

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 (VO₂)
- 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 VO₂
- 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 VO₂
- 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

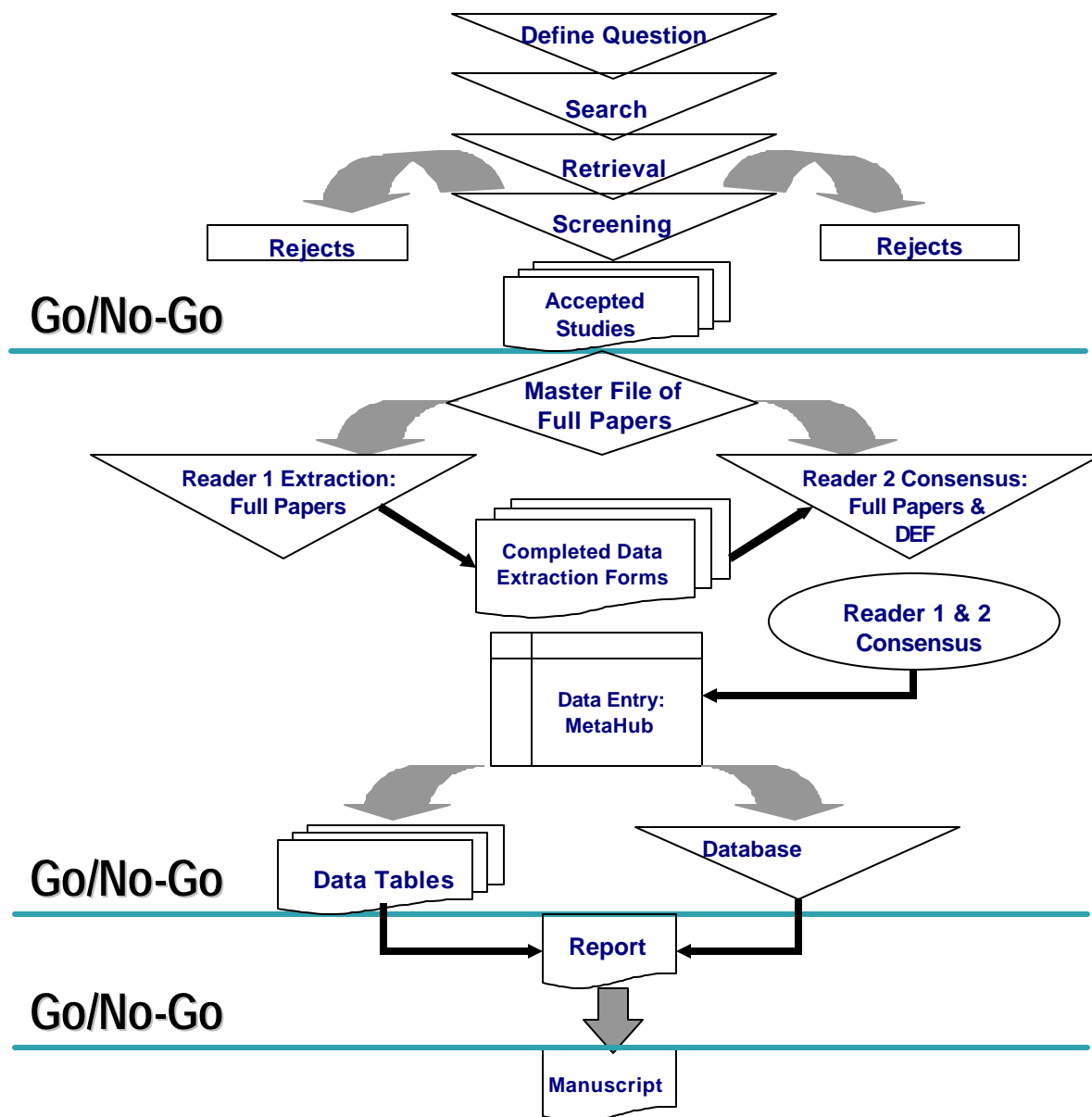
Attachment A: Flow Diagram Systematic Review

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, PO₄, 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 ≥ 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

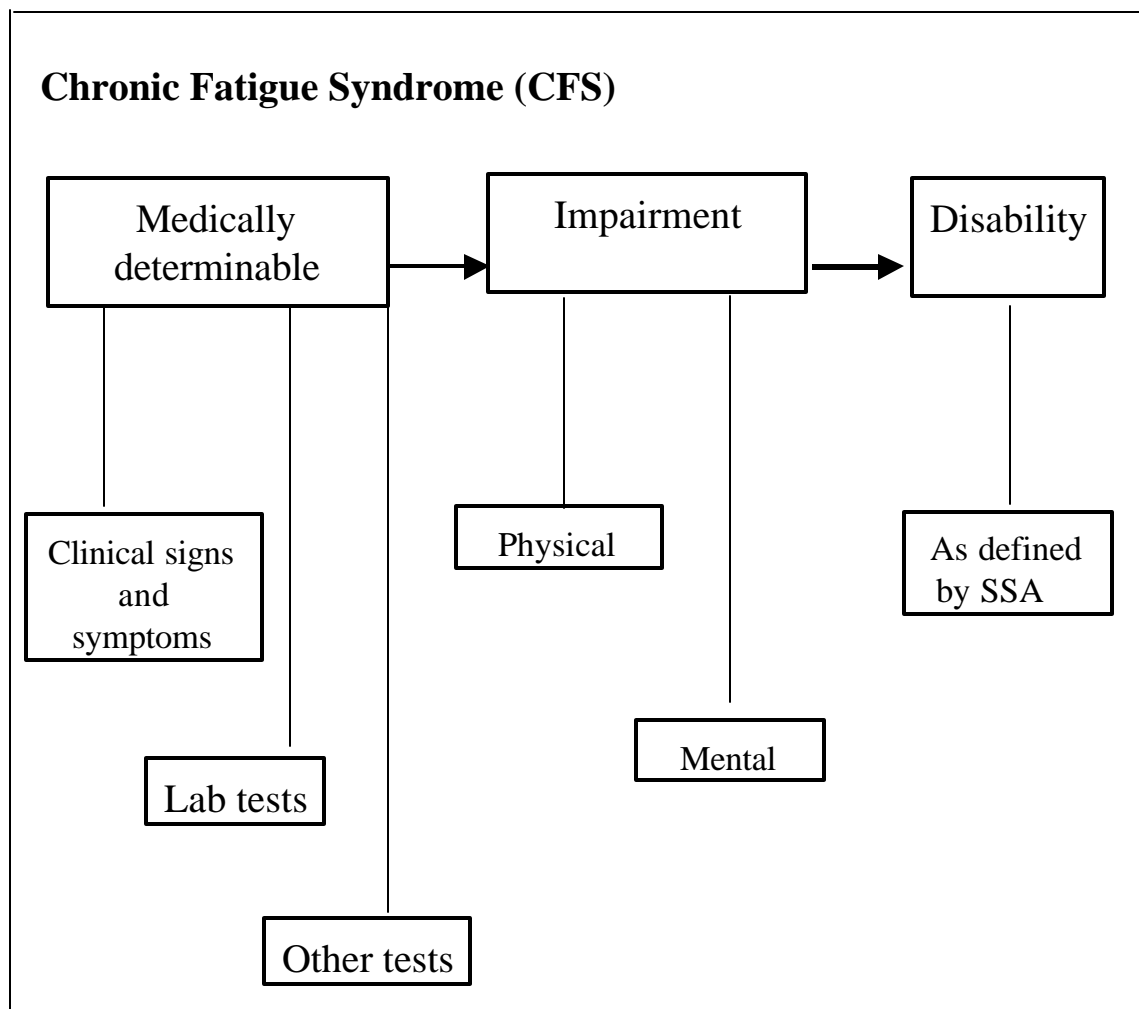
From: Sharpe MK, Archard LC, Banatvala JE, et al. A report - chronic fatigue syndrome: Guidelines for research. J R Soc Med 1991; 84: 118-21.

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

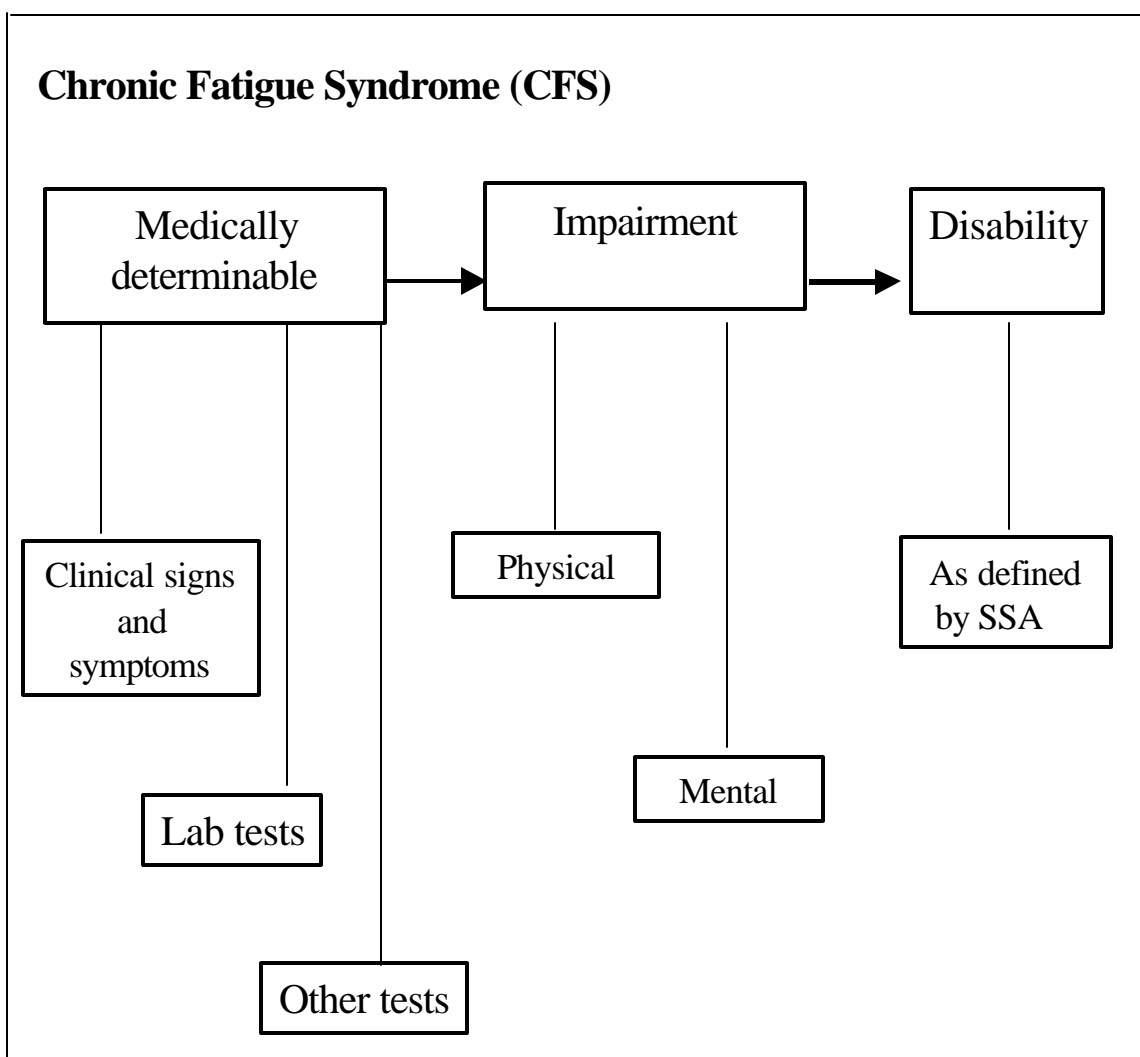
MetaWorks to:

- 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



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 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, PO₄, 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 ≥ 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.

Appendix C

Appendix D

Appendix D. Quality Scoring Tools

Study Quality Criteria¹

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, Schmalings 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

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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.				

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

This image shows a full page of white paper with horizontal blue or grey ruling lines. The lines are evenly spaced and run across the width of the page, providing a template for writing. There are no margins, text, or other markings on the page.

(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.
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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.
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Rejection Reason: Accepted CFS diagnostic criteria not defined or fulfilled

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Rejection Reason: Adult CFS patients not separately extractable

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Rejection Reason: CFS population mixed with other populations

1. Cope H, Pernet A, Kendall B, David A. Cognitive functioning and magnetic resonance imaging in chronic fatigue. *Br J Psychiatry* 1995; 167:86-94.
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Rejection Reason: No outcome related to disability

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Rejection Reason: No work data

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Rejection Reason: Not US, UK, Canada, Australia or Western Europe

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Rejection Reason: Outcomes not extractable

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Rejection Reason: Studies of lab findings/lab technique or focus on pathophysiology of CFS

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Rejection Reason: Work data not extractable

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