anticipated that the following data elements will be extracted.
These preliminary selections may change prior to finalization of the DEF, based on initial review of the literature.

Study level characteristics

- Publication year
- Geographical location of study
- Study design
- Methodological assessment
- Level of Evidence (I-V)
- Assessment of External and Internal Validity
- Total number of patients enrolled
- If RCT, number of patients randomized
- Funding source/industry sponsorship (name if yes or no/NR)
- Intervention duration
- Observation duration
- CFS definition used
  - CDC 1988
  - Revised CDC 1994
  - Oxford 1991
  - Australia 1990
- Elements of CFS definition identified
- Duration of symptoms
- Relation to exertion
- Relation to rest
- Reduction in previous levels of occupational, educational, social, or personal activity
- Laboratory screening tests
- Clinical findings (sore throat, tender lymphadenopathy, muscle pain, joint pain, new headaches)
- Unrefreshing sleep
- Postexertion malaise
- Neuropsychological symptoms

Patient characteristics (by group)

- Age: years (mean or median, range)
- Gender distribution
- Race and/or ethnicity
- Age at diagnosis
- Duration of symptoms
- Presence of symptoms listed in CFS diagnostic criteria
- Baseline healthcare utilization
- Hospitalizations or admissions to chronic care facilities
- Emergency room or clinic visits
- Other
- Baseline work-related characteristics
- Work or school absenteeism
- Use of sick leave
- Productivity

- Other
- Baseline occupation or employment status
- Baseline ADL assessment (instrument and score)
- Baseline QoL (instruments and score or result on domains related to impairment and/or disability
- Baseline VO_2
- Baseline impairment
- Physical _____ determined by _____test and baseline result
- Mental _____ determined by _____test and baseline result
- Other co-morbid conditions

Diagnostic Interventions (by group)

- Physical Impairment (test and baseline result)
- Mental Impairment (test and baseline result)

Treatment interventions (by group)

- Treatment of physical impairment
- Treatment of mental impairment

Impairment or Disability Outcomes (by group)

- Healthcare utilization outcomes
- Hospitalizations or admissions to chronic care facilities
- Emergency room or clinic visits
- Other
- Work-related outcomes
- Work or school absenteeism
- Use of sick leave
- Productivity
- Other
- Number of patients with changed occupation or employment status
- Other outcomes:
- Symptomatic improvement or worsening (documented motor improvement and other manifestations of disease severity)
- Follow-up ADL assessment (instrument and score)
- Follow-up QoL (instruments and score or results on domains related to impairment and/or disability)
- Follow-up VO_2
- Follow-up impairment
- Physical _____ determined by _____test and follow-up result
- Mental _____ determined by _____test and follow-up result

Database Development

All consensed data will be entered into the MetaWorks MetaHub™ database. 100% of entered data is checked back to the DEFs after each form is completely entered. In addition, a 20% random sampling of data in the completed database will be checked by the QC group at MetaWorks against the data extraction forms. All discrepancies in data are reconciled by referring back to the original papers. Error rates in excess of 2% of checked data will trigger a 100% check of all data elements in the data base.

Once the accuracy of the database has been verified as described above, it is locked. No further changes are allowed after the data is locked. This is the dataset that will be used by the statisticians for analysis and to create raw data tables displaying key data elements of interest, by study.

All data are maintained in the MetaHub database, in a manner suitable to allow outputs to: a) spreadsheet programs for customized evidence table displays; b) to statistical programs for analysis.

4. Data Synthesis & Reporting

Qualitative and quantitative syntheses will be performed, as data permit, in order to answer the key questions. Results will be provided in a draft Final Report.

5. Peer Review

The draft Evidence Report will be circulated for feedback to the TEP and external peer reviewers.

Each peer reviewer will also receive a reviewer's form to be completed and returned to MetaWorks. This form will contain a checklist of items to be assessed as well as provide room for free-form text comments. The form will be pre-screened by the AHRQ TOO and SSA representatives prior to being sent to the peer reviewers. Reviewers will be given at least 3 weeks to respond. All feedback will be stored in a project folder at MetaWorks. A statement of response to each reviewer's comments will be prepared and stored with each reviewer's comments. This response will also be returned to the reviewer.

A summary of the main comments and responses will be prepared and shared with the TOO. Reviewer comments and additional analyses and text resulting from the response to reviewer critique will be incorporated into the final iteration of the evidence report.

6. Manuscript

After completion of the final Evidence Report, MetaWorks will prepare a manuscript describing key aspects of the work for publication in a peer reviewed journal. An abstract of same may also be submitted for presentation at professional meetings.

Work Plan Acceptance

AHRQ

By: _____
Name: Marian James, PhD
Title: Task Order Officer

Social Security Administration

By: _____
Name: Frank Schuster, MD
Title: SSA Representative

MetaWorks Inc.

By: _____
Name: Cindy Levine, M.D.
Title: Principal Investigator, MetaWorks

By: _____
Name: Nelson Gantz, M.D.
Title: Co-Principal Investigator, Pinnacle Health System

Attachments

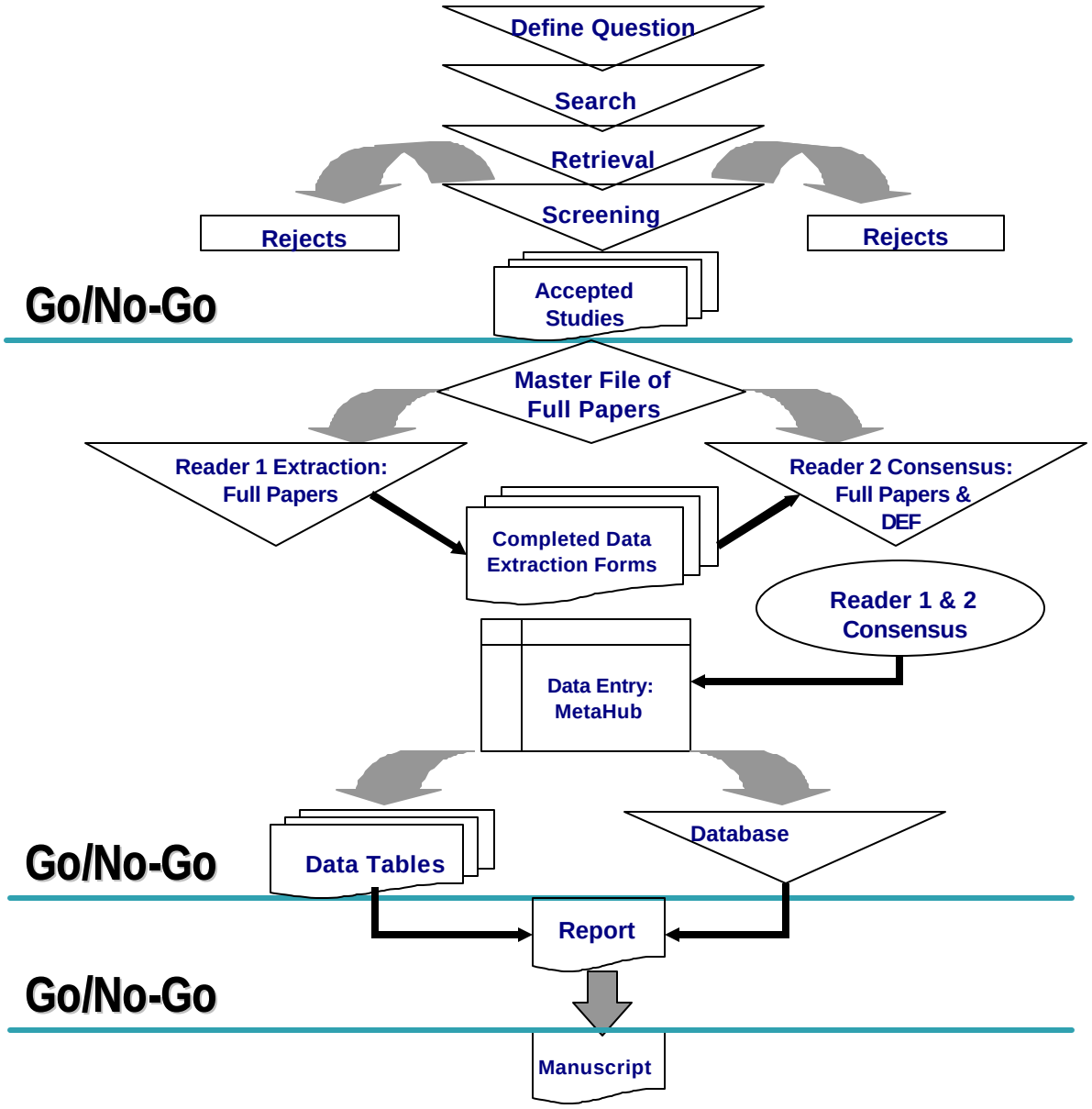
Attachment A: Flow Diagram Systematic Review

Attachment B: CFS Diagnostic Criteria

Attachment C: Causal Pathway

Attachment D: Level of Evidence

Attachment A: MetaWorks Flow Diagram



Attachment B: CFS Diagnostic Criteria

CDC 1988 CFS definition

- Major criteria:
  - new onset of persistent or relapsing, debilitating fatigue in a person without a previous history of such symptoms that does not resolve with bedrest and that is severe enough to reduce or impair average daily activity to less than 50% of the patient's premorbid activity level for at least 6 months
  - fatigue that is not explained by the presence of other evident medical or psychiatric illnesses

- Minor criteria:
  - at least six symptoms plus at least two signs, or at least eight symptoms from the list below
  - Symptoms:
    - mild fever or chills
    - sore throat
    - painful adenopathy (posterior or anterior, cervical or axillary)
    - generalized muscle weakness
    - myalgias
    - prolonged generalized fatigue after previously tolerated levels of physical activity
    - generalized headaches
    - migratory arthralgia without swelling or redness
    - neuropsychologic complaints
    - sleep disturbance
    - main symptom complex developing over a few hours to a few days
  - Physical Signs:
    - low-grade fever
    - nonexudative pharyngitis
    - palpable or tender anterior or posterior, cervical or axillary lymph nodes

From: Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: A working case definition. Ann Intern Med 1988; 108: 387-9.

CDC 1994 CFS definition

- Clinically evaluated, unexplained, persistent or relapsing chronic fatigue lasting > 6 months
  - of new or definite onset
  - not the result of ongoing exertion
  - not substantially alleviated by rest
  - substantial reduction in previous levels of occupational, educational, social, or personal activities
  - Clinical evaluation:

    History and Physical, Mental Status examination

    Laboratory screening including CBC, ESR, LFTs, TP, albumin, globulin, CA, PO_4, glucose, BUN, CRE, electrolytes, TSH, urinalysis

- 4 symptoms concurrently present for > 6 months
  - Sore throat
  - Tender cervical or axillary lymph nodes
  - Muscle pain
  - Multijoint pain
  - New headaches
  - Unrefreshing sleep
  - Postexertion malaise

- Exclusion criteria
  - Active, unresolved, or suspected disease likely to cause fatigue
  - Psychotic, melancholic or bipolar depression

    - (but not uncomplicated major depression)
  - Psychotic disorders
  - Dementia
  - Anorexia or bulimia nervosa
  - Alcohol or other substance misuse
  - Severe obesity

From: Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: A comprehensive approach to its definition and study. Ann Intern Med 1994; 121: 953-9.

Oxford CFS definition

- Severe, disabling fatigue lasting $\geq$ 6 months that:
  - affects both physical and mental functioning
  - is present for > 50% of the time

- Other symptoms may be present:
  - myalgia
  - sleep disturbances
  - mood disturbance

- Exclusion criteria:
  - Active, unresolved, or suspected disease likely to cause fatigue
  - Psychotic, melancholic or bipolar depression
    - (but not uncomplicated major depression)
  - Psychotic disorders
  - Dementia
  - Anorexia or bulimia nervosa

From: Sharpe MK, Archard LC, Banatvala JE, et al. A report - chronic fatigue syndrome: Guidelines for research. J R Soc Med 1991; 84: 118-21.

Australian CFS definition

- Disabling and prolonged feelings of physical tiredness or fatigue, exacerbated by physical activity.

- Present for at least 6 months.

- Unexplained by an alternative diagnosis reached by history, laboratory, or physical examinations.

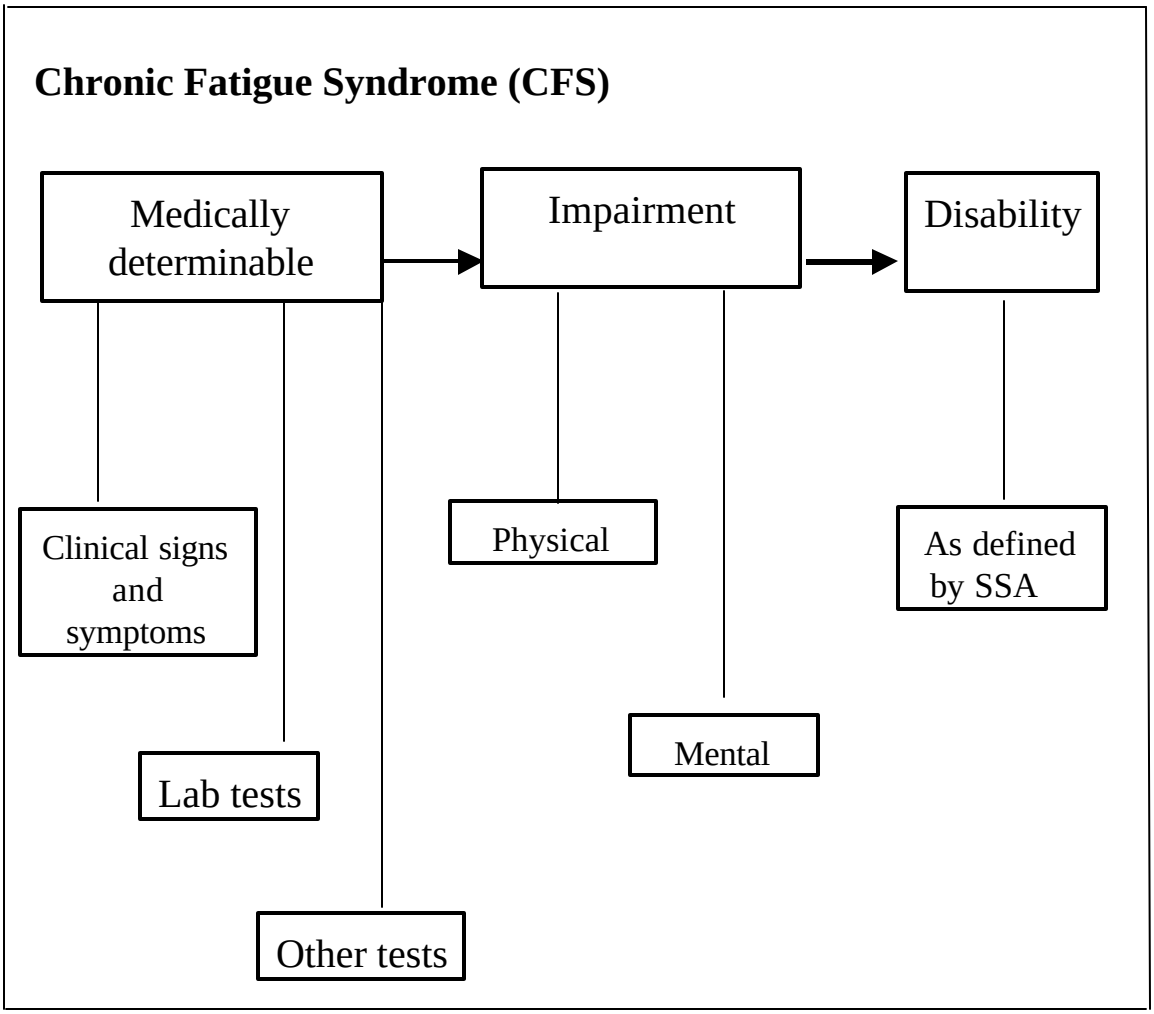
- Accompanied by new onset of neuropsychological symptoms including impaired short-term memory and concentration, decreased libido, and depressed mood. These symptoms usually have their onset at the same time as the physical fatigue, but are typically less severe and less persistent than those seen in classic depressive illness.

- Exclusion criteria:
  - Chronic medical condition that may result in fatigue
  - History of schizophrenia, other psychotic illnesses, or bipolar affective disorder

- Drug or alcohol dependence makes CFS very unlikely.

From: Lloyd AR, Hickie I, Boughton CR, et al. Prevalence of chronic fatigue syndrome in an Australian population. Med J Aust 1990; 153: 522-8.

Attachment C: Causal Pathway



References used:

1. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: A comprehensive approach to its definition and study. Ann Intern Med 1994; 121: 953-9.

2. SSR 99-2p: Policy interpretation ruling Titles II and XVI: Evaluating cases involving chronic fatigue syndrome (CFS).

Attachment D: Level of Evidence

I. Evidence based on randomized controlled clinical trials (or meta-analysis of such trials) of adequate size to ensure a low risk of incorporating false-positive or false-negative results.

II. Evidence based on randomized controlled trials that are too small to provide level I evidence. These may show either positive trends that are not statistically significant or no trends and are associated with a high risk of false-negative results.

III. Evidence based on nonrandomized, controlled or cohort studies, case series, case-controlled studies or cross-sectional studies.

IV. Evidence based on the opinion of respected authorities or that of expert committees as indicated in published consensus conferences or guidelines.

V. Evidence which expresses the opinion of those individuals who have written and reviewed these guidelines, based on their experience, knowledge of the relevant literature and discussion with their peers.

These 5 levels of evidence do not directly describe the quality or credibility of evidence. Rather, they indicate the nature of the evidence being used. In general, a randomized, controlled trial has the greatest credibility (level I); however, it may have defects that diminish its value, and these should be noted. Evidence that is based on too few observations to give a statistically significant result is classified as level II. In general, level III studies carry less credibility than level I or II studies, but credibility is increased when consistent results are obtained from several level III studies carried out at different times and in different places.

Decisions must often be made in the absence of published evidence. In these situations it is necessary to use the opinion of experts based on their knowledge and clinical experience. All such evidence is classified as "opinion" (levels IV and V). Distinction is made between the published opinion of authorities (level IV) and the opinion of those who have contributed to these guidelines (level V). However, it should be noted that by the time level V evidence has gone through the exhaustive consensus-building process used in the preparation of these guidelines, it has achieved a level of credibility that is at least equivalent to level IV evidence.

From: The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. CMAJ 1998:158

Appendix B

Appendix B. Expert Meeting Information

Review of Current Medical and Scientific Research Related to Disability and Chronic Fatigue Syndrome

AED Conference Center
Washington, DC
November 15, 2001

I. Introductions/Participants

Bernard J. Arseneau, DO, MPH, Chief Psychiatrist, Office of Disability, SSA.
Michael B. Brimacombe, PhD, Associate Professor, UMDNJ.
Lynn H. Gerber, MD, Chief, Rehabilitation Medicine Department, DHHS, NIH.
Marian James, PhD, Task Order Officer, AHRQ.
James F. Jones, MD, Professor of Pediatrics, University of Colorado School of Medicine, CDC.
Carolyn Kiefer, Policy Analyst, Office of Disability, SSA.
Gudrun Lange, PhD, Associate Professor, Clinical Neuropsychologist, UMDNJ.
Cindy Levine, MD, co-Principal Investigator, MetaWorks.
Paul H. Levine, MD, Clinical Professor of Medicine, GWU Medical Center.
Veronica Ludensky, BA, Research Assistant, MetaWorks.
Robert J. MacBride, MD, Medical Director, Disability Management, Prudential Group Insurance.
Benjamin H. Natelson, MD, Professor, Department of Neurosciences, UMDNJ.
Susan Ross, MD, FRCPC, EPC Director, President, MetaWorks.
Paul J. Scott, Policy Analyst, Office of Disability, SSA.
Frank Schuster, MD, Medical Officer - Musculoskeletal Branch, Office of Disability, SSA.
Norma C. Ware, PhD, Associate Professor, Harvard Medical School.

by phone:
Nelson Gantz, MD, co-Principal Investigator, MCP Hahnemann School of Medicine.

II. Social Security Administration (SSA) Comments on Current Policy (C.Kiefer)

The current state of the Disability Law has a sequential evaluation process in the SSA, which consists of five steps/questions:

1. Are you doing work activity?
2. Do you have a severe impairment? (symptoms, decrease in ability to function must be shown).
   If no, then do not proceed with other steps.
3. Listings – no listings level with CFS.

4. Functional capabilities (physical and mental activities, past employment must be investigated).
5. Can you do anything else? (unskilled sedentary work).

Longitudinal record is very important in the determination of the disability; it must be shown that the impairment has lasted for at least 12 months.

Currently the SSA uses the ruling SSR 99-2p to guide the decisions about the disability status of patients with CFS. The SSA hopes to use this project and its conclusions to identify items that need to be revised to make the ruling more useful and helpful.

III. Introduction of MetaWorks
(C. Levine)

Introduction of the MetaWorks team. Presentations of a brief history and description of MetaWorks Inc, the process it uses during systematic literature reviews and its goals for this project.

IV. Discussion of Causal Pathway
(S. Ross)

A Causal Pathway prepared especially for the purposes of this project was discussed, see Attachment A. All of the events described in this pathway take place within the CFS universe, i.e., only patients already diagnosed with CFS are included. Patients must have medically determinable condition (clinical signs and symptoms, lab results, or other), which leads to physical or mental impairment, which then leads to disability, as defined by the SSA.

V. Definition of disability and CFS
(C. Levine)

It was agreed that 4 definitions for CFS will be used in the scope of this project. These include: CDC 1988, CDC 1994, Oxford, and Australian. See Attachment B for descriptions of these definitions.

Discussion of the definition of disability. Per SSA definitions, disability is based upon inability to work. The disabled person cannot do work that was done before and cannot adjust to other work, and the disability must be expected to last for at least a year.

In the current literature, impairment and loss of function are not well linked to disability. Objective disability outcome measurements should be used (functional limitations, capacity, functional impairment, dysfunction).

VI. Refinement of key questions
(C. Levine)

Original Key Question 1:

What is the evidence that individuals with CFS have a discrete physical impairment? What is the evidence that individuals with CFS have a coexisting mental impairment? For example, what is the evidence that comorbid psychiatric/neurologic conditions frequently reported in CFS are present and, if present, are a result of CFS or are an integral part of the CFS disease process?

Revised Key Question 1:

What is the evidence that some individuals with CFS have discrete impairments that are associated with disability?
Impairment includes both physical and mental impairments.

Original Key Question 2:

What is the evidence that there are specific clinical tests that can be used to reliably diagnose CFS, for example, are there specific anatomical, psychological, physiological, or medical imaging indices that are diagnostic for CFS?

Revised Key Question 2:

It was agreed that this question does not pertain to disability and should be deleted.

Original Key Question 3:

When cognitive deficits are alleged, what is the evidence that individuals with CFS have such deficits and what is the evidence that these potential deficits contribute to functional limitations or inability to do work activity?

Revised Key Question 3:

Same as Revised Key Question 1.

Original Key Question 4:

Do current neuropsychological tests reliably detect cognitive or mental impairments in the CFS population? Are there certain tests that are preferred in terms of reliability and validity? Are there certain tests or diagnostic tools that contain reliable correlations between test result(s) and either ability or inability to perform designated work-related functions (e.g., ability to relate to coworkers and supervision appropriately, ability to maintain concentration or pace, suitable memory capacity for work activities, etc.).

Revised Key Question 4:

What is the evidence that in the CFS population, current neuropsychological tests detect cognitive or affective impairments associated with decreased ability to work?

Original Key Question 5:

What treatments have been shown to be most effective for CFS in terms of restoring an individual's ability to do work activity?

Revised Key Question 5:

What is the evidence that in some individuals with CFS, treatments are effective in restoring the ability to work?

Original Key Question 6:

What are the patient characteristics that best define improvement or positive outcomes in the CFS population such that they experience improvement in functioning? Where it occurs, how is this improvement in functioning related to the ability to engage in work activity?

Revised Key Question 6:

No change, but it was agreed that it was unlikely that the literature would allow us to address the last part of this question.

Original Key Question 7:

What evidence is available from related fields (e.g., sleep medicine, autonomic nervous system abnormalities, endocrinology, gastrointestinal illness, neurocognitive therapy) that would be applicable to the assessment, functional evaluation, and treatment for CFS?

Revised Key Question 7:

No change, although complete searches and reviews of the literature in other fields is beyond the scope of this project. SSA will discuss and propose a modified question.

It was agreed that this question will apply only to literature that pertains to CFS.

VII. Preliminary literature assessment
(C. Levine)

It was agreed that the search needs to be expanded to 1988, to match the first operational definition of CFS, which was published by CDC in 1988. Many important studies about CFS were published immediately after 1988, and need to be included in this project. Number of citations identified will increase; however, the overall number of eligible studies may not change too much, given requirements that studies contain information regarding impairment or disability.

Pubmed, PsychINFO, Current Contents, and Cochrane Database will be the only electronic sources searched for this literature review. Also Journal of Chronic Fatigue Syndrome (JCFS), which is not indexed by Medline, will be searched.

Any study with > than 1 patient with CFS will be included, but individual case reports will not. Fibromyalgia, Gulf War Syndrome, or other related disorders without CFS will

not be included within the scope of this project. Studies pertaining to multiple disorders will only be accepted if information regarding patients with CFS is separately extractable.

VIII. Conclusions/Next Steps
(S. Ross)

- Definitional issues must be recognized regarding disability and impairment.
- MetaWorks will be "monists," not mind-body dualists.
- The words "mental" and "physical" will be removed from the key questions, and the general term impairment will be used instead.
- Four operational definitions of CFS will be used.
- Key questions will be revised as discussed.
- Literature search will be expanded as discussed.

IX. Action Items

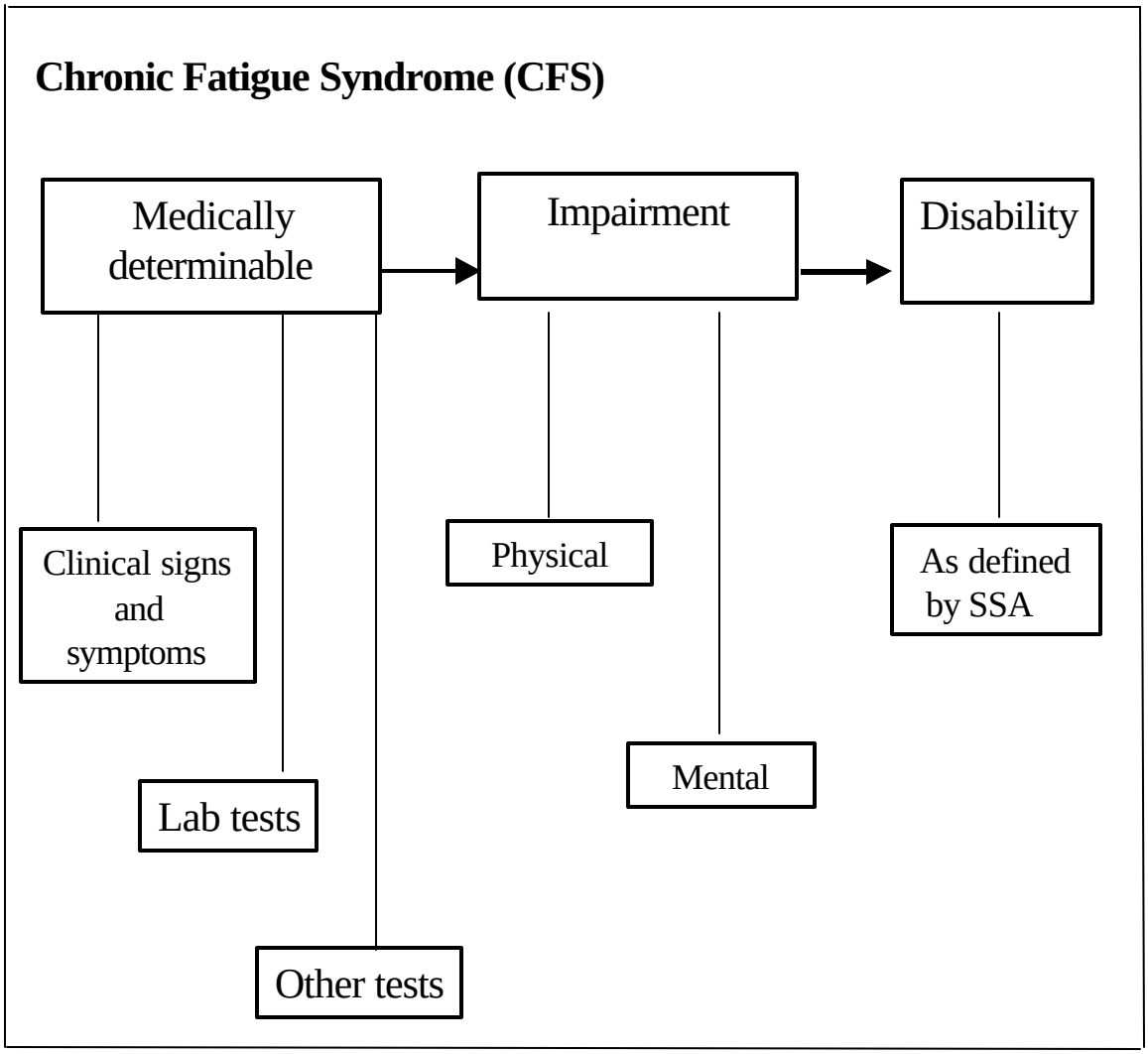
MetaWorks to:

- Distribute meeting minutes.
- Contact members of the expert panel regarding serving on the Technical Experts Panel (TEP).
- Adopt questions and literature search recommendations as discussed in the panel.

SSA to:

- Review Key Question 7 and propose modifications.

Attachment A: Causal Pathway



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  - fatigue that is not explained by the presence of other evident medical or psychiatric illnesses
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  - at least six symptoms plus at least two signs, or at least eight symptoms from the list below
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    - generalized headaches
    - migratory arthralgia without swelling or redness
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From: Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: A working case definition. Ann Intern Med 1988; 108: 387-9.

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  - Tender cervical or axillary lymph nodes
  - Muscle pain
  - Multijoint pain
  - New headaches
  - Unrefreshing sleep
  - Postexertion malaise

- Exclusion criteria
  - Active, unresolved, or suspected disease likely to cause fatigue
  - Psychotic, melancholic or bipolar depression
    - (but not uncomplicated major depression)
  - Psychotic disorders
  - Dementia
  - Anorexia or bulimia nervosa
  - Alcohol or other substance misuse
  - Severe obesity

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- Severe, disabling fatigue lasting $\geq$ 6 months that:
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- Disabling and prolonged feelings of physical tiredness or fatigue, exacerbated by physical activity.
- Present for at least 6 months.
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- Accompanied by new onset of neuropsychological symptoms including impaired short-term memory and concentration, decreased libido, and depressed mood. These symptoms usually have their onset at the same time as the physical fatigue, but are typically less severe and less persistent than those seen in classic depressive illness.

- Exclusion criteria:
  - Chronic medical condition that may result in fatigue
  - History of schizophrenia, other psychotic illnesses, or bipolar affective disorder

- Drug or alcohol dependence makes CFS very unlikely.

From: Lloyd AR, Hickie I, Boughton CR, et al. Prevalence of chronic fatigue syndrome in an Australian population. Med J Aust 1990; 153: 522-8.

Appendix C

Appendix C. Screening and Data Extraction Forms

AHRQ: DIAGNOSIS AND MANAGEMENT OF CFS DISABILITY
Level II Screening

Reviewed by_____ **MetaHub Study ID**_____
First Author_____ **Year Published**_____

Status: Accept Reject **If accepted, # of refs. from Bib:**_____

If REJECT, Specify Reason:

__ Abstracts, letters, comments, editorials, case report.
__ Animal or *in vitro* or tissue level studies
__ Fewer than 10 patients per study
__ Not related to CFS
__ Not specific to CFS
__ No outcome related to disability (*sample of signals*: disabled, unfit, incapacitated, lost worktime, sick leave, cost of illness, physical function, work endurance, absenteeism, ADL, productivity, days lost, light duty)
__ Languages other than English
__ Outcomes not extractable
__ Pediatric patients
__ Pharmacodynamic or Pharmacokinetic Study
__ Not US, UK, Canada, Australia or Western Europe
__ Studies published prior to 1996
__ Studies of lab findings/lab technique or focus on pathophysiology of CFS
__ Type of Study: Review or Meta-analysis (Reject for extraction, but hold study for discussion)
__ CFS population mixed with other populations
__ Other _____

If ACCEPT, then record:

Geographic location: US ___Western Europe ___UK ___Canada ___Australia ___

Patients Enrolled: _____

Type of Study:
Observational: __ Retrospective __Prospective __XS
Interventional: __ RCT __ non-RCT __XS

Elements of Causal Pathway present: Check all applicable elements

1. In the population of CFS patients __Yes __ No
   This paper focuses on
2. The __ diagnosis and/or __management
   Of a
3. Medically determinable (as demonstrated by __ clinical finding __ lab test finding __ other test result)
4. Impairment (__ physical __ mental)
5. Disability __Yes __ No

If yes, please record disability outcome: _____

If the answers to 1 and 5 are not both 'Yes**", REJECT PAPER** for reason: Not population of interest__ or No outcome of interest__

Extracted by: _____
Date: _____

Phase I
Data Extraction Form
AHRQ CFS

Consensed by: _____
Date: _____

Impairment: weakening, damage, or deterioration e.g., as a result of injury or disease

Disability: loss of function and earning power

Study Characteristics

Study ID: _____ **First Author:** _____ **Pub. Date:** _____

Study Location:

_____US _____Australia/NZ

____ Canada

____ Western Europe_____

Institution:_____

_____

Kin(s):_____

_____

Patients Enrolled: _____Total #
_____CFS
_____Controls
_____Other

_____

Intervention duration: (Max/median)_____mos

Observation duration (Max/median)_____mos

Funding Source/Industry Sponsorship:
YES_____
NR

Study Design:

Observational: Retrospective / Prospective

Interventional: RCT / nRCT / XS / Case-series

CFS Definition Used:

____ CDC 1988 _____Oxford 1991

____ CDC 1994 _____ Australia 1990

Patient Characteristics

	Group 1	Group 2
# Enrolled / Randomized	/	/
Age (Mean, Median, Range)		
# Male / # Female	/	/
Race and/or ethnicity		
Duration of CFS (yrs)		
Education (yrs)		

Study ID _____

Phase I
Data Extraction Form
AHRQ CFS

Impairment	Disability	Indeterminate

Activities of Daily Living (ADL)
Actometer
Beck Depression Inventory (BDI
Checklist Individual Strength (CI
Activities
CFS Severity Index
Fatigue Severity Scale
Fennell Phase Inventory
General Health Questionaire (GHQ)
Illness Management Questionaire (IMQ)
Karnofsky Scale
Likert Scale
Medical Outcomes Study
MOS-SF-23
MOS - SF - 36
Physical Activities Rating Scale (PARS)
Quality of Life (QoL)
Sickness Impact Profile (SIP)
Walking
Mobility
Work & Social Adjustment Scale

Study Characteristics

Study ID: _____ **First Author:** _____ **Pub. Date:** _____

Study Location:
_____US _____Australia/NZ
____ Canada
____ Western Europe_____

Institution:_____
_____
Kin(s):_____
_____

Patients Enrolled: ___ Total #
____ CFS
____ Healthy Controls
____ Other Controls
_____

____ **Single time point only**

CFS Definition Used (all that apply):
____ CDC 1988 _____Oxford 1991
____ CDC 1994 _____ Australia 1990

Study Design:
Retrospective / Prospective
RCT / nRCT / Case-series
XS

Quality Score:
_____(rand) +_____(blind) +_____(w/drwl) =_____(Total)

Accrual Years: _____ - _____

CFS Disability Validity Rating Scale:

Study Quality Criteria:

Internal Validity (0-1; 0 if absent, 1 if present):	**Points**	**Check the best one**
1. CFS is defined according to at least one of the acceptable criteria. All patients meet this criteria.	1	____ Ia: Prospective longitudinal study with sufficient patient number, well-matched groups, and well- validated measurement instruments.
2. Tests for medically determinable physical and/or mental impairment are specified and reported.		____ Ib: Prospective longitudinal study with low patient number, but with well-matched groups, and well-validated measurement instruments.
3. Control group was similar in clinically important demographic factors at start of the study (well-matched).		____ IIa: Cross-sectional study with sufficient patient number, well-matched groups, and well-validated measurement instruments.
4. All subjects enrolled (patients and control groups) were accounted for in followup.		____ IIb: Cross-sectional study with low patient number, but with well-matched groups, and well-validated measurement instruments.
5. 95% confidence limits and assessment of chance (p-values) are given for numerical results.		____ IIIa: Prospective, longitudinal study with sufficient patient number, but with poorly-matched groups, and/or less well-validated measurement instruments.
6. Work activity or work/disability status reported.		____ IIIb: Prospective, longitudinal study with low patient number, poorly-matched groups, and/or less well-validated measurement instruments.
External Validity (0-2 points):		____ IVa: Cross-sectional study with sufficient patient number, but with poorly-matched groups, and/or less well-validated measurement instruments.
7. Patient sample was ***not*** self-selected from CFS population (i.e., random or all comers).		____ IVb: Cross-sectional study with low patient number, poorly-matched groups, and/or less well-validated measurement instruments.
Total Validity Score:		

First Author _____
Study ID _____

Phase II DEF
AHRQ CFS

Patient Characteristics (Time$_0$)		
	Group 1	**Group 2**
Group Category:	CFS	
# Enrolled OR Randomized		
Age (Mean OR Median / Range)	/	/
# Male / # Female	/	/
Race and/or ethnicity:		
(W / B / H / A / ___)	/ / / /	/ / / /
CFS or symptom duration (years) Mean OR Median / Range	/	/
inclusion criteria min / max (yrs)	/	/
Total education (years)		
Employment Status:		
Employed (# of patients)		
Full time		
Part time		
Unemployed (# of patients)		
Disability benefits (# of patients)		
Disability or temporary sick leave (# pts)		
Work limitations due to illness (# pts)		
Mean OR Median # hours/week worked OR % of time worked		
Psychiatric and other history:		
# pts w/ any current psychiatric dx		
# pts w/ lifetime psychiatric dx (specify)		
Dysthymia		
Generalized anxiety disorder		
Major depression		
Panic disorder		
Somatization disorder		
Other lifetime diagnosis: (specify)		
# pts w/ other dx (specify):		
# pts currently on medication (specify):		

Entered: _____
QC'd: _____

First Author _____
Study ID _____

Phase II DEF
AHRQ CFS

Intervention					
Group 1 (CFS)					
Category	**Intervention**	**Dose (mean, range) (mg)**	**frequency**	**route**	**Duration (wks)**
Group 2: _____					
Category	**Intervention**	**Dose (mean, range) (mg)**	**frequency**	**route**	**Duration (wks)**

Categories:

B = Behavioral Therapy **E = Physical/Exercise Therapy**
Ψ = Psychiatric Therapy **D = Dietary Therapy**
Rx = Drug Therapy **P = Placebo** **O = Other: _____**

Outcomes @ T_1 (_____ months after T_0)		
	Group 1 (CFS)	**Group 2:**
# of pts. Evaluated at follow-up		
Employed (# of patients)		
Unemployed (# of patients)		
Disability benefits (# of patients)		
Disability benefits or temp. sick leave (# pts)		
Work limitations due to illness (# pts)		
Mean OR Median # hours/week worked		
Symptom Improvement:		
# pts Improved		
# pts No change		
# pts Worse		

Entered: _____
QC'd: _____

First Author _____
Study ID _____

Phase II DEF
AHRQ CFS

Group 1 (CFS)											
Measurement (scale name):	**# pts. Eval.**	**Domain**	**O/S***	**Scale Range**	**Dir. Improv**	**T_0**	**SD**	**T_1**	**SD**	**Change**	**SD**

* **O**bjective or **S**ubject Scale

Domain key:

C = Cognitive G = General Health L = Lab Measures P = Physical Activity

DS = Disease severity/symptoms E = Exercise Testing M = Mental (Psych/Affective) W = Work

O = Other _____

Other Outcomes (circle or specify) Between-scale correlations Work status correlations

_____ _____ _____ _____

_____ _____ _____ _____

Other groups/timepoints (specify): t_{nadir} type of profession Income level

_____ _____ _____ _____

Entered: _____
QC'd: _____

First Author _____
Study ID _____

Phase II DEF
AHRQ CFS

Group 2											
Measurement (scale name):	**# pts. Eval.**	**Domain**	**O/S***	**Scale Range**	**Dir. Improv**	**T_0**	**SD**	**T_1**	**SD**	**Change**	**SD**

* **O**bjective or **S**ubjective Scale

Domain key:

C = Cognitive
G = General Health
L = Lab Measures
P = Physical Activity
DS = Disease severity/symptoms
E = Exercise Testing
M = Mental (Psych/Affective)
W = Work
O = Other _____

Other Outcomes (circle or specify) Between-scale correlations Work status correlations

_____ _____ _____ _____
_____ _____ _____ _____

Other groups/timepoints (specify): t_{nadir} type of profession Income level

_____ _____ _____ _____

Entered: _____
QC'd: _____

Appendix D

Appendix D. Quality Scoring Tools

Study Quality Criteria[1]

Study quality was graded according to design follows:

Ia: Prospective longitudinal study with sufficient patient number, well-matched groups, and well-validated measurement instruments.

Ib: Prospective longitudinal study with low patient number, but with well-matched groups and well-validated measurement instruments.

IIa: Cross-sectional study with sufficient patient number, well-matched groups, and well-validated measurement instruments.

IIb: Cross-sectional study with low patient number, but with well-matched groups and well-validated measurement instruments.

IIIa: Prospective, longitudinal study with sufficient patient number, but with poorly matched groups and/or less well-validated measurement instruments.

IIIb: Prospective, longitudinal study with low patient number, poorly matched groups, and/or less well-validated measurement instruments.

IVa: Cross-sectional study with sufficient patient number, but with poorly matched groups and/or less well-validated measurement instruments.

IVb: Cross-sectional study with low patient number, poorly matched groups, and/or less well-validated measurement instruments.

CFS Disability Validity Rating Scale (developed internally)

Internal Validity

(0-1 points, 0 if absent, 1 if present)

1. CFS is defined according to at least one of the acceptable criteria. All patients meet these criteria.

2. Tests for medically determinable physical and/or mental impairment are specified and reported.

3. Control group was similar in clinically important demographic factors at start of the study (well matched).

4. All subjects enrolled (patients and control groups) were accounted for in follow-up.

5. 95% confidence limits and assessment of chance (p-values) are given for numerical results.

6. Work activity or work/disability status reported.

External Validity

(0-2 points)

7. Patient sample was not self-selected from CFS population (i.e., random or all comers).

Jadad Quality Score Assessment (RCTs only) [2]

Please read the articles and try to answer the following:

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?

2. Was the study described as double blind?

3. Was there a description of withdrawals and dropouts?

Scoring the items:

Either give a score of 1 point for each 'yes' or 0 for each 'no'. There are no in-between marks.

1 point if:

For question 1, the method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated, coin tossing, etc.)

and/or:

If for question 2 the method of double-blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.)

For question 1, the method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)

and/or:

For question 2 the study was described as double-blind but the method was inappropriate (e.g., comparison of tablet vs. injection with no double dummy)

Guidelines for assessment

1. Randomization:

A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers or alternation should not be regarded as appropriate.

2. Double-blinding:

A study must be regarded as double-blind if the word double-blind is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if the absence of such a statement the use of active placebos, identical placebos or dummies is mentioned.

3. Withdrawals and dropouts:

Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

References:

1. MacMahon KMA, Lip GYH. Psychological factors in heart failure: A review of the literature. Arch Intern Med 2002; 162: 509-16.

2. Jadad AR, Moore A, Carroll D, et al. Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? Controlled Clinical Trials 1996; 17: 1-12.

Appendix E. Scale Names and Citations

Scale Name	Acronym	Reference
Beck Depression Inventory	BDI	Beck AT, Ward H, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961; 561-71.
Chalder Fatigue Scale		Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. J Psychosom Res 1993; 37: 147-53.
Checklist of Individual Strength	CIS	Vercoulen JHMM, Swanink CMA, Galama JMD, Fennis JFM, van der Meer JWM, Bleijenberg G. Dimensional assessment in chronic fatigue syndrome. J Psychosom Res 1994; 38: 383-92.
Everyday Attention Questionnaire	EAQ	Martin M. Human Learning 1986; 5: 63-74.
Hopkins Verbal Learning		Claypoole K, Mahurin R, Fischer ME, Goldberg J, Schmaling KB, Schoene RB, et al. Cognitive compromise following exercise in monozygotic twins discordant for chronic fatigue syndrome: Fact or artifact. Appl Neuropsychol 2001; 8: 31-40.
Karnofsky Performance Score	KPS	Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: Macleod CM, ed. Evaluation of Chemotherapeutic Agents. New York: New York Columbia University Press; 1949; p.191-205.
Medical Outcomes Study - Short Form 36	MOS SF-36	Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Med Care 1992; 30: 473-83.
Physical Activity Rating Scale	PARS	Vercoulen JH, Bazelmans E, Swanink CM, Fennis JF, Galama JM, Jongen PJ, et al. Physical activity in chronic fatigue syndrome: Assessment and its role in fatigue. J Psychiatr Res 1997; 31: 661-73.
Profile of Fatigue-related Symptoms	PFRS	Ray C, Weir WRC, Phillips S, Cullen S. Development of a measure of symptoms in chronic fatigue syndrome: The Profile of Fatigue-Related Symptoms (PFRS). Psychology and Health. 1992; 7: 27-43.
Profile of Mood States	POMS	McNair DM, Lorr M, Droppelman LF. Profile of Mood States. San Diego, Calif: Educational and Industrial Testing Service, 1981.
Sickness Impact Profile	SIP	Bergner M, Bobbitt RA, Kressel S, Pollard WE, Gilson BS, Morris Jr. The Sickness Impact Profile: Conceptual formulation and methodology for the development of a health status measure. Int J Health Serv 1976; 6: 393-415.
Symptom Checklist 90 - Revised	SCL 90R	Derogatis LR, Melisaratos N. The brief symptom inventory. Psychol Med 1983; 13: 595-605.
Wechsler Adult Intelligence Scale - Revised	WAIS-R	Wechsler D. Wechsler Adult Intelligence Scale - Revised (WAIS-R). 1981. New York: Harcourt Brace.

Appendix F

Appendix F. Technical Expert Panel Members and Peer Reviewers

Members of the Technical Experts Panel

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Appendix G

Appendix G. Reviewer Questionnaire

The following two pages comprise the peer reviewer form to be used in providing comments on the draft evidence report, ***Review of the Current Medical and Scientific Research Related to Chronic Fatigue Syndrome.***

Page 2 is the reviewer "level of agreement"rating form, and page 3 provides a space for written comments. Here we would like you to provide: a) A brief explanation of both positive and negative answers;

b) Suggestions for improvement of the content or format of this review;
c) Suggestions for additional analyses of this dataset worth including in this report, or in future reports;
d) Any other comments you may wish to provide regarding this draft report.

**We would prefer that you complete and return this form electronically. However, you may also fax the forms back to us, or fax back an annotated version of the draft report if you prefer.

Please contact Cindy Levine, M.D., Principal Investigator with any questions regarding the content of the draft report.

As a reminder, the draft evidence report in your possession must remain confidential and is not to be shared or distributed. Once all reviewer comments are received, these will be incorporated as appropriate, into the **final** evidence report that is sent to AHRQ for publication. We ask for your cooperation in maintaining the confidentiality of all information contained in this draft evidence report.

Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts.

Please send the completed form and comments to MetaWorks by **July 29, 2002.**

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Reviewer Questionnaire

AHRQ Task Order: Review of the Current Medical and Scientific Research Related to Disability and Chronic Fatigue Syndrome

Please indicate your level of agreement with each of the following Statements, by placing an "X" in the appropriate column.				
Statements	**Very much agree**	**Moderately agree**	**Not very much in agreement**	**Do not agree at all**
Accuracy:				
1. Facts are easily distinguished from assumptions, assertions, or opinions in report.				
2. The author's interpretations and conclusions are sound.				
Attribution:				
3. The theoretical or scientific basis used to support assertions, conclusions and discussions within the report is clearly stated.				
4. Given the objectives of this project and the data, all clinically important outcomes were considered.				
Clarity and Composition:				
5. The purpose of the report is apparent and explicitly stated.				
6. The report is well-written and content is organized in a coherent fashion that facilitates understanding.				
7. Content is consistent with the purpose of the report.				
8. The methods are presented in such a way as to be reproducible.				
9. The results are clearly stated.				
Figures and Tables:				
10. Figures and tables are clear, useful, accurate and easy to interpret.				
11. Titles and legends are appropriate.				
Relevance:				
12. This topic is relevant to healthcare decision-making (clinical practice and policy making) in 2002.				
13. Authors should seek publication of a manuscript describing some or all aspects of this report. (please suggest possible journals and priority for publication)				
Study Selection:				
14. Based on selection criteria used, it is not likely that relevant studies were missed.				
Overall:				
15. I agree with the conclusions presented in the report.				

Reviewer Questionnaire

AHRQ Task Order: Review of the Current Medical and Scientific Research Related to Disability and Chronic Fatigue Syndrome

Please print legibly or type comments here:

(signature) (date)

(print name)

Appendix H

Appendix H. Accepted Studies Log

1. Akagi H, Klimes I, Bass C. Cognitive behavioral therapy for chronic fatigue syndrome in a general hospital-feasible and effective. Gen Hosp Psychiatry 2001; 23: 254-60.

2. Anderson JS, Ferrans CE. The quality of life of persons with chronic fatigue syndrome. J Nerv Ment Dis 1997; 185: 359-67.

3. Antoni MH, Brickman A, Lutgendorf S, Klimas N, Imia-Fins A, Ironson G, et al. Psychosocial correlates of illness burden in chronic fatigue syndrome. Clin Infect Dis 1994; 18 Suppl 1: S73-8.

4. Arpino C, Carrieri MP, Valesini G, Pizzigallo E, Rovere P, Tirelli U, et al. Idiopathic chronic fatigue and chronic fatigue syndrome: A comparison of two case-definitions. Ann Ist Super Sanita 1999; 35: 435-41.

5. Bombardier CH, Buchwald D. Outcome and prognosis of patients with chronic fatigue vs chronic fatigue syndrome. Arch Intern Med 1995; 155: 2105-10.

   Bombardier CH, Buchwald D. Chronic fatigue, chronic fatigue syndrome, and fibromyalgia. Disability and health-care use. Med Care 1996; 34: 924-30.

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12. Cruess SE, Klimas N, Antoni MH, Helder L, Maher K, Keller R, et al. Immunologic

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18. Garcia-Borreguero D, Dale JK, Rosenthal NE, Chiara A, O'Fallon A, Bartko JJ, et al. Lack of seasonal variation of symptoms in patients with chronic fatigue syndrome. Psychiatry Res 1998; 77: 71-7.

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    Straus SE, Dale JK, Tobi M, Lawley T, Preble O, Blaese RM, et al. Acyclovir treatment of the chronic fatigue syndrome. Lack of efficacy in a placebo-controlled trial. N Engl J Med 1988; 319: 1692-8.

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Peterson PK, Shepard J, Macres M, Schenck C, Crosson J, Rechtman D, et al. A controlled trial of intravenous immunoglobulin G in chronic fatigue syndrome. Am J Med 1990; 89: 554-60.

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in chronic fatigue syndrome. Minn Med 1999; 82: 52-6.

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Ray C, Jefferies S, Weir WR. Life-events and the course of chronic fatigue syndrome. Br J Med Psychol 1995; 68: 323-31.

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Morriss RK, Wearden AJ. Screening instruments for psychiatric morbidity in chronic fatigue syndrome. J R Soc Med 1998; 91: 365-8.

Morriss RK, Wearden AJ, Battersby L. The relation of sleep difficulties to fatigue, mood and disability in chronic fatigue syndrome. J Psychosom Res 1997; 42: 597-605.

Morriss RK, Wearden AJ, Mullis R. Exploring the validity of the Chalder Fatigue scale in chronic fatigue syndrome. J Psychosom Res 1998; 45: 411-7.

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53. Yeomans JD, Conway SP. Biopsychosocial aspects of chronic fatigue syndrome (myalgic encephalomyelitis). J Infect 1991; 23: 263-9.

Appendix I

Appendix I. Rejected Studies Log

Rejection Reason: Abstract, letter, comment, review, editorial, case-report, meta-analysis

1. Abbey SE, Garfinkel PE. Chronic fatigue syndrome and depression: Cause, effect, or covariate. Rev Infect Dis 1991; 13:S73-83.

2. Ax S, Gregg VH, Jones D. Coping and illness cognitions: Chronic fatigue syndrome. Clin Psychol Rev 2001; 21:161-82.

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8. Buchwald D, Komaroff AL. Review of laboratory findings for patients with chronic fatigue syndrome. Rev Infect Dis 1991; 13:S12-8.

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Rejection Reason: Adult CFS patients not separately extractable

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