http://www.mrc.ac.uk/index/public-interest/public-topical_issues/public-cfs_me/public-cfs_draft_research_strategy.htm

MEDICAL RESEARCH COUNCIL

MRC CFS/ME RESEARCH ADVISORY GROUP

CFS/ME RESEARCH STRATEGY

DRAFT DOCUMENT FOR PUBLIC CONSULTATION

17 December 2002

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1. SUMMARY

2. This research strategy for CFS/ME has been developed by a Medical Research Council CFS/ME Research Advisory Group. The Research Advisory Group was convened in response to the request of the Department of Health in England for the MRC to develop a broad strategy for advancing biomedical and health services research on CFS/ME, following the publication of the Report of the CMO's Independent Working Group in January 2002.

3. The MRC CFS/ME Research Advisory Group fully endorses the conclusions of the Report of the CMO's Independent Working Group, namely that CFS/ME is a real, serious and debilitating condition, and that research into all aspects of CFS/ME is needed.

4. The MRC CFS/ME Research Advisory Group has used the term "CFS/ME". The Research Advisory Group acknowledges that the descriptive term "CFS/ME" does not refer to a specific diagnosis. In the same manner, the singular term "condition" is used, but this does not indicate that the MRC CFS/ME Research Advisory Group holds any particular position on whether CFS/ME is one condition with heterogeneity of cause, pathogenesis and severity, or is a number of similar conditions with different individual characteristics.

5. The MRC CFS/ME Research Advisory Group met formally (*insert number*) times between September 2002 and (*insert date*), and held numerous other discussions. A consultation exercise was undertaken over July and August 2002 using a set of structured questions, which was independently analysed. The lay members of the MRC CFS/ME Research Advisory Group met with ME charities, and CFS/ ME patients and their carers, to better understand their perspectives. *Further details on the process to be drafted in due course.*

6. The MRC CFS/ME Research Advisory Group has not provided a detailed plan for the science, nor set out an agenda of the many research projects that

might merit support. A strategy is proposed which reflects the current state of knowledge in CFS/ME, and which aims to provide a rational framework for advancing the understanding of the illness and to reduce suffering.

7. In considering ways to advance research on CFS/ME, the Group has focused on a number of strategic themes: case definition, an epidemiological framework, pathophysiology, interventions, health service research, research capacity and the value of lay participation.

8. The MRC CFS/ME Research Advisory Group recommends that research studies should aim to be as inclusive as possible in terms of the recruitment of participants, and due consideration should be given to sample size to allow for possible subgroup effects. There should be clearly stated inclusion and exclusion criteria, with detailed justification if certain types of patients are not included.

9. The MRC CFS/ME Research Advisory Group considers there should be an agreed standardised case definition and a classification of severity and any other relevant characteristics that define subgroups. Improved definition of the phenotypes of potential subgroups that may come under the CFS/ME spectrum, and overlaps with other conditions, will underpin research on causes, mechanisms, and management. A definition of a clinically important improvement in disease status, with a classification of the degree of improvement, is essential for natural history and intervention studies.

10. In the short term, the MRC CFS/ME Research Advisory Group considers that the research community should be encouraged to develop high quality research proposals for funding that address key issues for CFS/ME research that are amenable for study at the present time: case-definition, understanding symptomology, and new approaches to management.

11. In view of the probable multiplicity of causal factors and the widely disparate findings so far reported, the MRC CFS/ME Research Advisory Group considers that studies investigating potential causal pathways and mechanisms, whilst having merit, would not have the same immediate impact on increasing understanding of CFS/ME, nor reducing the suffering of patients.

12. The MRC CFS/ME Research Advisory Group considers it is appropriate to explore potential interventions for CFS/ME in the absence of knowledge of causation or pathogenesis. Randomised controlled trials of adequate size, using standardised case definitions, eligibility criteria, and baseline and outcome assessments, could be used to evaluate one or more of the interventions which have been shown in one or more trials to have a benefit. Standardisation will allow results to be more widely generalised and compared between studies.

13. Given the present difficulties in identifying priorities for health services research in CFS/ME, it is not clear whether it is appropriate to make HSR a priority at this time.

14. It is essential that the researcher–funder-lay partnership is nurtured, to ensure that the best evidence is easily available to all, and to facilitate the growth of consumer involvement in the design, conduct and dissemination of research - as a means to enhancing its quality, relevance, and credibility. The MRC CFS/ME Research Advisory Group considers that there is a key role for patient organisations to help attract participants to research, especially the severely ill, and to help in the dissemination of research results.

15. **INTRODUCTION**

16. The Medical Research Council (MRC) CFS/ME Research Advisory Group fully endorses the conclusions of the Report of the Chief Medical Officer's (CMO) Independent Working Group (2002) that CFS/ME is a real, serious and debilitating condition.

17. The MRC CFS/ME Research Advisory Group agrees with the CMO's Independent Working Group that research into all aspects of CFS/ME is needed, and welcomes the opportunity to help advance research into this illness.

18. In considering ways to advance research on CFS/ME, the Group has focused on a number of strategic themes, which are reflected in the headings used in the remainder of this document. They correspond with the topics outlined in the research recommendations of the report of the CMO's Independent Working Group.

- Research and refinement of **case definition**
- Development of an **epidemiological framework**
- Developing and testing **hypotheses about pathophysiology**
- Design and evaluation of **interventions**
- **Health service research**
- **Research capacity** and the **interface with services**
- The value of **lay participation**

19. The MRC CFS/ME Research Advisory Group has not presumed to provide a detailed plan for the science, nor set out a prescriptive portfolio of the many research projects that might merit support. A strategy is proposed which reflects the current state of knowledge in CFS/ME, and which aims to provide a rational framework for advancing the understanding of the illness and its management.

20. The Group considers that this strategy should be available to all interested parties, to help take forward research in CFS/ME.

21. **BACKGROUND**

22. In 1998, the Chief Medical Officer (CMO) in England requested that an Independent Working Group be set up, whose terms of reference were:

- "to review management and practice in the field of CFS/ME with the aim of providing best practice guidance for professionals, patients, and carers to improve the quality of care and treatment for people with CFS/ME, in particular to:

- develop good clinical practice guidance on the healthcare management of CFS/ME for NHS professionals, using best available evidence;

- make recommendations for further research into the care and treatment of people with CFS/ME;

- identify areas which might require further work and make recommendations to CMO."

23. The Report of the CMO's Independent Working Group on CFS/ME was published in January 2002, recommending research on all aspects of CFS / ME. The Department of Health asked the MRC to develop a broad strategy for advancing biomedical and health services research on CFS/ME.

24. The MRC agreed to convene a CFS/ME Research Advisory Group (membership at Annex1), made up of individuals who were not active in the CFS/ME field, but had the relevant scientific expertise, to discuss the CMO's Independent Working Group report and make research recommendations to the MRC of possible ways forward.

25. The Terms of Reference for the MRC CFS/ME Research Advisory Group were:

- To consider the Report of the CMO's Independent Working Group on CFS/ME, including its recommendations for research,

- To consider other recent reviews of current knowledge and understanding of CFS/ME,

- To take account of patient and lay perspectives,

- To recommend to MRC a research strategy to advance understanding of the aetiology, epidemiology and biology of CFS/ME and,

- In the light of current knowledge suggest what areas of further research are needed with regard to possible prevention, management (including diagnosis) and treatment.

26. The MRC CFS/ME Research Advisory Group agreed not to revisit the areas considered by the CMO's Independent Working Group, but to recommend

how research that would improve understanding and treatment of CFS/ME might be undertaken. It was agreed that it was beyond the remit of the Research Advisory Group to decide how the recommendations for a research strategy should be implemented, as this would be the responsibility of funders and sponsors.

27. Whilst acknowledging the seriousness of the illness, not only to the affected individual but also to their carers, families and society, the MRC CFS/ME Research Advisory Group did not consider the issue of service provision as this area was not within its role.

28. **Method of Working** – *to be finalised*

29. The MRC CFS/ME Research Advisory Group met formally (*insert number*) times between September 2002 and (*insert date*), and held numerous other discussions. A public consultation exercise was undertaken over July and August 2002 using a set of structured questions. The NHS Public Health Resource Unit, Oxford (PHRU) undertook an independent qualitative analysis of the 187 responses received, and prepared a report for consideration by the Group (Annex 2).

30. The lay members of the MRC CFS/ME Research Advisory Group met with ME charities, and CFS/ ME patients and their carers, to better understand their perspectives. Their understanding of the illness was enhanced by numerous letters from individuals who gave a personal perspective.

31. All members of the Research Advisory Group contributed preliminary drafts in areas relevant to their expertise, which were brought together into a single document, which was discussed by the Research Advisory Group at its second meeting and revised subsequently.

32. A preliminary draft research strategy was made available for external, open consultation to key stakeholders, national and international researchers, and also considered by the MRC Research Boards between December 2002 and February 2003. *t*

33. – *to be completed and finalised in due course*

34. **Terminology**

35. Chronic fatigue syndrome (CFS) and myalgic encephalomyelitis or encephalopathy (ME) are two terms that have been used most often as the illness description given to patients with a combination of non-specific symptoms, but always with unexplained disabling fatigue. The CMO's Independent Working Group report discussed at length the issues surrounding nomenclature, and the MRC CFS/ME Research Advisory Group did not revisit this topic.

36. In order to develop a research strategy in this area without delay, the MRC CFS/ME Research Advisory Group agreed with CMO's Independent Working Group and used the term "CFS/ME". The Research Advisory Group

acknowledges that the descriptive term “CFS/ME” does not refer to a specific diagnosis, and that a number of diagnostic criteria are being used to define patients. There are separate entries in the World Health Organisation’s International Classification of Diseases (ICD-10) for “chronic fatigue syndrome” and “myalgic encephalomyelitis”, but it is not clear whether such a distinction has empirical validity. In the same manner, this report may use the singular term “condition”, but this should not indicate that the MRC CFS/ME Research Advisory Group holds any particular position on whether CFS/ME is one condition with heterogeneity of cause, pathogenesis and severity, or is a number of similar conditions with different individual characteristics.

37. To avoid potential confusion, in this report “CFS” will be used when discussing research findings where the specific diagnostic criteria for chronic fatigue syndrome were used in those studies, and “CFS/ME” will be used as the descriptive term for the illness.

38. It is acknowledged that, as our understanding of the area increases, such an umbrella term as CFS/ME may no longer be appropriate. However, at the present time it is considered that an inclusive approach is beneficial in the development of a research strategy.

39. **TAKING FORWARD RESEARCH INTO CFS/ME**

40. *There are a number of challenges to advancing the understanding of CFS/ME, which arise from the heterogeneous nature of the condition, the individual symptoms that may be associated with it and their variation in severity, co-morbidity with other conditions, and the variability of response to potential interventions.*

41. *The MRC CFS/ME Research Advisory Group recognises the urgent need for research into CFS/ME, and that there are certain groups of patients who have not been adequately included in research. The report of the CMO’s Independent Working Group highlighted the severely ill, children, ethnic minorities and the recovered patient. In the consultation exercise undertaken at the start of the process of developing a research strategy for CFS/ME, the inclusion of these patient groups was emphasised as being essential. The MRC CFS/ME Research Advisory Group reaffirms the need for these groups to be fully involved in the research effort to understand CFS/ME.*

42. CFS/ME patients may vary in the intensity and nature of their symptoms, both between patients and over time for individuals, and it will be important to ensure that adequate consideration is given to how these potential confounding factors are addressed. An important question is the extent to which CFS/ME overlaps with other disorders.

43. In addition to these symptomatic issues, CFS/ME affects the whole age range, which brings additional complexities to undertaking research. The understanding of the aetiology and outcome for children with CFS/ME is, at present, an area that is under-researched. It is likely that interventions developed for an adult may need significant modification before they could be evaluated in children. There are particular ethical dimensions to children

participating in research which must be considered in great depth by researchers, and the rights of the child must remain paramount. Whilst acknowledging the importance of research with children, the MRC CFS/ME Research Advisory Group endorses the principle that for ethical reasons research involving children should only be undertaken when it is not appropriate to undertake such studies in adults.

44. The report of the CMO's Independent Working Group highlighted the importance of understanding the particular problems experienced by the most severely ill patients. This patient group was also identified by many respondents of the MRC consultation exercise as being a priority area for research. There are many potentially informative comparisons to be made between severely affected patients, who tend to have a poor prognosis, and those individuals who recover, to a greater or lesser extent, both in terms of understanding aetiology and of the reported differential outcomes to a number of potential management or treatment strategies. Such comparisons may help to identify subgroups, either in terms of aetiological mechanisms or predictors of response to interventions. The pathways to chronicity and severity are not at present understood, and this is a key area for research. There should be a concerted effort to engage severely affected patients in research. At present there is a danger that these individuals, who sometimes experience difficulties in accessing care, might not be included in studies either based in, or recruited from, that care setting.

45. The MRC CFS/ME Research Advisory Group recommends that research studies should aim to be as inclusive as possible in terms of the recruitment of participants, and due consideration should be given to sample size to allow for possible subgroup effects. There should be clearly stated inclusion and exclusion criteria, with detailed justification if certain types of patient are not included.

46. The range and severity of symptoms for people with CFS/ME mean that researchers must bear such variability in mind when designing studies. It is important that the possibility of selection bias is considered at the earliest stages of any study, as symptomatic patients referred to speciality clinics may not reflect accurately the majority of patients in the general medical setting.

47. An integrated approach to determining causal pathways is needed. It could combine structural, functional, behavioural and possibly genetic approaches. As is the case for many chronic diseases, there is limited utility in considering particular symptoms in isolation. It is likely that a more holistic approach may be more fruitful in understanding CFS/ME, and potential therapeutic interventions. There is undoubted benefit to employing a multidisciplinary approach to research on CFS/ME, where experience and expertise from appropriate disciplines can be brought together.

48. The current understanding of CFS/ME would imply that there are a number of potential triggering factors for the illness. The report of the CMO's Independent Working Group cited infections, immunisations, life events, physical injuries and environmental toxins as potential triggers, although the strength of evidence is extremely variable, as discussed by the recent report

of a Working Group convened under the auspices of the Royal Australasian College of Physicians (2002). Predisposing factors included gender, familial, personality, other disorders and previous mood disorder. Given that the causes of CFS/ME are probably diverse and multi-factorial, identification of specific causal pathways may be of limited value in understanding and treating the illness. It is entirely possible that an original precipitating factor may no longer be detectable in a person with CFS/ME, or was present at a subclinical level, and thus reported abnormalities may not reflect a true causal association.

49. Many reported findings in the area of pathophysiology are not published in the peer-reviewed literature, or are not well described. Such preliminary findings need to be confirmed by independent replication in other centres. Currently, the low volume of research and the lack of methodological rigour and independent replication mean that many of these claims find little support from the wider scientific community, but may have strong currency among some patients and practitioners.

50. Findings need be subjected to rigorous and objective scientific analysis and published in high quality, peer reviewed journals, not least so that the methods can be replicated and the findings and hypotheses tested independently by other approaches. Where independent replication and different approaches fail to demonstrate a significant association, the case for further work is likely to be weak. Well substantiated, refined hypotheses can then be tested through a variety of other designs.

51. The MRC CFS/ME Research Advisory Group is aware of the difficulty in publishing negative results, especially in peer-reviewed journals. The Group considered it important, especially in an area as complex as CFS/ME, that the results of such research should be disseminated to avoid unnecessary repetition of studies and the inefficient use of resources. There may be a need for funders and sponsors of research to investigate additional alternative mechanisms of dissemination, preferably involving an independent peerreview mechanism to provide scientific credibility to the results. The MRC has a reputation for rigorous peer-review, and may need to take the lead in such an endeavour, in partnership with other funders and sponsors if necessary.

52. The MRC CFS/ME Research Advisory Group has been mindful throughout the development of the research strategy for CFS/ME of the importance of following existing guidance and approval systems in research. The MRC, amongst others, has published a number of relevant guidance documents, to which researchers should refer (e.g. MRC Ethics Series *Human Tissue and Biological Samples for Use in Research, Good Clinical Practice in Clinical Trials*). It is the responsibility of all researchers to ensure that any research they wish to undertake has obtained the relevant ethical approvals.

53. The MRC CFS/ME Research Advisory Group acknowledges the importance of understanding the international research effort for CFS/ME, in order to optimise the likely success of any research strategy. There are substantial programmes of research currently underway in other countries, such as the United States of America, Australia, and a number of European countries.

The Research Advisory Group was grateful for the information provided by the US Center for Disease Control about its current research programmes. It will be important that researchers and funders take an international perspective when considering the funding of specific research proposals.

54. **Research and Refinement of Case Definition**

55. *Improved definition of the phenotypes of potential subgroups that may come under the CFS/ME spectrum, and overlaps with other conditions, will underpin research on causes and mechanisms. Accuracy and consistency of case definition and diagnosis is a crucial issue both for services and for research. Improvements will help researchers compare different studies with each other and across time. Further research is needed to develop and evaluate the tools for case definition. The lack of validated biological markers for CFS/ME has further hampered diagnosis.*

56. Case definition is fundamental for the assessment, frequency, causes, outcomes and management of any disease or illness. The development and validation of instruments for use in research and in services is currently a key area for research. Consistency between studies and over time can significantly affect the interpretation of research findings.

57. There is clearly an overlap between the need for case definitions that have utility in the clinical and service context with those specifically designed for research. For this reason a continuing cross-reference between research targeting fundamental questions and that aimed at developing and evaluating tools for services is essential.

58. There is some international consensus on the broad criteria used to identify people with CFS, as demonstrated by the current consensus-based definitions from the US Centers for Disease Control (CDC), currently known as the Fukuda criteria (Fukuda *et al*. 1994). However, questions remain about the interpretation of conditions that fall within these broad criteria. Some consider that this inclusive approach compromises research on specific groups of individuals whose symptoms are considered to be predominantly neurological, as indicated in the Consultation exercise.

59. The MRC CFS/ME Research Advisory Group is aware of the ongoing effort of the CDC, through an International CFS Study Group, to refine the current research case definition of CFS. There have been three meetings of international experts from a wide range of disciplines and perspectives, coordinated by the CDC, in an effort to identify ambiguities in the current CFS case definition and to recommend improvements. We understand that this International CFS Study Group is currently preparing a report for peer-reviewed publication in an academic journal, and we would anticipate that this consensus-derived research case definition will help in the development of well-designed studies. Any new or revised case definition must be subjected to rigorous and objective scientific analysis and testing to demonstrate its usefulness.

60. The MRC CFS/ME Research Advisory Group has noted that there is support

among some sections of the community for the use of the description of M.E. from Ramsay (Ramsay, 1998) to identify and study a discrete population of patients. Whilst acknowledging the potential importance of the identification of subgroups, the Group does not consider that the current descriptive nature of these criteria has sufficient methodological rigour to be used in an epidemiologically robust manner for research. The MRC CFS/ME Research Advisory Group believes that researchers who wish to pursue this approach will need to operationalise the Ramsay criteria and then demonstrate their validity through peer-reviewed publication.

61. The MRC CFS/ME Research Advisory Group considers that case definition is a key area for research, but believes that it is possible that some studies can be undertaken without delay in reaching consensus. The use of broad, but clearly and explicitly defined, inclusion and exclusion criteria should allow subsequent re-appraisal of experimental results in the light of developments in case definition. It would not be possible to identify potential subgroups unless inclusion criteria are broad enough to encompass the necessary heterogeneity.

62. **Developing the Epidemiological Framework**

63. *Epidemiology has a central role in addressing questions about prevalence, incidence and their relation to time, place and person within populations. It is key in formal testing of causal hypotheses, specifically in working out the contributions of environment and genetic influences. Such a framework is also necessary for research on case definition, co-morbidity, natural history and outcome.*

64. Population-based studies that identify affected individuals using active ascertainment and agreed diagnostic criteria have several advantages, including the provision of adequate numbers of affected individuals, identified using a common methodology, to test important hypotheses about causes and to provide unbiased estimates of outcome. The fact that CFS/ME affects the whole age-range, including children, means that such population-based studies will need to have considered the adequacy of case ascertainment across the whole age spectrum.

65. Considerable advances are being made internationally towards identifying candidate genes for a wide variety of disorders. New, large epidemiological studies that include genetic data could allow such advances in CFS/ME to be taken forward fairly rapidly, in the context of a general population sample, to address questions about genes and environment. While there is excitement about these advances, examples from other areas of biomedicine make it clear that to identify genetic susceptibility loci and determine how they interact is a complex task requiring a substantial, multidisciplinary research effort. As with all other genetic studies, precise case definition and phenotypic categorisation of each case is vital, and it may be premature at this stage to undertake large scale genetic studies of CFS/ME until there are clearly agreed and validated diagnostic tools.

66. Large epidemiological studies can contribute well-characterised cohorts for

prospective investigation of longer term outcomes. Such a cohort, of affected people ascertained over a relatively short period of time, is likely to be qualitatively different from health service registers developed for needs assessment and health service planning. However, some overlap may exist where researchers work particularly closely with health services.

67. There is a lack of basic epidemiological evidence to help develop effective prevention strategies and management options for CFS/ME. This may stem from difficulties about definition and diagnosis of CFS/ME, as well as from the historical failure to recognise CFS/ME as an illness. Once these constraints are removed a programme of epidemiological research will become an important priority. Three types of study are needed: descriptive epidemiology, studies of aetiology, and epidemiological studies of characteristics associated with outcome.

68. *Descriptive Epidemiology*

69. Basic descriptive epidemiology of population patterns is required to describe both the incidence and prevalence of CFS/ME, and its duration, nature, and severity, in terms of patient characteristics. Studies should pay particular attention to the duration and nature of the symptoms experienced, especially in terms of whether CFS/ME is a single syndrome or whether there are several distinct sub-groups; the severity of symptoms, especially in terms of the extent and types of disability (physical and cognitive) and pain experienced and the age, sex and ethnicity of patients.

70. The UK is uniquely placed to undertake studies of prevalence and incidence through primary care. Primary care research networks, such as the MRC General Practice Framework, could provide a study population. If studies were undertaken in practices which are linked into computerised practice management systems, incidence could be studied as well as prevalence. Fundamental to such a study would be an agreed research case definition.

71. A linked natural history study might be undertaken based on primary care and using those practices in computer-based networks, relying largely on routine health records. A standardised follow-up of cases identified either from prevalence or incidence studies would be a much larger undertaking but not impossible within primary care networks. An important caveat to be borne in mind is the quality and reliability of computerised health records.

72. *Aetiology*

73. Aetiological studies could be used to identify characteristics of people, their physical, work, and social environments, and health histories associated with the development of CFS/ME by duration, nature and severity of CFS/ME.

These studies would need to follow on from basic research into possible mechanisms of the development of chronic fatigue so that hypotheses about aetiological factors can be clearly formulated (e.g. to environmental factors), and will need to pay particular attention to physical and psychological challenges. Such studies could be conducted as prospective cohort studies

comparing populations exposed and unexposed to putative aetiological agents. However, it is possible that incidence would be too low to make such studies feasible and it may be necessary to consider case-control studies that retrospectively examine exposure.

74. It would be particularly helpful if such studies were designed so that they could answer important outstanding issues around whether neurological and psychological symptoms found in CFS/ME patients are causally related, are consequences of the illness, or a combination of the two.

75. *Outcome Studies*

76. The current evidence indicates that CFS/ME patients exhibit wide variation in the time to recovery, with some seriously affected patients never fully recovering. There is, however, little evidence about which patients recover, or what factors pre-dispose to recovery. Once outcomes have been clearly defined, longitudinal studies of cohorts of CFS/ME patients are needed to try to identify these factors. Very few studies have looked at patterns of recovery, which the MRC CFS/ME Research Advisory Group considers to be a potentially fruitful area of research.

77. Possibilities for research into potential treatments and management strategies are considered in more detail below.

78. **Developing Hypotheses about Pathophysiology**

79. *A wide range and variety of factors have been suggested to play a role in the pathophysiology of CFS/ME, but the evidence is generally either weak or contradictory. Greater methodological rigour and independent replication are crucial in much of this work.*

80. *Many of the observations are interesting and in principle worth investigating. Moreover, potentially modifiable risk factors are possible targets for interventions. A useful start might be made to test such hypotheses in robust but relatively simple research designs, so that the less likely ideas can be put to one side and further effort and investment can focus on the areas that preliminary evidence identifies as more likely to be productive.*

81. In all studies, choices of sampling strategy, case-definition, measures and controls are crucial and a multidisciplinary collaborative approach is likely to be beneficial. Some studies will be amenable to case-control or other epidemiologically- and genetically-sensitive designs, and others to investigation in experimental models.

82. The MRC CFS/ME Research Advisory Group has not undertaken a detailed review of the current level of scientific knowledge on the aetiology or pathogenesis of CFS/ME, as this was not its function. The Group notes that the recent report of a Working Group convened under the auspices of the Royal Australasian College of Physicians (2002) has assessed the strength of evidence for a number of factors in the pathophysiology of CFS, including infections, immunological factors, central nervous system disturbances and a

number of other factors postulated to be involved. In most cases, the evidence base was not large, with information coming from only a few studies, and often conflicting. As a consequence of the lack of consistent evidence, the MRC CFS/ME Research Advisory Group has considered a number of broad thematic areas with regard to research on CFS/ME.

83. It should be emphasised that the research areas discussed below are not the only ones where there is potential for advancing our understanding of the pathogenesis of CFS/ME, but reflect the areas that currently show the most promise. As scientific knowledge increases, other avenues of research may become increasingly attractive.

84. **Infections**

85. *Fatigue, cognitive disability and musculo-skeletal pain are commonly found during the acute phase of many infectious diseases, and generally disappear spontaneously with the emergence of a normal immune response. However, following certain infections, a proportion of patients develop prolonged fatigue. For example, up to 10% of patients with diagnosed infectious mononucleosis (infection with the Epstein-Barr virus, EBV) or Q fever (Coxiella burnetti infection) can develop chronic post-infectious fatigue. However the causes of these chronic responses to infections in a minority of patients are not known.*

86. It is clear that no single infectious cause of CFS/ME has been identified. Although EBV can lead to CFS/ME, in the great majority of cases no infectious cause can be found by routine microbiological investigation. There is reasonably strong evidence that retroviruses and enteroviruses are not causally related to CFS/ME.

87. Infection with the hepatitis C virus (HCV) may lead to fatigue, and treatment of HCV-infected patients with interferon-alpha leads to symptoms indistinguishable from CFS/ME, including fatigue, cognitive dysfunction and pain. Pathophysiological investigation of well-defined conditions such as this may represent a reproducible model for CFS/ME.

88. Many studies that report a causal association between an infection and subsequent CFS/ME have reported the detection of antibodies against the viral or non-viral agent in patients with CFS/ME, and draw the conclusion that such raised levels of antibodies reflect chronic active infection. However healthy individuals may also demonstrate raised antibody levels, many years after the original infection. The Working Group of the Royal College of Australasian Physicians noted that raised titres of antibodies against common viruses are often found, but are not of pathophysiological or diagnostic significance.

89. Recent advances in virology and bacteriology enable the detection and quantification of organisms directly through amplification of their genomes, by the polymerase chain reaction (PCR). PCR technology will provide a more robust methodology than antibody detection for the association of known organisms with CFS/ME within cohort studies.

90. The discovery and gene sequencing of new viruses and application of PCR will allow the investigation of patients with CFS/ME for novel viruses, for example through the use of degenerative primers or differential display PCR.

91. The application of the novel technologies to bacteriology has allowed the identification of non-culturable organisms, for example through the 16S rRNA PCR assay. Assays such as these would allow the exploration of a CFS/ME patient cohort for novel bacterial infection.

92. Advances in genomics brought about through the human genome programme will also allow the investigation of DNA from patients and controls for the expression of novel mRNAs associated with CFS/ME.

93. Application of these new technologies for the investigation of new or known organisms with CFS/ME would be most epidemiologically relevant within a cohort study, where defined patients and controls could be studied.

94. **Neurology**

95. *As the report of the Working Group of the Royal College of Australasian Physicians indicated, there is conflicting evidence for neurological abnormalities in CFS/ME, but good evidence that muscle strength, endurance and recovery are normal. The early reports of inflammation of the brain, spinal cord or muscles have not been confirmed. It should be borne in mind that it is likely that abnormalities may be detected in the neuromuscular system of patients who are severely ill with CFS/ME and possibly immobile, in comparison to healthy controls. However, abnormalities have been demonstrated in individuals who have restricted mobility for other clinical reasons.*

96. Clinical experience would indicate that most patients with CFS/ME have neurological signs that lie within the normal range. The initial reports of inflammation of the brain, spinal cord or muscles have not been confirmed. Imaging studies using computerised tomography or magnetic resonance scans can demonstrate detailed brain structure but do not provide information about brain function. There are reports in the literature of white matter changes but these are variable and non-specific. Furthermore such imaging techniques are prone to misinterpretation if there are subtle differences in brain structure.

97. Functional imaging of various types (magnetic resonance (MR), single photon emission computerised tomography (SPECT) and positron emission tomography (PET)) are relatively new techniques to have been developed. Studies from other conditions have demonstrated the many difficulties in interpreting abnormalities – particularly in determining whether or not such suspected abnormalities are primary or secondary phenomena. It would seem possible that functional imaging might be used in the study of CFS/ME, but such studies are heavily reliant upon clearly defined, homogeneous groups of participants who are investigated in a consistent manner, with appropriate controls (and not just healthy volunteers).

98. At present, it is not clear that performing invasive, and hence potentially dangerous, tests such as obtaining cerebrospinal fluid at lumbar puncture or performing muscle biopsy would be appropriate, unless clinically justified. Therefore any studies that proposed such tests would need to be very carefully considered, as there may be serious ethical dilemmas, especially in the case of children.

99. **Muscle Fatigue and Weakness**

100. Muscle weakness can be defined as the inability to generate the required or expected force output, whilst muscle fatigue can be defined as the inability to maintain the required or expected force output. Problems with the generation or maintenance of force output can occur at any point in the 'chain of contraction command' ranging from the brain to the muscle architecture itself. In terms of muscle weakness problems may occur with electro-mechanical activation (e.g. impaired neuromuscular transmission; impaired excitation contraction coupling), fuel supply (e.g. reduced short term energy stores; impaired energy exchange) and/or the contractile machinery (e.g. smaller muscle cells, fewer muscle cells).

101. Muscle fatigue can be considered in terms of its central or peripheral origin. If the fatigue is centrally mediated, the mechanisms, if not due to problems with motivation, are likely to be due to a failure to sustain the number and/or stimulation frequency of recruited motor units. If peripherally mediated, mechanisms of fatigue can include impaired neuromuscular transmission and/or propagation of the muscle action potential and/or impaired excitation/contraction coupling.

102. Many well-validated scientific techniques now exist to determine at which point in the command chain problems may arise. These techniques in turn enable the elucidation of the mechanisms responsible for the weakness or fatigue, including for example: muscle biopsy, strength testing (voluntary and electrical), electromyography, ultrasonography and magnetic resonance imaging. Many of these techniques have already been employed in the assessment of muscle weakness and fatigue associated with CFS/ME. The general opinion arising from these studies is that there is no physiological basis to the weakness and/or fatigue. These are general assertions however, and at no point has the literature been systematically reviewed to determine the scientific rigor or generalisability of the research findings.

103. A key step with regard to undertaking further research in this area might be to undertake a full systematic review of the literature relating to the assessment of musculo-skeletal weakness and fatigue associated with CFS/ME. Such a review could establish current gaps in the research evidence and could inform recommendations for any further physiological assessments.

104. **Immunology**

105. *There does not seem to be a consensus on the nature and extent of immunological disturbances in CFS/ME, even though there are numerous reports of immunological alterations. There appears to be conflicting evidence*

for a variety of potential immunological factors in the pathophysiology of CFS/ME (such as reduced lymphoctye proliferation and activation status, levels of specific immunoglobulins, or autoimmune conditions). The Report of the Royal Australasian College of Physicians Working Group suggested that the heterogeneity of findings might be explained in terms of variations in methodology and also inadequate consideration of potential confounding variables.

106. Bidirectional interactions between the immune system, inflammatory or infected tissue(s) and the central nervous system (CNS) are now well established, particularly in experimental animal models. Thus systemic or local disease or injury in peripheral tissues activates neural and humoral afferent signals to the CNS. The brain regulates and co-ordinates many aspects of the acute phase response including induction of fever, slow wave sleep, lethargy, loss of appetite and body weight, and modulation of endocrine, immune and cardiovascular systems. Furthermore the brain, previously considered as an "immune privileged organ", can exhibit inflammatory responses which contribute to local and systemic disease. Cytokines are primary mediators and modulators of these responses, and proinflammatory cytokines act in the brain to induce a syndrome known as "sickness behaviour syndrome" which includes reduced motivation and responsiveness, lethargy and loss of appetite (Konsman *et al*., 2002). All of these responses are profoundly influenced by environmental stress, by endocrine status (particularly the activity of the hypothalamic-pituitary-adrenal axis) and by genetic background and gender in experimental animals.

107. Obvious parallels can be drawn between the findings of research on neuroimmune interactions, the CNS response to injury, cytokine neurobiology and CFS/ME. The growing field of psycho-neuro-endocrine-immunology, which seeks to understand the interactions between environmental stresses (including psychological and immune factors) and the immune, endocrine and nervous systems may by of direct relevance to our understanding of some aspects of CFS/ME. Limited data provide some support for the roles of cytokines in CFS/ME, but this is a notoriously difficult area to study because cytokines generally act locally within tissues rather than in circulation (and therefore their concentrations and actions are difficult to access), and exhibit complex and diverse actions.

108. Animal studies in the area of neuroimmunology, particularly in "sickness behaviour syndrome", have potential implications for CFS/ME. It will be important to develop and study chronic, rather than acute, models of "sickness behaviour syndrome", to assess outcomes and influences relevant to CFS/ME (such as objective measures of lethargy, fatigue, and impact of exercise) and to elucidate potential mechanisms and interventions.

109. Clinical neuroimmunological studies are much more difficult to undertake, and measurements of inflammatory mediators (e.g. cytokines) in the blood circulation are likely to be of limited value (see above). However, comparisons of cytokine responses to immune/inflammatory challenges or levels within some tissues can be assessed, and may be compared in patients with varying severity of CFS/ME or after recovery, with healthy controls.

110. Understanding inflammation in the brain has generally been restricted to post mortem studies or analysis of brain tissue or cerebrospinal fluid – techniques which are not readily amenable in CFS/ME patients. However recent developments in PET imaging allow assessment of activated microglia. Analysis of known polymorphisms in the genes of inflammatory mediators, which have been linked to other chronic inflammatory diseases, may be of some value within large epidemiological studies of CFS/ME.

111. **Neuroendocrinology**

112. Several lines of evidence would indicate that there are neuroendocrinological abnormalities found in some CFS/ME patients, although it is unclear whether these are causal or secondary in nature. The reported disturbances in the hypothalamic-pituitary-adrenal (HPA) axis could be due to a number of factors, including disturbance of central neurotransmitters such as serotonin or, more likely, a malfunctioning of the complex relationship between cortisol and these transmitters. The reported abnormalities are dissimilar to those found in patients with major depression, which would indicate that there are different underlying processes for the two conditions. The high degree of comorbidity of CFS/ME and depression would, however, mean that studies in this area are fraught with potential confounds.

113. The interpretation of basal cortisol levels is problematic, and experiences from studies of other conditions have demonstrated many potential pitfalls. However, investigations into disordered functioning of the HPA axis can be undertaken through the use of specific challenge studies, using for example corticotrophin releasing hormone, adrenocorticotrophic hormone or serotonin agonists. However studies to date have provided equivocal data, possibly due to the heterogeneous nature of the patient groups being studied, although methodological problems may also have contributed to the uncertainty.

114. One area where neuroendocrinological studies may prove informative is in the study of circadian rhythms and sleep architecture, both of which are affected by disordered neuroendocrine function. There is currently conflicting evidence of disturbed circadian rhythms in people with CFS/ME, but sleep disruption is a commonly reported symptom of the illness.

115. There have been a small number of studies investigating the potential therapeutic benefit of neuroendocrinological manipulations. However, whilst some studies have shown some promise, the serious side-effects associated with long term use of corticosteroids would indicate that more basic research would be needed to justify their use as a therapeutic agent.

116. **Central Nervous System Function**

117. *Key symptoms of CFS/ME include fatigue, cognitive dysfunction and sleep disturbance, which are associated with disordered functioning of the CNS. It is uncertain whether this disordered functioning is solely a consequence of a primary abnormality in the brain or is mediated by changes in circulating CNS modulators such as hormones and cytokines, or neural afferent signals.*

118. *Limited laboratory studies of people with CFS suggest abnormalities in the function of the hypothalamic-pituitary-adrenal axis and brain monoamine pathways, particularly serotonin. Changes in sleep architecture are also frequent. The abnormalities reported differ clearly from those observed in patients with depressive disorders, though the two conditions commonly coexist.*

119. It is also uncertain whether the various neurobiological changes that have been reported in CFS/ME are involved in the pathophysiology of the disorder or are a consequence of the illness and persistent inactivity. To resolve this important issue, longitudinal studies of people throughout the course of their illness may be required. Such work could be usefully integrated with psychological treatment studies. In this way it should be possible to see if abnormalities are trait or state markers and whether their presence has prognostic significance. Another, potentially quicker, approach would be to carry out cross-sectional studies of people who have made good clinical recoveries from CFS/ME to find evidence of enduring biological “vulnerability” factors.

120. It could also be informative to carry out neurobiological studies of prospectively selected groups of participants who are known to be at high risk of CFS/ME-like symptoms (e.g. those infected with Epstein-Barr virus and patients receiving treatment with interferon for hepatitis). Such an approach may reveal which biological abnormalities appear to be associated with the development of fatigue symptoms and might therefore be involved in their pathophysiology.

121. It will also be important to investigate the brain pathways that underlie the symptoms of CFS/ME. The use of SPECT imaging to study regional cerebral blood flow in CFS has yielded inconsistent results. However specific ligands for PET and SPECT are becoming increasingly available and may allow the delineation of regional neurotransmitter and neurochemical abnormalities. Functional magnetic resonance imaging (fMRI) studies may help elucidate the brain pathways that underpin the cognitive impairments in CFS/ME, in a similar way to that employed in the study of cognitive deficits in mood disorders. These imaging changes might provide clues for the development of novel treatments for the cognitive dysfunction in CFS/ME, as well as a way of monitoring changes in cortical functioning through rehabilitation and clinical improvement.

122. Chronic pain is a widely reported symptom of CFS/ME, but there would appear to be little research into this aspect of the illness. There are a number of potential avenues for research, which could build on the knowledge gained in other chronic conditions such as multiple sclerosis. The use of functional imaging techniques may be especially useful in elucidating the centrally mediated aspects of pain perception.

123. It will also be important to obtain more understanding of the central processes that mediate fatigue in healthy animals and humans. A better knowledge of the neurobiology might yield clues to the pathophysiology of clinical fatigue states and provide new targets for treatment.

124. **Cognitive Performance**

125. *People with CFS/ME not only report difficulties with disabling fatigue but also with cognition. Any studies in cognition must consider a number of key factors in assessing the levels of impairment that are present in the disorder. These factors include the heterogeneity of presentations and levels of severity, the presence of psychiatric factors such as co-morbid mood disorder, as well as possible relationships between brain dysfunction and cognition.*

126. *The majority of studies have shown little change in overall intellectual functioning. There is good evidence of attention and concentration problems in CFS/ME. However, despite reproducible demonstration of some reduction in performance, the specific nature of such deficits has not been identified. In particular the attention dysfunction may be a global non-specific impairment or a specific one relating to selective attention.*

127. The research in this area has tended to involve small samples of patients and a small number of tasks, with few studies involving more than 40 participants per group. Any study attempting to identify subtle deficits will need to include an adequate number of participants. The variability of results in this area may be due to the small numbers in most previous studies.

128. The understanding of memory impairment in CFS/ME is, at present, limited. The effects of suggestibility on the subjective and objective experience of impairment have only recently begun to be investigated.

129. There seems to be a positive relationship between objective measures of cognitive impairment and symptoms of depression in CFS patients. However depression in CFS patients only accounts for a small amount of the variance in the subjective complaints of poor cognitive performance, even when there are no differences between CFS patients and healthy controls.

130. The level of model testing in the area of cognitive impairment in CFS/ME is poor. The variability in the results of studies in this area mirrors that of studies of other symptom areas. It seems highly likely that a number of different variables will affect both objective and subjective cognitive performance. These variables need to be identified and tested with confirmatory, as opposed to exploratory, analyses in studies with sufficiently large sample sizes to prevent statistical errors (both Type I and Type II). It will also be necessary to find objective tests of memory that have some ecological validity.

131. Knowledge of the relevant cognitive factors could contribute to the diagnosis of CFS/ME, a description of the changes that are seen over time as the disorder develops (in the same way that they are used in Alzheimer's disease), and to the description of the impact of CFS/ME on functioning.

132. Cognitive factors could also be used as outcome measures for trials of interventions. There is a need for agreement about how such measurements should be made. CFS/ME patients report problems with everyday cognitive tasks, but are tested on laboratory tasks of specific list learning or dual

tasking. These tasks do not take into account the lengthy practice that provides the pattern or strategy for performance in everyday tasks. The mismatch of what people thought they should be able to do and their actual subjective assessment of their current performance also needs to be measured.

133. It is clear that the cognitive dysfunctions in CFS/ME cannot be entirely explained by mood variations. It should be noted that, even when cognitive capacity is intact, cognitive performance may be affected by factors such as arousal, mood, and strategy use.

134. **Psychological factors**

135. *The presentation, symptoms and effects on functioning of all illnesses, both physical and psychiatric, are affected by a variety of factors including personality factors, coping mechanisms and social support. For example even when it is possible to measure the scope of a disability with a physical cause, (e.g. arthritis) the effects on quality of life can differ between individuals depending on non-illness specific factors. The same will be true of CFS/ME, irrespective of any causal mechanism.*

136. Several studies have suggested that personality factors may differ between those with CFS and other disorders but the available evidence is equivocal. A prospectively designed study could allow the differentiation of the interplay between biological and psychological factors which may influence not only the maintenance of the disorder, but also possible types of intervention that might be developed. Definitions of CFS/ME that include co-morbid psychiatric problems may produce confusing evidence of the role of personality factors. Future studies to test hypothesised models of the relationship between biological and psychological factors must consider this potentially confounding variable carefully.

137. A key problem when considering CFS/ME is that it is not clear when psychological factors might play a part. Given that the co-morbidity of CFS/ME with depression may be as high as 50%, it is often concluded that it is integral to the disorder rather than a response to it. However there a few studies that have addressed this issue directly. The studies have often recruited participants from secondary care, who are therefore generally at the more severe end of the spectrum of severity. It is, at present, not clear whether a broader population of CFS/ME patients would allow a clearer understanding of the influence of psychological factors.

138. **INTERVENTIONS**

139. *The Chief Medical Officer's Independent Working Group, in considering therapeutic interventions, drew on a specifically commissioned systematic review of management strategies undertaken by the NHS Centre for Reviews and Dissemination (Whiting et al., 2001). The systematic review identified 350 studies that were considered relevant, but only 43 of these met the inclusion criteria. Within these 43 studies, 14 different diagnostic criteria were used to characterise participants, with 31 different interventions being tested*

using 39 different outcome measures with 203 outcomes evaluated. Two specific strategies were identified which potentially may be beneficial for CFS/ME, graded exercise therapy (GET) and cognitive behavioural therapy (CBT) techniques. These strategies have been tested individually, together and in treatments that incorporate numerous different treatment approaches including adjunctive pharmacotherapy (Whiting et al., 2001; Mulrow et al., 2001).

140. *The MRC CFS/ME Research Advisory Group has not considered in detail the information included in the systematic review, but chosen instead to consider how the evidence-base for potentially effective management options can be strengthened.*

141. The MRC CFS/ME Research Advisory Group considers that there are a number of important steps to advance the evaluation of potential management strategies or treatments for CFS/ME. There should be agreement on a case definition and a classification of severity and any other relevant characteristics which define subgroups (such as specific symptoms or co-morbidities). This step is fundamental to any epidemiological study, including clinical trials.

142. A definition of a clinically important improvement in disease status, with a classification of the degree of improvement, is essential for natural history and intervention studies. Thus the validation of a range of outcome measures, and associated changes, is a key step. A review of the many measures used to date and some pilot work to develop a package of a small number of existing outcome measures (which have already been tested for validity and reliability) to be widely adopted would be an important step forward.

143. A careful review of studies which have shown positive differences between treatments and those which have not (testing the same treatments) could be useful to understand the reasons for the differences (e.g. outcome measures, details of interventions or chance), as most differences are small.

144. **Clinical trials of interventions**

145. All new potential interventions, including complex packages of care, should ideally first be evaluated in small studies using markers of disease activity to decide whether to proceed to larger trials. The difficulties in defining objective outcome measures means that such studies may have positive results even with ineffective interventions. Alternatively, interventions with only a modest benefit might be rejected.

146. The Medical Research Council has previously considered the challenging area of the development and evaluation of complex packages of care, and produced a guidance document for investigators, *A Framework for Development and Evaluation of RCTs for Complex Interventions in Health* (2001). The MRC CFS/ME Research Advisory Group would strongly recommend that researchers consider the guidance contained within that document, which provides detailed discussion of many salient points.

147. Fundamental to all considerations about intervention studies is the need for outcome measures which are:-

- as objective as possible (this does not mean that patients' perceptions of improvement are not important but relates to the difficulties in truly blinding interventions);

- sensitive to clinically relevant changes (spontaneous or intervention–related);

- consistent;

- represent different aspects of the syndrome;

- if appropriate, have a clinically relevant grading system;

- can be documented and consistently applied; and

- limited in number (one or a small number of primary outcomes).

148. The MRC CFS/ME Research Advisory Group considers that every attempt should be made to reduce potential bias in clinical trials (e.g. by use of randomisation and blinding). The attraction of cross-over designs needs to be weighed against the problem of blinding, which is even more difficult within individual patients. Factorial designs may be valuable to assess more than one intervention but the possibilities of interactions must be kept in mind.

149. For each trial the balance between broad eligibility criteria with consequent generalisability and selection of subgroups most likely to respond to a specific intervention must be considered. The need to assess a promising intervention in all types of patients must be balanced against the demonstration of 'proof of concept' in a well-defined group. The latter may be the first stage before extending to a broader group. People who cannot attend clinics should not be excluded, and efforts should be made to allow the most severely ill to participate.

150. It is appropriate to explore potential interventions in the absence of knowledge of causation or pathogenesis. The need to adequately define and document complex interventions so that they can be replicated accurately is crucial. The duration of the intervention should be adequate to achieve benefit and the follow-up after the intervention should be long enough to determine if the effect is sustained.

151. All trials should be large enough to have reasonable power to detect a clinically useful effect in the primary outcome. The need to have more than one trial to reliably assess risks and benefits is even greater in these circumstances, with added benefits of being able to combine the results later.

152. The importance of following up all the participants, even if they withdraw from treatment and of undertaking an intention to treat analysis on as complete a population as possible cannot be emphasised too strongly. The problems of

interpretation associated with other techniques such as excluding withdrawals, “on treatment” analyses and “last observation carried forward” which may over-estimate treatment effects are well-known.

153. The problems with most of the trials to date, as described in the review from Whiting *et al.* (2001) is that very few fulfil all of these criteria. The MRC CFS/ME Research Advisory Group believe that researchers should consider from the outset the comprehensive reporting required of any intervention study, to allow others to understand the design, conduct, analysis and interpretation of that study. The use of the CONSORT recommendations (Moher et al., 2001) should allow others in the field to assess the validity of the results, and will facilitate systematic reviews and meta-analyses.

154. *Musculo-skeletal-Based Interventions*

155. There is considerable confusion and disagreement surrounding the optimum approach to the rehabilitation of people with CFS/ME. It has been suggested that the greater the fatigability and disability and the longer the illness duration for an individual, the stronger the associations with a psychological component to the process (Royal Colleges of Physicians, Psychiatrists and General Practitioners, 1996). It is not clear whether the psychological component is a result of the CFS/ME, or vice versa, or indeed whether there is a mixture of the two. There are parallels to be drawn between patients with CFS/ME and patients with chronic low back pain of non-specific origin. These patients are severely disabled, frequently depressed and are wary of participating in a rehabilitation programme in case it exacerbates their back pain.

156. Despite the assertion from the CMO’s Independent Working Group that patients with CFS/ME are no less fit than sedentary people, they themselves recognise that prolonged inactivity leads to muscle wasting. This inactivity results in a decline into a “vicious spiral of immobility”. It is very difficult to break into this downward cycle and the key to any effective rehabilitation programme should be to support the patient through this process.

157. The CMO’s Independent Working Group agreed that rehabilitation is important but it should be graded, tailored to the individuals’ own needs and must recognise that the whole process invariably needs to start from a low baseline. Despite the recommendation that this is the best way forwards, patients remain sceptical, as many believe the graded exercise approach makes them worse. Any research into rehabilitation must take into account these concerns and establish why some people experience a deterioration whilst others find the process beneficial.

158. The MRC CFS/ME Research Advisory Group believe that it likely that an integrated package of care will be the most beneficial in the management of CFS/ME, as has been shown for other chronic illnesses and conditions. Graded exercise and cognitive behavioural therapy could be considered in isolation but the existing literature from research on both ME/CFS and chronic low back pain would suggest this would not provide optimal benefits.

159. The multi-disciplinary, holistic ”back school” approach is an example of a complex package of care that has proved extremely effective for those patients with chronic intractable back pain for whom no other approach has been effective (Nielson & Weir, 2001). This approach incorporates for example: graded exercise, cognitive behavioural theory, pain management and relaxation therapy. There is obvious merit in drawing upon other well researched areas when developing and evaluating packages of care for CFS/ME.

160. It will be important to understand why some people with CFS/ME experience a deterioration when participating in an exercise approach to treatment. The wealth of experience from the back pain literature should be drawn upon when addressing how “graded” should graded exercise be and how the optimum progression points in treatment should be determined.

161. The report of the CMO’s Independent Working Group highlighted the support by some patients for “pacing” as a management strategy, which was also evident from the responses received as part of the consultation process during the development of this research strategy. At present there is no empirical evidence of efficacy for “pacing”, which should come from randomised controlled trials.

162. *Psychologically-Based Interventions for CFS/ME*

163. Evidence on the effectiveness of treatments needs to take into account the specific outcomes that are being measured which may change at differing rates. Various outcomes have been suggested for the evaluation of psychological interventions, not all of which are psychologically assessed. For example, primary outcome measurement of anxiety and depression may be early results of psychological treatments that may be expected to be observable as soon as therapy has ended. In contrast to these proximal results, quality of life and use of resources may be later changes which cannot be measured for some time after therapy has discontinued or will only become apparent following specific levels of changes in other factors such as subjective assessments of fatigue or cognitive changes.

164. CBT encompasses a variety of different therapeutic techniques. The general principle of CBT techniques begin with the engagement of the person in a shared goal and after a number of sessions the identification of a model of the development and maintenance of the problem which will include psychological, biological and social variables. The next part of therapy is to help the person identify any possible barriers to the attainment of a goal. The technique is essentially the same when CBT is used in health psychology to improve outcomes for people with physical illness as it is in the treatment of specific psychiatric disorders.

165. The recent systematic review (Whiting *et al.*) concluded that CBT and GET therapies were effective. Treatments that lasted a longer time (more than 20 weeks) seemed to have been more successful than those providing brief therapy. There is some concern about drop out from treatment and this needs to be investigated in more detail in new trials.

166. Many of the intervention studies using CBT and GET for CFS have been focussed on the effects of therapy on people who have attended outpatient clinics. This is likely to be a subset of the people who have a diagnosis of CFS and will miss both the more severe cases as well as the least severe and least chronic. Further research should concentrate on the effects of these interventions across the spectrum of the disorder. Larger scale trials would also allow the intervention to be assessed in a targeted way, to allow consideration of possible factors that may affect the outcome of therapy e.g. significant cognitive difficulties in attention and concentration. It may also be useful to consider specific biological outcomes such as functional brain imaging in parallel.

167. *Other Interventions*

168. There are many pharmacological, behavioural or complementary therapy interventions that have been proposed for CFS/ME, but for which the evidence of efficacy is lacking (Whiting *et al*., 2001; Mulrow *et al*., 2001), and in some cases there is no underpinning theoretical scientific rationale. The MRC CFS/ME Research Advisory Group considers that, in the absence of knowledge of causation or pathogenesis it can still be appropriate to explore potential interventions. However, any such study must apply the same methodological rigour as more conventional therapies.

169. **HEALTH SERVICES RESEARCH**

170. *Health Services Research (HSR) is used both to help guide evaluative research into the cost-effectiveness of management strategies and to evaluate the cost-effectiveness of ways of organising and delivering effective care. The former research combines descriptive HSR and Health Care Needs Assessment, and the latter Health Technology Assessment and Service Delivery Organisation research.*

171. One difficulty in identifying priorities for HSR in CFS/ME at the current time is that basic information on the epidemiology of CFS/ME and clinically effective treatments is lacking. For example it is not known which groups, or subgroups, of patients might benefit from any particular treatment and hence health care needs assessments would be premature. The rigorous evaluation of service delivery models cannot be undertaken until it is clear what services should be delivered. However, once fundamental research into the definition, diagnosis, epidemiology, outcomes, and effective management strategies for CFS/ME begin to clarify the evidence, then HSR will become increasingly important.

172. *Health Care Needs Assessment*

173. Descriptive population-based studies are needed to quantify the incidence and prevalence of CFS/ME in terms of characteristics which identify groups of patients that could benefit from different types of management. For example, age (particularly distinguishing children and adults), gender, and duration, severity and nature of symptoms might all affect management options. This

research could be combined with epidemiological research into factors associated with the incidence of CFS/ME. In either case the key methodological issue is the need for population-based studies.

174. *Descriptive Health Services Research*

175. Descriptive health services research should allow greater understanding of the services that are in place at present to deliver care. As with other chronic illnesses, there are important issues concerning how these services are distributed and accessed. Furthermore, it will be important to understand whether access to these services is equal or does it reflect frequently observed patterns of socio-economic inequality. Variations in patterns of care and service provision can often be helpful in identifying areas of need for evaluative research since they suggest uncertainty around best practice.

176. *Health Technology Assessment*

177. Health Technology Assessment considers the effectiveness, appropriateness and cost of health "technologies", which can be any method used by those working in the health services to promote health, prevent and treat disease and improve rehabilitation and long term care. As well as studies of clinical effectiveness, it is important that the success of management options for CFS/ME are evaluated in practical, real-world settings and that a broad range of consequences are understood. These consequences include acceptability, costs, effects on carers and families, and training, education and workload for health service professionals. As well as being pragmatic it is important that such evaluative research should investigate any variation in costeffectiveness between sub-groups of patients for which different management strategies might have different effects. The MRC CFS/ME Research Advisory Group considers that such studies should utilise pragmatic randomised controlled trial methodology if possible.

178. *Service Delivery and Organisation*

179. Current evidence suggests that CFS/ME patients receive care from a wide variety of different services based in different settings, and from health care professionals with different training. The issue of service provision was not considered by the MRC CFS/ME Research Advisory Group. Service delivery and organisation research is concerned with understanding which service model is most cost-effective from the perspective of patients, their families and carers, the Health Services, and others. Key questions surround the training and education that doctors and nurses should receive in the care of CFS/ME, and how services staffed by appropriately trained professionals should be organised, and accessed. It would be particularly important to understand whether management of CFS/ME should be part of general services, or should be provided in specialist centres by appropriately trained specialists, and if the latter how should these specialist centres themselves be organised, administered, and located.

180. Appropriately designed trials of these 'complex interventions' should include research from the patient perspective around issues of acceptability and accessibility.

181. **RESEARCH CAPACITY AND THE INTERFACE WITH SERVICES**

182. *Researchers, funders and service providers need to consider how best to achieve strategic, integrated research alliances both to sustain excellence and to develop new areas of enquiry, and to ensure the availability of sufficient and appropriately skilled manpower at the research-service interface.*

183. *Strengthening Research Capacity*

184. There may be a need for specific measures to promote multidisciplinary collaboration around shared strategic goals, including allied health professionals. Such collaboration offers established centres of excellence the kind of new scientific opportunities that are essential if they are to sustain their competitiveness internationally. In relation to emerging or currently fragmented national effort, such collaboration can provide access to crucial partners and expertise. The MRC CFS/ME Research Advisory Group is conscious of the need to attract high quality researchers, from both basic scientific and clinical disciplines, to undertake research in CFS/ME.

185. Large-scale prospective epidemiological and genetic studies would require high quality, trained and motivated clinical and basic science researchers to be based in a number of UK centres that combine service and research.

186. *Nurturing the Research – Service Interface*

187. The links between research and services need to be strong in order to recruit and gain access to participants. Consequently, much research needs to work through service providers. In this respect, the National Health Service provides the UK with significant opportunities. As discussed above, the most severely affected often experience difficulties in accessing services, and particular efforts should be made to include this patient group.

188. **THE VALUE OF LAY PARTICIPATION**

189. The participation of affected individuals and their carers, researchers with experience of patient support, and advocacy groups has enriched the process of developing a research strategy for CFS/ME. However, the above stakeholders have indicated that there are also broader issues, which, although outside the terms of reference of this research strategy, are important and to which research could make a significant contribution.

190. Further partnerships are likely to be of benefit by providing researchers and funders with access to user perspectives, and lay organisations with access to scientific expertise. Specifically, aspects of patient and carer experience can help scientists better frame their research questions and to work towards outcomes that are more relevant to the intended beneficiaries.

191. In principle, there are important two-way benefits in the active involvement of consumers in the research process. In the case of the development of a CFS/ME research strategy, there has already been a high level of

involvement and a range of diverse views expressed, particularly at the strategic level. This diversity does present some difficulties as it will not be possible to achieve the approval of all concerned.

192. Consumers can participate in research at the strategic level by being involved in setting the research agenda, and also during the research process within a particular study.

193. *Research agenda*

194. Consumers have been closely involved in the development of this research strategy, both by major inputs at the start of the process, and also during the deliberations of the group. Representatives of the MRC Consumer Liaison Group are members of the MRC CFS/ME Research Advisory Group and have met with consumers groups to access their views. In addition, a survey of priorities for research was undertaken and independently analysed by the NHS Public Health Resource Unit (Annex 2). *Consumers have also involved in the consultation about a preliminary draft of this document (Annex 3). – delete from consultation document.*

195. *Within specific research studies*

196. Consumers have the potential to be involved at every stage of the research process, and there have been studies exploring the extent and perceived effects of such involvement. By being involved at the earliest stages, consumers of research can play important roles in the design of a study and can ensure that multiple perspectives are taken into account. Consumers can then often liaise with broader groups with which they are associated to ensure that the perspectives can include a wider constituency. This liaison can also be beneficial in publicising the studies so that a wider group can be aware of the issues around participating in, for example, a clinical trial. By being involved in a research project, consumers can also have an important role in interpreting the study findings and ensuring that these are widely disseminated (and implemented) throughout the relevant constituencies. This involvement could feed back into considering what further research might be needed.

197. The MRC CFS/ME Research Advisory Group believes that patient organisations and support groups can play an important role in involving participants in research. The severely ill, who sometimes experience difficulties in accessing care, have not been adequately represented in research studies. Patient organisations who represent and are in contact with severely ill people with CFS/ME should work in partnership with researchers to identify potential participants, including alerting their constituents to current projects.

198. **CONCLUSIONS AND RECOMMENDATIONS**

199. The MRC CFS/ME Research Advisory Group fully endorses the conclusions of the Report of the CMO's Independent Working Group, namely that CFS/ME is a real, serious and debilitating condition, and that research into all aspects of

CFS/ME is needed.

200. In considering ways to advance research on CFS/ME, the Group has focused on a number of strategic themes: case definition, an epidemiological framework, pathophysiology, interventions, health service research, research capacity and the value of lay participation.

201. The MRC CFS/ME Research Advisory Group has not provided a detailed plan for the science, nor set out an agenda of the many research projects that might merit support. A strategy is proposed which reflects the current state of knowledge in CFS/ME, and which aims to provide a rational framework for advancing the understanding of the illness and to reduce suffering.

202. The MRC CFS/ME Research Advisory Group considers there should be an agreed standardised case definition and a classification of severity and any other relevant characteristics that define subgroups. A definition of a clinically important improvement in disease status, with a classification of the degree of improvement, is essential for natural history and intervention studies. Thus the validation of a range of outcome measures, and associated changes, is a key step.

203. Much of the basic research on the causes and aetiology of CFS/ME will be long term in nature. New and important findings will emerge, from the current UK and international research effort, and these too should inform longer term research and funding strategies.

204. It is essential that the researcher–funder-lay partnership is nurtured, to ensure that the best evidence is easily available to all, and to facilitate the growth of consumer involvement in the design, conduct and dissemination of research - as a means to enhancing its quality, relevance, and credibility.

205. In the short term, the MRC CFS/ME Research Advisory Group consider that the research community should be encouraged to develop high quality research proposals for funding that address key issues for CFS/ME research that are amenable for study at the present time:

- case-definition;
- understanding symptomology; and
- new approaches to management.

206. In view of the probable multiplicity of causal factors and the widely disparate findings so far reported, the MRC CFS/ME Research Advisory Group considers that studies investigating potential causal pathways and mechanisms, whilst having merit, would not have the same immediate impact on increasing understanding of CFS/ME, nor reducing the suffering of patients.

207. The MRC CFS/ME Research Advisory Group recommends that research studies should aim to be as inclusive as possible in terms of the recruitment of

participants, and due consideration should be given to sample size to allow for possible subgroup effects. There should be clearly stated inclusion and exclusion criteria, with detailed justification if certain types of patients are not included, with every effort being made to include the severely ill.

208. Randomised controlled trials of adequate size, using standardised case definitions, eligibility criteria, and baseline and outcome assessments, could be used to evaluate one or more of the interventions which have been shown in one or more trials to have a benefit. Smaller trials could be undertaken to study new potential approaches to management or treatment.

Standardisation of entry criteria, case definitions and outcome measures will allow results to be more widely generalised and compared between studies.

209. Given the present difficulties in identifying priorities for HSR in CFS/ME outlined above, it is not clear whether it is appropriate to make HSR a priority at this time. However, once fundamental research into the definition, diagnosis, epidemiology, outcomes, and effective management strategies for CFS/ME begin to clarify the evidence, then HSR will become increasingly important.

210. The MRC CFS/ME Research Advisory Group considers that there is a key role for patient organisations to help attract participants to research, especially the severely ill, and to help in the dissemination of research results.

211. Findings need to be subjected to rigorous and objective scientific analysis and published in high quality, peer reviewed journals. The Group considered it important that research results should be disseminated to avoid unnecessary repetition of studies and the inefficient use of resources. There may be a need for funders and sponsors of research to investigate additional alternative mechanisms of dissemination, preferably involving an independent peer review mechanism to provide scientific credibility to the results.

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Annex 1

Membership of MRC CFS/ME Research Advisory Group

		Affiliation	Area of expertise
Chair	Professor Nancy Rothwell	University of Manchester	Neuroinflammation

Members	Jacqueline Apperley	MRC Consumer Liaison Group	*Lay member*
	Professor Philip Cowen	University of Oxford	Psychopharmacology
	Professor Janet Darbyshire	MRC Clinical Trials Unit	Clinical Trials
	Professor Diana Elbourne	London School of Hygiene and Tropical Medicine and Institute of Education	Epidemiology
	Sue Haselhurst	MRC Consumer Liaison Group	*Lay member*
	Professor Alan McGregor	Guys, Kings and St Thomas's Medical School	Immunology/ endocrinology
	Professor Jon Nicholl	University of Sheffield	Health Services Research
	Professor Jackie Oldham	University of Manchester	Muscle physiology
	Dr Chris Verity	Addenbrooke's hospital	Paediatric neurology
	Professor Jonathan Weber	Imperial College School of Medicine	Infections
	Professor Til Wykes	Institute of Psychiatry	Psychological Medicine

Annex 2

Public Health Resource Unit

Summary Report on Medical Research Council CFS/ME Consultation Questionnaire November 2002

In brief…

To be honest, there is no single area of research that could currently claim to provide a "strong research evidence base" for understanding CFS/ME. There are fragments of information and partial data sets, separated by large tracts of ignorance. The gaps are usually filled by enthusiastically held hypotheses that have yet to be evaluated or falsified. There is a wealth of unanalysed and unpublished data held by clinicians and patients which could be seen as a research base that could and should be tapped in, at the least, a hypothesis-generating way (charity representative)

I regard all of these [areas for research] as of equal importance. In my view they should all be approached in a co-ordinated manner and with equal vigour. If we concentrate on only one or two, we are in danger of perpetuating problems of the past. (person with).

We need to understand the patient's story and the infinitely changing pattern that CFS/ME may adopt in any individual. As a consequence, the research teams will need to combine the extremes of narrative medicine with good quality genetic engineers (researcher/clinician).

Kate Saffin
Annette Hackett
Adele Wright

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Introduction & method

As part of the consultation process to inform the MRC CFS/ME research strategy advisory group the Public Health Resource Unit (www. phru.org.uk).were asked to analyse the consultation qustionnaire. This report is a summary of the analysis. People with CFS/ME (both current and recovered), carers, charity representatives, researchers, clinicians and specialists were offered the opportunity to give their views via a postal and web based questionnaire.

Response rates

In total 187 responses were received. The majority (131, 70%) were received electronically. The respondents are a self selected group rather than statistically representative of any perspective or group. In addition the high rate of electronic responses means that the majority have access to both a computer and the Internet. It is likely that people with CFS/ME who are disadvantaged because they are severely affected, isolated or undiagnosed may be underepresented in the responses.

Half the respondents were people with CFS/ME (35%) or recovered (5%) from CFS/ME or a carer (10%). A quarter were researchers (22%). Most researchers also described themselves as clinicians. There is some overlap between categories of perspective with a number of respondents classifying themselves as belonging to more than one group.

Results

The broad themes that emerged were:

- Understandings of CFS/ME

- Issues in communication
- Gaps in the research
- Barriers & obstacles to improving research
- The important areas for research
- Moving forward, making a research strategy work

Understandings of CFS/ME

- There is a wide range of understandings and meanings for each of the terms. For some, one exists but not the other; for others, one is a sub-set of the other. Some feel there are precise criteria, for others no criterion currently in existence means anything useful, perhaps even damaging understanding. Some feel it is a single entity, others that there is a range of sub-groups. Overall, there is no agreement where the boundaries between groups fall.

- There are many shades of opinion and they provide the first evidence of the considerable tensions and frustrations that are currently shaping not only the research, but the management and treatment of people with CFS/ME.

All of which loses sight of the fact that for people with CFS/ME "none of the definitions match up to how it feels to have the illness (person with)

Communication issues

In this area there is a clear division between those with personal experience of the illness and the researcher/clinicians.

People with experience of CFS/ME:

- have encountered endless disbelief, unhelpful interventions and unsupportive health professionals.
- have little faith in the system and see little point in research.
- in particular they criticise what they see as a dominance by psychiatry of research in the area.

The researcher/clinicians who responded are probably among the most committed clinicians and researchers to be found and they recognise:

- that the lack of trust that has developed is a major problem
- that the lack of consensus about diagnosis and treatment hinders progress

However, some also feel:

- frustrated and under attack from patient organisations

- a reluctance to engage in an area where there are "*with such powerful views from some support groups with aggressive stance towards clinicians*" *(researcher/clinician)*

Gaps in research

There are three broad areas.

1. Defining the condition and the research agenda

- There appears to be no agreed starting point – in defining or agreeing understandings.

- In particular there is a need to find a cause, to understand better the condition.

- Many see the potential physical causes as neglected in favour of psychiatric research.

2. Specific gaps in knowledge

- Aetiology, epidemiology and prevalence.

- Physical cause including infection, especially viral.

- Presentation and management in primary care

- Physical effects and impact (with particular mention of adolescents and children)

3. The organisation & process of research

- There has been little structure or planning in research in the field

- There have been no long term studies

- Where research is happening there is little or no co-ordination between researchers or teams.

- There has been little patient involvement, especially those who are severely affected and very isolated.

Very little sufferer input - this is the first time in ten years that I have been approached regarding research (person with).

Important areas for research

The identified areas spanned an enormous range from the potential biological, biochemical, or genetic causes, to exploring the experience of people with CFS/ME

to better understanding the complex factors influencing the course of the condition. A detailed summary of the suggestions grouped by: finding the cause, what it does to the body and the person, treatment & management and finding a cure can be found at the Appendix.

Obstacles

- Funding & resources - One of the commonest topics with a total of 364 references from 135 people, thus 72% of respondents mention it at least once. Resources include funding, time and expertise.

- The low status of research in this area. Respondents perceive a lack of political will to support work in this area, 'limited interest from serious academic researchers'. They feel it is difficult to get work on physical causes accepted and published.

- Some feel that young researchers are discouraged, other areas such as cancer and heart disease are 'more appealing' politically.

- As a condition it is complex and affects people in a wide range of ways that span existing service boundaries. No one service 'claims' it.

- There seems to be general agreement that not enough is known about who has CFS/ME, where they are, what their experiences/symptoms/needs are. There is no baseline.

- Recruitment & exclusions. There is concern that criteria for inclusion in studies are not uniform so comparison is difficult. The current diagnostic criteria of symptoms for more than six months means that a potentially valuable group are never included in studies (if the cause is an infection or virus it is unlikely that there will be any trace of it by six months later). Finally those who are severely affected and housebound may be excluded because they do not attend outpatient departments.

- The dominance of psychiatric research. This was primarily a concern of those with CFS/ME but not exclusively. Some go as far as to say that they consider that psychology and psychiatry have no place in the research strategy at all:

…we refuse to accept the validity of any research funded by or carried out by psychiatrists who have no place researching this disease other than to mitigate the distress it causes (whilst in fact they do the opposite). Any attempt to produce strategies based on information provided by psychiatrists will be met by heavy resistance from the "severely affected" patient community. (person with 081302)

Whilst this is understandable given their experiences, it is in conflict with the view that this condition needs and deserves a comprehensive research programme.

- The boundaries - between clinicians, between clinician and researcher, between researchers and between patients and health professionals.

- The lack of suitable tools eg measures of fatigue, with criticism about the validity

of existing ones. People with CFS/ME point out that their level of energy/fatigue change markedly over a day or days and that current snapshot measures are inadequate.

Moving forward

In the short term (3yrs)

- Implement the CMO report recommendations and create a programme of good quality, comprehensive research.

- Improved management and symptom control

- Agree definitions

In the longer term (5yrs)

Most people with CFS/ME would like to see a cure within five years. However, there is also a sense of realism that the search will continue.

The key issues raised were:

- Resources - getting funding and directing it in the right way.

- Commitment to the strategy and process from everyone involved. The notion of commitment is expressed as listening, belief in, trust, and for one researcher – "*dissolving artificial boundaries*".

- More co-operation and collaboration - involving everyone with an interest: from people with experience of the condition (including those who are severely ill), through the clinicians, and other providers of care and treatment (including complementary therapists) to researchers and the academic scientists whose focus is cell biology or genetics.

Get the politics out of this illness. An open-minded approach firstly, especially amongst the medical and scientific community A commitment to funding. Talking to patients and their caregivers at all times. Involving the charities active in this field (researcher/ person recovered/clinician)

- The process needs to be led and many call on the MRC to provide strong leadership, including the facilitation of better collaboration. One researcher raised the issue of job insecurity, that few researchers have a contract beyond their current project and need constantly to be seeking funding.

- Most would like to see a managing body of some sort co-ordinating and disseminating findings. However, there are some tensions in who should provide this co-ordination Some suggested this might be a specialised centre or an academic department with others saying that it should be led by organisations representing people with CFS/ME. This body (however organised) would create national and international networks, co-ordinate research and disseminate findings. One respondent suggested a centre for research that would include

facilities for the severely ill to be included as in-patients so that they could take part in studies/trials.

- The calls for a good baseline survey and review are repeated throughout this section.

- 'Keep an open mind' is said by a number of respondents – although said mostly by people with CFS/ME of clinicians it is an essential activity by everyone involved if the strategy is to progress.

- Getting the priorities right. For many this means a shift to biological, biomedical research

- An open debate and opportunities to negotiate meanings & definitions as well as challenge the contradictions that currently exist.

- Finally, whilst not strictly speaking the remit of this strategy development process, many raised the importance of education, not just in terms of improving diagnosis, treatment and management but in raising awareness and recruiting future researchers.

Conclusion

Overall, many with CFS/ME feel unheard and many researchers feel under attack. Many see the development of a strategy as an opportunity to improve communication and make a real difference to the lives of those with CFS/ME

A number commented that the consultation exercise was a positive one and that it was the first time anyone had asked them for their views.

I don't know anything about research strategies, but I know that one is vitally important because so little is known about the illness (person with)

PHRU
November 2002

Appendix: Important areas for research

One respondent with CFS/ME made a succinct list that provides a framework from the point of view of the person with CFS/ME rather than the clinician.

1) Finding the cause of the illness.
2) What it does to the body.
3) Medication and treatment.
4) A cure please

Finding the cause.

The identified areas spanned an enormous range from the biological, biochemical,

genetic, to exploring the experience of people with CFS/ME to better understand the complex factors influencing the course of the condition.

Approach Examples

Cell biology Cell biology, cell metabolism, chemical abnormalities
Genetics Genetic association studies with carefully defined phenotype, Incidence in closed communities and families, genetic predisposition, molecular pathogenesis of CFS/ME in immune cells,

Environmental

factors/influences

Impact of everyday additives, toxins and chemicals, organophosphates, stress, mercury used in dental treatment, vaccines, food or chemical sensitivities, toxins from metals, diet, mineral deficiencies, Virology/infection Is there a viral cause? Infections e.g. herpes/cocksackie, a family of infective agents yet to be identified (as H Pylori), serology, Cytokine regulation and fatigue following viral infection,

Epidemiology Looking at common factors, why some people develop it following infections, the complexity of the conditions, long-term studies to follow up populations with CFS/ME, demographic patterns, identifying sub-groups, large scale surveys, defining the boundaries of CFS, prevalence studies,

Diagnosis Criteria, triggers, include those with early symptoms, use of imaging, reliable tests,

Other Similarities to Gulf War syndrome or other medically unexplained syndromes – chronic pain, irritable bowel syndrome.

Narrative patient histories (esp. re the changing nature of the condition day to day), illness career, illness beliefs, how do sufferers talk about their condition? How is it constructed by sufferers and by 'experts' and to what effect?

Definition Unpack the wide and insensitive construct CDC-1994 CFS, defining outcome measures, aetiology,

What it does to the body (and the person).

The following are presented broadly by body system as that was the predominant framework used by respondents. However, throughout the responses there was also an emphasis on the need to look across systems and traditional boundaries.

Area Examples

Central Nervous system Brain function & abnormalities, sleep disorders, myelin sheath degradation, endocrine, Cortisol levels, musculo-skeletal What happens in muscles of person with CFS/ME, recovery from fatigue/exercise, study over time, Gastro-intestinal Liver function, immune Fatigue Why some relapse after minimal exertion, Circulatory Blood volume, Red blood cell shape, mitochondria, red blood cell damage, orthostatic intolerance, elevation of nitric oxide, Other Hyperventilation, magnetic fields and low frequency radio, why do women often improve during pregnancy?, child/adult differences, impact of other/underlying conditions, Social impact On claiming benefits, workplace pressures, the cost of social & healthcare, Psychological/emotional Assessment
of psychiatric co-morbidity in primary care (most so far has been in specialist centres), links between cognitive & behaviour and physiological mechanisms, Interfaces Between neurology and biological psychiatry, between mentalphysical symptoms, neuro-endocrine
changes

Treatment & management

Approach Examples

Management Identifying the techniques/interventions that have helped, include severe sufferers who cannot access trials and research easily, symptom control, communication between doctor & patient, attitudes of health professionals, Learning from others Replication of fruitful studies in other countries,

Treatment interventions

Trials comparing graded exercise to PACING, alternative & complementary therapies, multi-centre trial of GET, intervention studies on fatigue with healthy populations, rehabilitation, Measurement and Monitoring Pain scales,

Cure

There are, understandably, many requests for a cure but the suggestions as to how to achieve it are covered by the previous sections. There is also recognition throughout the responses that this is a complex condition and it is unlikely that there is a single cause with a single cure.