Status	SH organisation	Order no.	Document	Page No.	Line no.	Comments	Response
SH	25% ME Group	132	FULL	88	1-25	The diagnostic criteria are something of a dustbin: with fatigue plus one other symptom. This will therefore include such conditions as burn-out, stress and somatisation disorders. Actual M.E. may well be a minority condition within this umbrella. Bear in mind that fatigue is often one of the lesser symptoms of the condition – the main symptoms are usually muscle pain, severe headaches, cognitive problems and sleep disturbance. These criteria are therefore totally naïve and unacceptable and must have been compiled without reference to qualified researchers in the bio-medical field. The GDG need to highlight the difficulty posed by the lack of clear definition in research and other papers between 'chronic fatigue, Chronic Fatigue Syndrome, and ME.' This must be recognised as an important block in accepting the findings of research in to CBT and GET. While we know that there is not as yet a diagnostic test for M.E., there are objective tests that fit a diagnostic signature and provide good circumstantial evidence. One such test may be a SPECT scan. For MS diagnoses, MRI scans are used, even though it is known that these are not	Issue 1 – Diagnostic criteria:The intention is to raise awareness that the individual may have CFS/ME to manage symptoms at an early stage prior to a diagnosis. We have redrafted this section in order to make this clearer. Issue 2 – Lack of clear definition: This section has been revised.

						definitive. So, where there is a serious doubt by a clinician over a diagnosis of M.E,. I feel the guidelines should suggest the use of SPECT scans to assist in diagnosis. M.E.-friendly paediatricians are currently reporting a worrying trend in diagnosing Munchausen's by Proxy. In such circumstances the parents/carers of sufferers ought to have access to equipment and tests that may vindicate them.	Issue 3 – SPECT scans: No evidence was found for the use of scans. If evidence arises, it will be considered in the revision of the guideline. Issue 4 Patient Access - The publication and implementation of a national guideline on CFS/ME with the accompanying document 'Understanding NICE guidance' will raise awareness of the condition and give both patients and health care professionals access to information on recognising and managing CFS/ME.
SH	25% ME Group	133	FULL	88	1-25	http://www.investinme.org/Documents/PDFdocuments/Byron%20Hyde%20Little%20Red%20Book%20for%20www.investinme.org.pdf SEE PAGE 2-3 **A new and simple definition of Myalgic Encephalomyelitis and a new simple definition of Chronic Fatigue Syndrome** As presented at the Invest in ME London Conference of May 12, 2006 by Byron Hyde MD: ME/ ICD-CFS is a multi-system disorder,	We have revised the relevant chapter and recommendations to clarify the diagnosis process. The submitted evidence, however, does not meet our inclusion criteria, so although considered, has not been added to the evidence review.

						one form of which can be associated with enteroviruses related to the poliomyelitis virus. Virally-induced ME used to be known as "atypical poliomyelitis". There are acknowledged similarities and overlaps between ME and the post-polio syndrome (PPS), particularly concerning the nature and source of the pathophysiology, including virological evidence that enteroviruses persist in the human central nervous system. Specifically, the mechanism of the incapacitating exhaustion is identical in the two conditions (ie. in ME and PPS). In ME there are chronic sequelae and the effects may be neurological, hormonal, autoimmune and myalgic, which may include the myocardium.	
SH	25% ME Group	134	FULL	88	4	Myalgic Encephal**opathy** is not a terminology that is acceptable or registered with WHO.	The title of the guideline was amended to 'Chronic fatigue syndrome/myalgic encephalomyelitis (encephalopathy)' in response to the scope consultation with stakeholders.
SH	25% ME Group	136	FULL	88	18	*"CFS/ME cannot be diagnosed by any test currently available"* That may be true for "CFS/ME" but it is not true for ME/CFS: although there is as yet no single, definitive and specific test, there is a recognised pattern of reproducible abnormality on the appropriate testing that, if positive, is virtually diagnostic.	No evidence was found for a definitive set of tests.

SH	25% ME Group	137	FULL	88	25	The phrase 'will also share' implies that the clinician will understand the patient's worries, whereas with CFS/M.E. misunderstandings are common e.g. the doctor may think that it is a relief if the patient is found not to have cancer, but for someone who is severely affected they may be more worried about having CFS/M.E.	This has been reworded to reflect these concerns.
SH	25% ME Group	138	FULL	90	Box	*"Evidence Statements: there is limited evidence for a wide range of risk factors including higher social class in childhood"* This is untrue: there is ample published evidence that ME/CFS affects all social classes	This is an evidence statement which is a statement that synthesises the evidence findings. However, because of the lack of utility of this evidence statement, this has been deleted.
SH	25% ME Group	139	FULL	104	5.3.8	**Myalgic Encephalomyelitis has nothing to do with 'fatigue'** If you are tired all the time, you do not have ME. The terms 'fatigue' and 'chronic fatigue' were not associated with this illness at all until the name Chronic Fatigue Syndrome was coined in 1988 (this despite the fact the illness had already been legitimately named Myalgic Encephalomyelitis in 1956) (Hyde 2005, [online]). The 'f' word was selected in 1988 entirely for what it could achieve politically: it was never intended to be a genuine medical description of the symptomatology of the illness. In reality having M.E. is like having parts of Multiple Sclerosis, AIDS, Alzheimers, Arthritis and Epilepsy all mixed together at once, with some extra horrific symptoms thrown in that are entirely its own.	The GDG considered that we should accept that ' Chronic Fatigue Syndrome', rightly or wrongly, is now well established in the medical and scientific vocabulary, as well as in common English usage. A pragmatic decision was taken therefore to use CFS/ME as there seemed little point in departing from the accepted 'CFS/ME' terminology (also supported by use in many other reports}.

						M.E. is a neurological illness of extraordinarily incapacitating dimensions that affects virtually every bodily system – not a problem of 'chronic fatigue.' **Fatigue is a symptom common to hundreds of diseases and to normal life, but is not a distinguishing feature of Myalgic Encephalomyelitis.** The most apparent features are extreme post-exertional muscle fatiguability, which is quite distinct from chronic "fatigue" or tiredness, together with recurrent nausea and profound, incapacitating malaise. It is striking how consistent are the symptoms that characterize this condition. The exhaustion experienced by patients is extreme: "the disabling weakness and exhaustion a patient with ME / ICD-CFS experiences is so profound that "fatigue" is probably an insult".	
SH	25% ME Group	140	FULL	105	Box	*"The following should be regarded as 'red flags', indicating suspicion of serious underlying pathology: abnormal neurological signs (and) features of cardiovascular problems"* There is abundant published evidence of substantial neurological deficit in the ME/CFS literature. Both neurological signs and cardiovascular abnormalities are well-documented features of ME/CFS and the Draft Guideline acknowledges on page 112, lines 2/3/4 that the Canadian definition requires such features to be present.	The 'red flags' are to alert clinicians to other serious conditions that may have similar presenting symptoms.

						"before diagnosis of CFS/ME, assessment of mental health should be carried out" ME/CFS is just as much a physical disorder as cancer, lupus or multiple sclerosis, in none of which is a mental health assessment obligatory before diagnosis, so why is there special pleading for ME/CFS?	We have recommended that an assessment of psychological wellbeing be targeted to symptoms, so is not an obligatory assessment, but is targeted as appropriate.
SH	25% ME Group	141	FULL	106	2nd box	Instinctively, all patients yearn to get back to a previous (better) level. To say that 'advice should focus on …a gradual return to a normal daily routine' belittles the severity of the condition and implies that setting the goal of recovery is sufficient to induce it.	Noted. This wording has been changed.
SH	25% ME Group	142	FULL	107	5.2.8	The evidence is there, and to deny it is to deny reality. However, it is easier to deny the evidence if the tests necessary to prove these anomalies are proscribed. For example, the Draft Guideline specifically recommends (5.2.8, page 107) that serology testing for viral or bacterial infections (including other chronic and latent infections) should not be carried out, yet Professor Maes et al (see above) recommend that all patients with ME/CFS should be checked by means of the IgA panel, which is another test that is not approved in the Draft Guideline.	We have revised the recommendations to emphasise the role of investigations in diagnosis, including the role of serology testing.

						Equally, in cases of suspected ME/CFS, informed clinicians believe that patients should be tested for borreliosis, one of most important differential diagnoses, yet this, too is proscribed, despite the fact that a leading UK microbiologist recognises that some people who are thought to have ME/CFS may actually have borreliosis. As BADA (Borreliosis & Associated Diseases Awareness: www.bada-uk.org) points out, it is recognised by the scientific establishment that Borrelia is able to evade immune surveillance. Lyme Disease (LD) may be misdiagnosed as multiple sclerosis, ME/CFS or other autoimmune disorders. The symptom list for ME/CFS and for borreliosis has considerable overlap, for example: fatigue, myalgia, migratory joint pain, neuropathy (including numbness, tingling, burning and itching, hypersensitivity), tremor, muscle twitching, vision problems such as double vision, photophobia, hyperacusis, balance problems and vertigo, severe startle factor, NICE-term memory loss, sleep disturbance, cardiac arrhythmia, tachycardia, nausea / vomiting, adrenal dysfunction and immune system disturbances. To reiterate: the longer the tests that reveal serious (but sometimes treatable) organic pathology continue to be disallowed, the longer the psychiatric paradigm will prevail and patients will continue to be neglected and abused by some members of the	

						medical profession. There are many illustrations of the biomedical problems in ME.Please see [my comments elsewhere]	
SH	25% ME Group	143	FULL	111	27-28	It is widely accepted in the ME community and researchers looking at ME, that the Canadian criteria are much more reliable in diagnosing true ME	The evidence review concluded that no current case definitions are established as being superior to the others. The Canadian criteria are based on expert opinion, and not research evidence.
SH	25% ME Group	144	FULL	124	Box	*"some will recover FULLy"* This is misleading, as the statistics show that only 4% had FULL remission (not recovery) at 24 months (US CDC statistics	Noted and reworded.
SH	25% ME Group	145	FULL	124	12-16	It must be remembered that NICEis preparing Guidelines for ME, not a broad spectrum of chronic fatigue conditions. So it is important that a more precise diagnostic tool; like the Canadian criteria is used to diagnose true ME	The diagnosis recommendations have been revised. The evidence review concluded that no current case definitions are established as being superior to the others. The Canadian criteria are based on expert opinion, and not research evidence.
SH	25% ME Group	146	FULL	124	4-16	Taken from: Handbook of Chronic Fatigue Syndrome by Leonard A. Jason, Patricia A. Fennell and Renée R. Taylor)	Noted.

						The physician and patient alike should remember that CFS is *not* a disease. It is a chronic fatigue state as described in four definitions starting with that published by Dr. Gary Holmes of the CDC and others in 1988 (Holmes, Kaplan, Gantz, et al., 1988; Holmes, Kaplan, Schonberger, et .al., 1988). The definition created by Lloyd, Hickie, Boughton, Spencer, and Wakefield (1990) is also widely used in Australia. There are two subsequent definitions. The Oxford definition of 1991 (Sharpe et al., 1991) and the 1994 NIH/CDC definitions (Fukuda et al., 1994) are basically, with a few modifications, copies of the first definition. Whereas the one essential characteristic of ME is acquired CNS dysfunction, that of CFS is primarily chronic fatigue. By assumption, this CFS fatigue can be acquired abruptly or gradually. Secondary symptoms and signs were then added to this primary fatigue anomaly. None of these secondary symptoms is individually essential for the definition and few are scientifically testable. Despite the list of signs and symptoms and test exclusions in these definitions, patients who conform to any of these four CFS definitions may still have an undiagnosed major illness, certain of which are potentially treatable. Although the authors of these definitions have repeatedly stated that they are defining a syndrome and not a specific disease, patient, physician, and insurer alike have tended to treat this syndrome as	

						a specific disease or illness, with at times a potentially specific treatment and a specific outcome. This has resulted in much confusion, and many physicians are now diagnosing CFS as though it were a specific illness. They either refer the patient to pharmaceutical, psychiatric, psychological, or social treatment or simply say, "You have CFS and nothing can be done about it."	
SH	25% ME Group	147	FULL	126	1	*"Spatial disorientation is not Generally characteristic of CFS/ME and is indicative of brain damage"* Spatial disorientation is documented in the ME/CFS literature: see, for example: Neuropsychological Deficits in CFS. Sheila Bastien. CFIDS Chronicle Fall 1989:24-26 (abnormalities consistent with organic brain syndrome) Alteration of spatial-temporal parameters of gait in CFS. Saggini R et al. J Neurol Sci 1998:154:1:18-25 (abnormalities consistent with involvement of the central nervous system) Patterns of Neuropsychological Abnormalities and Cognitive Impairment in Adults and Children. Sheila Bastien. In: the Clinical and Scientific Basis of ME/CFS; ed. BM Hyde, J Levy and Paul Levine; pub. The Nightingale Research	Noted but is not characteristic.

						Foundation, Ottawa, 1992: 453-460 Neuropsychological Function in Patients with Chronic Fatigue Syndrome, Multiple Sclerosis and Depression. Ella Daly, Anthony Komaroff et al. Applied Neuropsychology 2001:8(1):12-22 (spatial abnormalities consistent with brain alteration in ME/CFS	
SH	25% ME Group	148	FULL	126	1-3	In Moderate and severe ME spatial disorientation is a problem. Many cannot drive, walk through door ways etc properly because of this symptom	Noted but is not characteristic.
SH	25% ME Group	149	FULL	126	20	'… dependant **on** the …'	Revised.
SH	25% ME Group	150	FULL	133	16	*"There is little understanding of the nature of the disease"* This is an astonishing statement, as there is a significant body of scientific literature that documents the multi-system, multi-organ dysfunction that over the last 50 years has been demonstrated in ME/CFS (for example, the vascular abnormalities that have demonstrated a novel finding not seen in any other known disorder.)	We have followed the findings of the Gibson Inquiry, which has concluded that no current theory of causation is supported by sufficient evidence to gain general acceptance. We agree that more high quality biomedical research is required.
SH	25% ME Group	151	FULL	133	17	*'A view held by a few individuals on the GDG was that CFS/ ME could not be identified or managed unless a broader view was taken, This perspective is put forward below.'* Why are the views of only a 'few' (which is a vague number) allowed to dominate this	The framework has been revised in the light of the comments received.

						document? What about other views?	
SH	25% ME Group	152	FULL	133	20	Line 20 onwards refers again only to CFS. , not to ME. Are we to believe that not all the document actually is referring to and therefore aimed at helping people with ME? If this is so, it needs to be made clear. Also, if only a broad view is taken, then the real needs of people with ME are in danger of being dismissed or overlooked or not seen. By taking a wide view and a limited criteria to define the illness, this is almost certainly what will happen.	This has been revised. The GDG wants to encourage the provision of services to all who could benefit. Current understanding of the nature of CFS/ME is insufficient to justify tight criteria that exclude some people from potentially helpful therapies.
SH	25% ME Group	153	FULL	133	24-25	*"there are no objective abnormalities to account for the illness experienced"* This is untrue: there are numerous indisputable abnormalities, but these are seen only on appropriate testing, not on basic screening (which is the only permitted level of investigation on ME/CFS patients in the UK NHS).	This issue is now clarified in the text.
SH	25% ME Group	154	FULL	133	16 & 24-25	These statements are absolutely not true. NICEGDG need to read the research, see the biomedical evidence for this illness. There is overwhelming research to show the abnormalities in MYALGIC ENCEPHALOMYELITIS, unless the majority of the group is only reading and accepting the mis-information from the psychiatrists and the very weak 'evidence based medicine' that they present?	In considering the explanation for CFS/ME, we have followed the report of the Gibson Inquiry, which accepts that there is insufficient evidence to fully substantiate any of the current theories of causation, and that more high quality biomedical research is needed. The framework has

						What about [X] who died [x] and who was found to have viruses affecting 75% of her spinal nerves. At the inquest they said she had died of CFS/ME. How can that be explained by the psychiatric view? It can by the biomedical research. But they just choose to ignore it. It is critical to the issue that the people making up these guidelines only reflect one viewpoint which is held and promoted by a few very vociferous people who have a lot to gain by promoting this and a lot to lose when the truth is finally accepted. And that time is surely getting close.	been revised to make this clear.
SH	25% ME Group	155	FULL	134	14-16	*"CFS has been described as part of a broader condition that includes a range of disorders including fibromyalgia, irritable bowel syndrome…."* There is no doubt that this statement is here intended to refer to somatisation disorder but there is no credible evidence to support such an assertion: it is singularly unscientific and is merely the belief of the Wessely School psychiatrists. There is, however, a school of thought that believes such disorders may all be metabolic or neuro-immune in origin.	This section has been revised. We seek to acknowledge that different people hold different views on causation, and sometimes these views are strongly held. Since we do not know what the cause of CFS/ME is, the GDG cannot accept any of the current theories, but must instead encourage more basic research and encourage those who hold strong views to take a more tolerant, open-minded attitude to ensure that patients who may benefit from various interventions do have access to those interventions.

SH	25% ME Group	156	FULL	134	25-26	*"Terminology used by doctors such as 'functional syndrome' and 'medically unexplained symptoms' are part of common usage in clinical practice today".* Such terms are used in relation to perceived psychiatric disorders only, never to medical disorders	See response above.
SH	25% ME Group	157	FULL	134	27	*"The terms have arisen to describe non-conventional diseases"* ME is not a 'non-conventional' disease: it is a formally classified neurological disease and has been so since 1969.	The wording has been revised.
SH	25% ME Group	158	FULL	135	1-5	ME is a distinct disease from the 'medically unexplained' conditions that are referred to by psychiatrists and often show clear medical problems that have been recorded In a separate response to NICEsome of these anomalies were laid out. **Problem: Continued refusal to heed the biomedical evidence that disproves the biopsychosocial model of ME/CFS pages 5-8** No matter how much biomedical evidence about ME/CFS is submitted to UK official bodies, it is ignored, even when sent by Recorded Delivery. For illustrations of what has been submitted to various official bodies over the years, see the www.meactionuk.org.uk website. The only feasible conclusion is that no biomedical evidence, however relevant to ME/CFS patients' wellbeing, will be allowed to displace the pre-determined agenda of	The GDG accepts the Gibson Inquiry's conclusion that no current theory on the causes of CFS/ME is, as yet, supported by sufficient evidence, and that further biomedical research is necessary. This section has been revised and is intended to recognise that different people hold different views about the cause(s) of CFS/ME, and to encourage more biomedical research.

						imposing CBT/GET on patients diagnosed with “CFS/ME”, nor will biomedical evidence be allowed to displace the determination of the influential psychiatric lobby to re-classify ME as a behavioural disorder by subsuming it within the heterogeneous term “CFS/ME”, the intention being to drop the term “ME” as soon as expediently possible, thereby achieving the long-held goal of “eradicating” ME (see page 20 below). There can be no acceptable rationale for this continued ignoring by Government bodies of the evidence that ME/CFS is a multi-system, multi-organ disorder at endothelial level ie. that it is an inflammatory-mediated response causing endothelial swelling and arterial stiffness with hard evidence of raised isoprostanes not seen in any other known disorder. Although the precise cause is yet to be determined, the symptoms of ME/CFS are not, as stated in the Draft Guideline (page 135, line 1), “medically unexplained”: as noted in our article “ME Exists: True or False?”, it remains beyond reason that the existence of so many documented abnormalities in people with ME/CFS should simply be disregarded and denied, including the following: □ abnormalities of the central nervous system include abnormalities of brain cognition, brain perfusion, brain metabolism and brain chemistry; there is evidence of low blood flow in multiple areas of the brain;	

						neuro-imaging has revealed lesions in the brain of approximately 80% of those tested and according to the researchers, these lesions are probably caused by inflammation: there is a correlation between the areas involved and the symptoms experienced; abnormalities on SPECT scans provide objective evidence of central nervous system dysfunction; there is evidence of a chronic inflammatory process of the CNS, with oedema or demyelination in 78% of patients tested; there is evidence of a significant and irreversible reduction in grey matter volume (especially in Brodmann's area 9) which is related to physical impairment and may indicate major trauma to the brain (which could also explain the low recovery rate); there is evidence of seizures; a positive Romberg is frequently seen in authentic ME/CFS patients.	
SH	25% ME Group	159	FULL	135	1	There can be no acceptable rationale for this continued ignoring by Government bodies of the evidence that ME/CFS is a multi-system, multi-organ disorder at endothelial level ie. that it is an inflammatory-mediated response causing endothelial swelling and arterial stiffness with hard evidence of raised isoprostanes not seen in any other known disorder. Although the precise cause is yet to be determined, the symptoms of ME/CFS are not, as stated in the Draft Guideline (page 135, line 1), "medically unexplained": as noted in our article "ME Exists: True or	Review of evidence about the cause of CFS/ME was outside the scope of the guideline. We follow the report of the recent Gibson Inquiry, which has looked at this question in some detail.

						False?", it remains beyond reason that the existence of so many documented abnormalities in people with ME/CFS should simply be disregarded and denied, including the following:	
SH	25% ME Group	160	FULL	135	4	"*The mental or physical condition debate predominates in the clinical encounter undermining the doctor patient relationship."* This debate is important because the psychiatric lobby has introduced confusion by its involvement in a neurological illness and thus of course the relationship will be undermined if a patient is being seen by someone who actually believes the underlying reason for the illness is 'misguided illness belief.' This seems quite reasonable to me.	We hope the revised wording in this section is helpful.
SH	25% ME Group	161	FULL	135	16	*'The definition and concept of CFS through a biopsychosocial model acknowledges the role of both external and internal influences on the development of and recovery from CFS. The Biopsychosocial model negates the duality of mind and body and a significant cause of conflict between the patient and the healthcare professional.* The biopschosocial model negates the true neurological illness that ME is and the complexity of symptoms.It implies it does not matter what the cause is. If doctors believe that ME is purely psychiatric this will impact negatively on the relationship. It cannot be covered over. Also this reference only refers to CFS not	This section has been revised. We follow the Gibson Inquiry's conclusion on the causes of CFS/ME.

						ME. It has not even said CFS/ME. So who exactly is this document for? Not, it appears for people with neurological Ramsay defined ME?	It should have been CFS/ME – this has now been corrected.
SH	25% ME Group	162	FULL	135	1-24	P135 lines 1 - 24 are again only referring to CFS. Is this because it is actually inappropriate recommendation for ME? The changing from CFS to CFS/ME is confusing and inconsistent and needs addressing.	This was an error, and should have been CFS/ME as elsewhere in the guideline.
SH	Action for M.E.	29	FULL	104	5.2.8	"Primary healthcare professionals should be familiar with the presenting features of CFS/ME..." recent research indicates that this is not the case. Some reference to primary healthcare training would be helpful. (Ref: Primary healthcare provision and Chronic Fatigue Syndrome: a survey of patients' and General Practitioners' beliefs. BMC Family Practice. 6:49, 2005) The list of symptoms does not delineate all of those which can be experienced by people with M.E./CFS, particularly by those with severe M.E. Pain is a significant problem for many people with M.E./CFS and this needs to be noted (in both sets of guidelines). We would like to see the healthcare provider be required to direct the patient to an	The aim of the recommendation is to encourage training in this area to avoid this happening in future. We have given guidance on broad criteria to alert the clinician to the possibility of CFS/ME, not for use as diagnostic criteria specifically. This has been clarified in the guideline.

						appropriate form of pain management.	Re pain – we have added a recommendation on the need for appropriate pain management
SH	Action for M.E.	30	FULL	106	5.2.8	Risks of prolonged bed rest: while this is accepted wisdom, constituents, particularly those with severe M.E., felt this was unhelpful, if not dangerous, to their condition. Indeed, some constituents with milder forms of M.E. have also expressed concern that the guidelines emphasise the need for exercise without necessary provisos (in relation to need, appropriately qualified practitioners etc.). In response to our online survey, 34.3% strongly agreed and 37.2% agreed that rest and minimal activity - at levels well below FULL capacity - help people with severe M.E./CFS to manage their illness. And when asked, during a setback, Activity Management should be maintained but not include prolonged rest unless absolutely necessary, 46.3% strongly disagreed and 27.8% disagreed with this statement. These differing views need to be addressed.	Prolonged bed rest: This section has been changed to make it clear that this area of the guideline refers to pre-diagnosis.
SH	Action for M.E.	31	FULL	107		The number of recommended tests is limited. For example, it seems illogical that the test for Creatinine Kinase is limited to children only.	Noted, but the list is not intended as a definitive, complete list, as clinical judgment should be exercised.
SH	Action for M.E.	32	FULL	110	5.3.1 .1-	Criteria: The guidelines state "No studies have established the superiority of one case	Noted and we have revised the diagnosis

					5.3.1.3	definition over another". Given this, there is patient support for the Canadian Guidelines; and many have felt dismayed at the wider definition of M.E./CFS used. While we acknowledged an understandable desire to ensure no one falls through the net, there is a need for clearer case definition. Given that recent research has indicated that GPs are not confident about making a diagnosis, greater detail re. diagnosis would seem logical. It would also be helpful if there were a recommendation for research into case definition.	recommendations to clarify. The GDG have made research recommendations according to the NICE methods (see the Guidelines Manual for details)
SH	Action for M.E.	33	FULL	116	5.3.4 ln7	The assumption that the patient can refuse treatment without compromising the therapeutic relationship needs to be stated as a requirement in all guidelines.	Noted and we will pass the information on to NICE.
SH	Action for M.E.	34	FULL	124	5.3.6	We appreciate the concerns of the GDG re. ensuring an early diagnosis and the accompanying problem of a false diagnosis. This would lead one to presume that a recommendation of biomedical research and research into subsets would be appropriate (see P28 FULL guidelines).	The GDG have made research recommendations according to the NICE methods (see the Guidelines Manual for details)
SH	Action for M.E.	35	FULL	126	4-6	Sleep apnoea merits prompt investigation and referral - This is not expressed as clearly or with the same urgency in the	The investigation and referral of sleep apnoea is outside the

						NICEer guidelines (see NICEguidelines P27, 1.3.2.4)	scope of this guideline.
SH	Action for M.E.	36	FULL	132	5.4.5 .1	The partnership approach between patients and healthcare professionals is welcomed.	Thank you.
SH	Action for M.E.	37	FULL	132	5.4.5 .2	These recommended timeframes for referral were Generally well received. Our survey found that 44.3% strongly agreed, and 35.9% agreed, that adults and children with mild M.E./CFS should be referred within 6 months. This rose to 58% strongly agreeing and 29.3% agreeing that the moderately affected should be referred within 3-4 months; and increased to 69.8% strongly agreeing and 19.1% agreeing that the severely affected should be referred immediately.	Thank you.
SH	Action for M.E.	38	FULL	133 – 135	5.5	We expected reference to the WHO definition, or the Department of Health's classification of M.E. as a long-term, neurological illness to be made. NICE's implicit rejection - given here - of the psychosomatic viewpoint is extremely important. This position needs to be made crystal clear and included in the NICEguidelines. The emphasis on using appropriate language and sensitivity in dealing with patients is welcomed. Feedback we have received, however, indicates that there are still major problems in terms of how health practitioners relate to people with M.E/CFS. Some reference to training in relation to this	We have revised this section and hope the changes make the views of the GDG clearer.

						would be helpful. Our constituents would welcome a clearer acknowledgement by health professionals that: a) the illness is a real, physical illness; and b) M.E./CFS is not a somatic condition. Again, a clear statement by NICEis required here.	
SH	Association for Psychoanalytic Psychotherapy in the NHS (APP)	13	FULL	115	table	because the costs of counsellors have not been included - even though elsewhere (p. 269) a study is quoted which analyses these costs - the wrong conclusion has been arrived at - that specialist care is as cost effective (for all cases) as primary care - why is this stated when it is not true?	This section in the consultation draft did not state that specialist care was cost-effective. However, it was felt that this crude estimate of cost implications was not conclusive and this section has consequently been revised.
SH	Association for Psychoanalytic Psychotherapy in the NHS (APP)	15	FULL	135	6-20	given the emphasis on the importance of establishing a good therapeutic relationship, it is surprising that no reference is included here to the role of the practice counsellor - why is this?	The potential of counselling in supporting patients was considered in the reviews of evidence about the effectiveness of different interventions, discussed elsewhere in the guideline.
SH	Association of British Neurologists	9	FULL	88	9-10	By definition, fatigue is always the hallmark feature of CFS/ME (major criteria): can the GDG offer appropriate citation to their claim that “fatigue and pain are not always the prominent features”? Perhaps they are talking about a different condition rather than CFS/ME	The sentence relates to fatigue and pain at onset of the condition. The sentence has been reworded so that this is now clear.
SH	Association of British Neurologists	10	FULL	90	5	Preceding infection is a clear risk factor for CFS/ME and there are epidemiological studies showing clear link of CFS/ME to	The GDG did not consider that the evidence of a link of CFS/ME to specific infections

						infections other than just infectious mononucleosis	was convincing.
SH	Association of British Neurologists	11	FULL	104		GDG is neither competent nor empowered to redefine CFS/ME by using only one of all the minor criteria: by doing so, the group is tactically promoting Oxford criteria over the more widely used and recognised international (modified CDC) criteria-again, a clear evidence of psychiatrists' influence on this group.	The GDG have not attempted to define CFS/ME, e.g. for research purposes, but instead have provided clinical indicators which should raise suspicion of the condition.
SH	Association of British Neurologists	12	FULL	104		Specifically, why the symptoms of "dizziness, nausea and palpitations" (last bullet point) have been included as one of the criteria and what is the research evidence to do so?	The experience of the members of the GDG were that these symptoms were common.
SH	Association of British Neurologists	13	FULL	106		Ferritin level should be routinely measured in all women of child bearing age as recent iron-deficiency may present without hypochromic anaemia	The GDG did not consider that estimation of serum ferritin provided information over and above that provided by full blood count in adults and therefore did not include it as a recommended screening test (though it could be undertaken at the discretion of the diagnosing physician).
SH	Association of British Neurologists	14	FULL	107		Creatinine Kinase should be routinely done both in the adults and in children, as it is an important biochemical test to identify primary and metabolic muscle disease presenting as fatigue, post-exertional malaise and myalgia from CFS/ME.	Noted and revised.

SH	Association of British Neurologists	15	FULL	109		In selected cases, neurological opinion and formal brain imaging (MRI) may be required to exclude multiple sclerosis which may present with fatigue, pain and related symptoms very similar to CFS/ME	Abnormal neurological signs are stipulated as requiring further investigation. The GDG did not consider that fatigue or muscle pain in the absence of abnormal neurological signs or a history suggestive of MS merited a recommendation for brain imaging.
SH	Association of British Neurologists	16	FULL	126	19 - 23	Given that a proper neurological examination is mandatory for patients with suspected CFS/ME and relatively few non-specialist GPs are competent in doing so, the threshold for referral to a neurologist should be low	The GDG did not consider that the diagnosis of CFS/ME required a neurologist, but stipulates that where there is doubt about the diagnosis specialist opinion and investigation may be required.
SH	Association of British Neurologists	17	FULL	134	14-24	This paragraph deals with a publication (Wessely et al, Lancet 1999) which was published as a HYPOTHESIS and which remains to be proven. However, the GDG seems to have taken it as a matter of fact. Please refer to the criticisms of this article in the subsequent correspondence in the Lancet. By the same logic, one can argue that fatigue in CFS/ME is very similar to fatigue in other medical diseases, multiple sclerosis and cancer. This particular paragraph, being only a hypothesis, is totally irrelevant for the purpose of a dedicated guideline on CFS/ME.	This paragraph does not reflect any opinion published in the literature but rather summarises the consensus view of the GDG.
SH	Association of British	18	FULL	134	14 -	I would advise the GDG to read [the] Lancet article (Fatigue in neurological	The literature review searched for evidence on

	Neurologists				24	disorders), which has been widely cited as the most definitive work in this area, to understand fatigue and its inter-relationship with physical, cognitive an d psychiatric symptoms. Indeed, nowhere in this document there has been any conscious attempt to explain the multi-dimensional nature of fatigue succinctly.	CFS/ME exclusively, not for evidence of management of fatigue. The GDG recognise that some concepts in the paper are useful.
SH	Association of British Neurologists	19	FULL	134	25-29	The GDG should also be criticised for its total lack of reference to the neurological aspect of fatigue and its overemphasis and over-reliance on the psychiatric literature from a group of psychiatrists	The literature review searched for evidence on CFS/ME exclusively, not for evidence of management of fatigue, and the GDG reviewed all the relevant published literature impartially. Representatives were drawn from a variety of stakeholders; psychiatrists did not have a disproportionate representation on the GDG and the views expressed a consensus.
SH	Association of British Neurologists	22	FULL	88 onwards		With possible exception of some psychiatrists, most specialists prefer the international criteria in order to diagnose CFS/ME. Clearly therefore, there is very little compelling evidence at present that these patients benefit from CBT and GET	The intention is to raise awareness that the individual may have CFS/ME to manage symptoms at an early stage prior to a diagnosis. We have redrafted this section in order to make this clearer.
SH	Association of British	23	FULL	88		The GDG must acknowledge that difference	Noted.

	Neurologists			onwards		in the selection criteria for diagnosing patients is an important factor for predicting outcome	
SH	Association of British Neurologists	40	FULL	106		There is selective omission of research literature on reproducible neuroendocrine tests (e.g. buspirone test), brain imaging (MR spectroscopy), cognitive disability with an overemphasis on research data from certain psychiatrists	Research in these aspects was not considered convincing by the GDG
SH	Association of Medical Microbiologists	1	FULL	107 (table)		The AMM welcomes the opportunity to comment on the guidelines with respect to microbiological investigations. The Association agrees that serology for General or chronic virus infections and serology for chronic bacterial infections (e.g. borelliosis) should not be undertaken in the absence of any indicative history (i.e. should not be done routinely)	Thank you.
SH	Association of Young People with ME	5	FULL	106		Children and Young People AYME recognises that CFS/ME is the same illness for children and adults. However, the impact of the illness is very different for children and this has not been sufficiently addressed. More reference needs to be made to the NSF 'ME exemplar' and to the RCPCH Guidance 2004, particularly with reference to the very small child needing constant vigilance (Pg 38 3.1.3 RCPCH) and the General relationship with the family (page 43 management of CFS/ME RCPCH 2004). In addition, diagnosis of children and young people could be enhanced by referencing	We have made some additional recommendations on the need for specific management principles for children.

						the RCPCH Guidance on P106.	
SH	BRAME Blue Ribbon for the Awareness of ME	81	FULL	88	9-10	5.1: We are pleased that you acknowledge that whilst fatigue may be a symptom, that for many, other symptoms are far more debilitating and dominating eg pain, and that when patients first approach the doctors, and throughout their illness, fatigue may be the last thing they mention, if at all. This just shows why the Oxford criteria are completely inappropriate – as can be seen in your quote by Wessely and Sharpe about their Oxford Criteria (p111 4-8) about it being a syndrome around fatigue, and other symptoms may be present. This is not appropriate for ME/CFS. The fatigue experienced may also only be down to the body's reaction to the other symptoms eg. sleep dysfunction and pain, so therefore the fatigue is a secondary/reactive symptom, rather than a primary/core symptom.	Thank you. This section you mention serves as an introduction to the evidence found rather than an endorsement of set of one criteria over another. This has been revised to include other criteria as highlighted in the comments.
SH	BRAME Blue Ribbon for the Awareness of ME	82	FULL	88	18	5.1: At present there is no specific definitive test to diagnose ME/CFS but there are tests that, along with a FULL history of illness, and FULL physical examination, that can help support the diagnosis. (see the Canadian Clinical Guidelines previously referred to). There is also research showing that possible testing may be soon, especially given the recent research by Kerr and Gow on genetics.	The guideline recommends a full history and examination. If evidence of testing is published, it will be considered in the revision of this guideline.
SH	BRAME Blue Ribbon for the Awareness of ME	83	FULL	89	13	5.2.2.1: These tests would prove useful as a secondary line of testing and should be	We have noted only that they are not to be used routinely,

						included. Orthostatic intolerance is a real problem for most ME/CFS patients, and the GDG did see a number of papers showing the usefulness of the tilt-test, so why were these dismissed? The 5 lab tests for fibrinogen prothrombin platelets etc should definitely be tested at regular intervals on the severely affected who are often bedbound and the risk of blood clots/DVT forming, especially as those with ME/CFS, are thought by many doctors/researchers, including the work of Dr Les Simpson, to have 'sticky blood'. Dr Les Simpson showed a changed in the shape of red blood cells, causing difficulty in micro-circulation and leading to tissues not receiving sufficient oxygen and nutrients to sustain normal functioning.	but that clinical indications should guide investigations. Issue 2 - The 5 lab tests: This section is about investigations to diagnose the condition. It is not about management of the condition.
SH	BRAME Blue Ribbon for the Awareness of ME	84	FULL	89	14	5.2.2.2: This illness is the same disease whether you are an adult or a child, the disease process does not change as soon as you become 16 or 18, and tests should be done if needed to help with diagnosis. Obviously clinicians should be sensitive to their age, if tests were of a more invasive nature, or when thinking of medication or treatments, and to the effects of some drugs or therapies, when a child is still growing and developing.	This is an evidence statement which is intended to reflect the quality of research evidence pertaining to children in this area.
SH	BRAME Blue Ribbon for the Awareness of ME	85	FULL	90	5	5.2.4.1: We feel there are some clear risk factors of someone developing ME/CFS eg viral infection like glandular fever, multiple insults to the body with repeated infections, environmental factors such as exposure to organo-phosphates and other chemicals,	This section has now been removed.

						vaccinations/immunisations, and as research is now confirming a genetic susceptibility (as shown by separate studies by Dr J Kerr and Dr J Gow), or, of course a combination of multiple risk factors coming together.	
SH	BRAME Blue Ribbon for the Awareness of ME	86	FULL	90	5	5.2.4.2: We cannot agree with some of these, and they certainly need further explanation. Feel this is an unhelpful evidence statement in its current form.	This is an evidence statement which is a statement that synthesises the evidence findings. However, because of the lack of utility of this evidence statement, this has been deleted.
SH	BRAME Blue Ribbon for the Awareness of ME	87	FULL	90	5	5.2.4.3: This illness is the same whether you are a child or an adult and so the risk factors are basically the same – trying to continue with education is similar to an adult trying to continue with work. The added risk for children is being forced to attend school, being classed as school phobic, being misdiagnosed with Munchausens by proxy, or if social workers are involved, the risk and fear of children being taken into care, forced into treatments or at worst physically removed from their home by medical professionals, social workers, and police, who fail to comprehend the true physical nature of the illness ME/CFS.	This is an evidence statement which is a statement that synthesises the evidence findings.
SH	BRAME Blue Ribbon for the Awareness of ME	88	FULL	91	7-13	5.2.5.1: See responses already made in 5.2.2.1. These tests may be very helpful, certainly with the moderate and severely affected. If electrodermal analysis is useful in differentiating a diagnosis between ME/CFS and depression, then it should be	The evidence reviewed in this guideline does not allow us to distinguish between these groups when making recommendations.

						considered if appropriate. No mention anywhere of Tony Cleare's research which shows a difference in serotonin levels between those with ME/CFS and depression, and also shows why a difference in Serotonin levels indicate those who did not respond well to GET. If sub-groups were identified it would help in offering appropriate management.	However, we have stressed the need to consider both preferences and needs of the individual throughout the recommendations.
SH	BRAME Blue Ribbon for the Awareness of ME	89	FULL	92	6-7	5.2.6. Patients do not find it a negative experience to have numerous tests, as they feel so ill and want a correct diagnosis, and even if they do not get a positive answer, it can be a relief and reassuring to know what illness it is not. Unfortunately many doctors consider comprehensive testing as 'reinforcing the patient's belief in an organic cause to their illness' – this is disgraceful, ME is a physical organic illness – comprehensive testing is necessary – no wonder so many people are being misdiagnosed in this country.	Point well taken. It should be noted that diagnostic testing, especially invasive tools, will incur immediate disutility due to an impact on quality of life or risk of adverse events. However, following the diagnostic procedure, there may be benefit from increased certainty that a condition is confirmed or ruled out. The correct valuation of all benefits and harms to patients will make appropriate decisions for patients and doctors possible.
SH	BRAME Blue Ribbon for the Awareness of ME	90	FULL	92	12-17	5.2.6. Investigations are cost effective as they enable an earlier accurate diagnosis, and appropriate advice and management, rather than perhaps months or years of ill-health, the cost of multiple doctor/hospital visits and cost of symptom management, apart from the cost of the personal impact on the patient of being so unwell, and having no real understanding of what is wrong with them - that does have a	It should be noted that "the same [effectiveness] outcome" means per definition that items such as 'diagnostic precision' will not be compromised by an alternative programme. For the evaluation of cost-effectiveness, both costs and

						negative impact on a patient. How is it cost-effective to not do the tests and to possibly misdiagnose a patient as having ME/CFS, when in actuality they may have another chronic/fatal condition which could be appropriately treated? There have been many instances of this, most recently that of a young man being diagnosed as ME/CFS when it was actually CJD, and one of our respondents highlighted a recent case of someone with Alzheimers being misdiagnosed as having MECFS.	consequences of an intervention are examined. Therefore, the quoted paragraph has to be viewed in context of the prior section. It can be assumed that patients accrue disutility over time while they go through multiple investigative procedures until a final diagnosis is made. This means that the longer this period is, the greater the quality of life loss in absolute terms. Necessary staff time is directly linked to the costs of a test, and with the disutility to the patient over time, less time intensive interventions are expected to be more cost-effective. We have also recommended that appropriate investigations should be done as indicated by clinical signs and symptoms.
SH	BRAME Blue Ribbon for the Awareness of ME	91	FULL	94 - 103		5.2.7: See comments made in previous line – tests can help to make an effective diagnosis, or help to pick up any co-morbid illnesses, and to enable good management There is also a danger of valuable epidemiological data being lost by certain tests not being included – especially tests for viruses in early stages of the illness, allowing risk factors to be identified eg.	This table documents the questions and responses to the questionnaire for transparency. They cannot be changed now.

						EBV.	
SH	BRAME Blue Ribbon for the Awareness of ME	92	FULL	104	1	5.2.8: Delayed onset of fatigue is a characteristic of this illness. The CMO Report (2001) 4.2.1.1 states clearly that "*other fatigue states do not present with the characteristic delayed fatigue seen in CFS/ME. Another distinguishing feature of the illness, in comparison with other 'fatigue states', is its prolonged relapsing and remitting course over months or years*." The Canadian Clinical Case Definition and Guideline states "*Chronic fatigue must not be confused with ME/CFS because the 'fatigue' of ME/CFS represents pathophysiological exhaustion and is only one of many symptoms. Compelling research evidence of physiological and biochemical abnormalities identifies ME/CFS as a distinct, biological, clinical disorder*." This recommendation reads as a new diagnostic criterion for ME/CFS. We cannot agree with fatigue and 'one or more of the following symptoms' as a diagnostic criteria, ME/CFs should not even be considered if there is only fatigue and one other symptom present. This, like the Oxford Criteria, will lead to many people being misdiagnosed and mismanaged. In comparison to the 'NICEcriteria', these are the other criteria, for all of which symptoms must be new onset and present for 6 months:-	We have given guidance on broad criteria to alert the clinician to the possibility of CFS/ME, not for use as diagnostic criteria specifically. This has been clarified in the guideline.

						The Canadian Criteria – patient must have fatigue, post-exertional malaise and/or fatigue, sleep dysfunction, and pain, plus 2 or more neurological/cognitive manifestations, and one or more symptoms from two of the categories autonomic, neuroendocrine and immune manifestations. These criteria include an alternative diagnosis of Idiopathic Chronic Fatigue for those who do not fulfil the criteria for ME/CFS, allowing those patients to still receive advice and management and be monitored. From the CMO Report (2002) CDC – Holmes (1988) requires fatigue of 6 months plus 6-8 symptoms CDC – Fukuda (1994) requires fatigue of 6 months plus at least 4 other core symptoms. London (1990) derived from Dowsett and Ramsey – includes General or local muscular fatigue following minimal exertion with prolonged recovery time. Neurological disturbance of cognitive, autonomic and sensory functions, with involvement of cardiac, endocrine and other systems with a prolonged relapsing course. Whereas the Oxford Criteria (Sharpe) 1991 and the Australian Criteria (Lloyd) 1990 only mention fatigue of 6 months with disabling functional impairment, cognitive or neuropsychiatric symptoms. No other symptoms are specified and neurological	

						symptoms, suffered by all ME patients, are specifically excluded. The other major problem with the Oxford and Australian criteria is that neither has psychiatric diagnosis as an excluding condition eg. Depressive illness and anxiety disorders (there is multiple research papers showing that ME and ME/CFS are not depression or a psychiatric condition). Therefore the group comprised of those diagnosed using either of these criteria only need to have chronic fatigue for more than six months. This means that they could have multiple causes, and alternative diagnoses, as well as those whose fatigue is due to psychiatric conditions – therefore these criteria are totally useless for diagnosing ME/CFS, and all research based on groups selected using either of these diagnostic criteria are flawed/invalid, because the results are unable to be extrapolated for use on the ME/CFS population. Many ME/CFS specialists both in the UK and around the world, along with patient groups, and patients themselves, strongly believe that the Canadian Clinical Criteria is currently the criteria which best fits their symptoms and illness experience of ME/CFS. We strongly recommend the use of the Canadian Clinical Diagnostic Criteria. Recommendation of the use of the Canadian Clinical Criteria by the	

						NICEGuideline would have been very constructive and positive for patients with ME/CFS – enabling a more accurate diagnosis, and helping to exclude or differentiate ME/CFS from other illnesses. The CDC states that ME and CFS are similar but different illnesses. To really help patients and medical professionals care for patients with ME/CFS, they have to be identified from the larger spectrum of patients with chronic fatigue states.	
SH	BRAME Blue Ribbon for the Awareness of ME	93	FULL	106	Box 1	When using symptom management, the clinician must be alerted to the fact that, if the patient does have ME/CFS they may well be more sensitive to medication and to use considerable caution on dosage	There does not appear to be evidence to support this. Many drugs will not be effective if not given at least the minimum advised dosage. However, we have made a recommendation on this issue.
SH	BRAME Blue Ribbon for the Awareness of ME	94	FULL	106	Box 2	Sleep dysfunction is a core symptom of ME/CFS and most patients have tried everything to try and improve sleep and to have quality sleep. Prolonged bed rest in an acute phase or severe relapse is not an option; it is a necessity, as patients are frequently just too ill to even lift their head off the pillow. Everyone with ME/CFS, including the long-term severely affected, still live with the hope that one day they will be able to return to life which bears some semblance to normality. This statement is an insult to patients, as it does not acknowledge the severity of the illness, and	Noted: this wording has been changed to clarify this.

						with all the talk of behavioural therapies, this can have a very negative impact on patients making them feel that they have not tried hard enough to get better.	
SH	BRAME Blue Ribbon for the Awareness of ME	95	FULL	106	Box 4 /5	5.2.8 (Please also refer to responses already given on 5.2.2.1, 5.2.5.1, 5.2.6, and 5.2.7.) FULL and thorough investigations should be done to enable an accurate diagnosis of ME/CFS, whilst also identifying any other underlying or co-morbid condition eg ferritin levels only to be done in children, when it should be included for adults as well. We feel that cholesterol should also be included, as this is often found to be slightly raised in ME/CFS patients, but also as most ME/CFS patients have dietary problems, 'sticky blood' and many have cardiovascular problems, the baseline should be found and monitored at intervals.	The GDG considered that ferritin should only be done routinely in children, but that clinical judgment should be used. Regarding cholesterol, the investigations listed here are to aid diagnosis, not ongoing management.
SH	BRAME Blue Ribbon for the Awareness of ME	96	FULL	107	Box2	We feel that these tests are important to also be included in order to give an accurate diagnosis of ME/CFS. The serology for infections, and along with Folate levels, B12 should also be included. Orthostatic intolerance is a major problem for most patients, the moderately, and especially, the severely affected. This should be identified and monitored, and has been shown in some studies to be a diagnostic marker.	There are clearly many tests that should be carried out to assist with management in individual cases. The GDG did not, however, find sufficient evidence for any test which diagnoses CFS/ME. The tests listed are those which would assist in ruling out other conditions
SH	BRAME Blue Ribbon for	97	FULL	108	25-	You say 4 times as many women as men	There are clearly many tests

	the Awareness of ME			109	29 1-4	get ME/CFS. There is a known endocrine involvement in ME, and for many women, any iron deficiency may be exacerbated, as the CMO Report clearly acknowledges. With many women having menstrual difficulties, prolonged and heavy menstruation, as well as co-morbid gynaecological conditions. It has also been found in ME/CFS clinics, and is well documented by haematologists, that adults may show an 'acceptable' blood picture on normal testing, not immediately alerting the clinician to the presence of an underlying abnormality/deficiency eg very low ferritin, folic acid or B12 levels (B12 would help to diagnose/eliminate Pernicious Anaemia.) The symptoms for these deficiencies are similar to those experienced with ME/CFS. Ferritin levels should be recommended for both adults and children, and continually monitored throughout the patient's illness, especially for the long term severely affected.	that should be carried out to assist with management in individual cases. The GDG did not, ,however, find sufficient evidence for any test which diagnoses CFS/ME. The tests listed are those which would assist in ruling out other conditions.
SH	BRAME Blue Ribbon for the Awareness of ME	98	FULL	107 109	Box 1 5-6	Again why is creatinine kinase only recommended for being tested in children when it could help to identify muscle disease in adults. Creatinine kinase should be recommended for both adults and children.	Changed.
SH	BRAME Blue Ribbon for the Awareness of ME	100	FULL	108	10-16	Should be some reference, even if not used as a diagnostic tool, to make clinicians aware that research has shown that there is a reduced blood flow, in particular to the	No evidence was found for the use of these tests as diagnostic tools. If evidence arises, it will be considered in

						brain of ME/CFS patients. Many of our respondents are bewildered at the lack of inclusion of research produced by SPECT scans, and mentioned the work of Durval Costa.	the revision of the guideline.
SH	BRAME Blue Ribbon for the Awareness of ME	101	FULL	110	1–Box 1	5.3.1.1 We would challenge this statement saying that there is no evidence to say that one case definition is better than another. This has been articulately debated for years. The York review itself showed that the Canadian Guidelines, Holmes et al 1988 and the London/Dowsett criteria are all better accurate diagnosis and at creating more homogeneous groups than the Fukuda et al 1994 criteria.	This comment refers to an evidence statement which is a statement that synthesises the evidence findings. The GDG discussed the evidence and agreed this statement.
SH	BRAME Blue Ribbon for the Awareness of ME	102	FULL	110	1-Box 2	5.3.1.2 The CDC Holmes 1988 criteria requires patients to have fatigue of at least 6 months duration, at least 50% reduction in function, and 6 to 8 core symptoms. This criteria therefore identifies a more homogenous group of patients presenting with a larger number of core symptoms. The CDC Fukuda 1994 criteria require patients to have 6 months of fatigue with substantial functional impairment with at least 4 other core symptoms. These therefore open the criteria up to embrace a larger and more heterogenous group of patients.	The recommendations on diagnosis have been revised and clarified. However, as stated in the evidence review, there is no clear research evidence on the most appropriate case definitions to be used.
SH	BRAME Blue Ribbon for the Awareness of ME	103	FULL	110	1-Box 3	5.3.1.3 As explained above the CDC 94 criteria requires fewer symptoms, whereas the Dowsett ME and Canadian Criteria have much more precise and targeted clinical	The recommendations on diagnosis have been revised and clarified.

						criteria allowing for those with the illness to be properly, and correctly diagnosed, creating the homogeneous group that is needed for correct diagnosis, management and research.	However, as stated in the evidence review, there is no clear research evidence on the most appropriate case definitions to be used.
SH	BRAME Blue Ribbon for the Awareness of ME	104	FULL	110	2-Box 1	5.3.1.4: Why is there a need for a separate case definition for children? This illness, and its symptoms, are the same whether you are a child or an adult. The only difference to be acknowledged is the sensitivity needed for management and education, and the need for diagnosis to occur earlier than in adults.	Noted, but there may be different patterns of presentation in children
SH	BRAME Blue Ribbon for the Awareness of ME	105	FULL	110	2-Box 2	5.3.1.5: Why do guidelines, recommendations, management and research always take on the more psychiatric/psychological approach with children? This is neither acceptable nor helpful. If the study listed here is true, we would question more whether the diagnosis was correct, or whether the children were being brought down by multitudes of medical professionals/educationalists who are trying to convince the child that their problems are not physical – you try having no-one believe or support you and see how you feel.	This is an evidence statement which is intended to reflect the quality of research evidence pertaining to children in this area.
SH	BRAME Blue Ribbon for the Awareness of ME	106	FULL	111	1-26	We have already given our reasons why we find even the mention of the Oxford criteria within this document unacceptable, but mentioning it first – words fail us! If the intention is to include all research and diagnostic criteria in chronological order – where are the Ramsay criteria for ME which	The evidence review applied agreed inclusion and exclusion criteria, and in the full guideline, we have reported details of some of the most commonly cited criteria in chronological order

						were the first created in this country? Why is there no mention of the Holmes et al CDC criteria from 1988? This predates the Oxford and were found in the research review to more accurately identify those with ME than the Fukuda criteria, and to show those that are more severely affected. To include the Oxford criteria, which have never been held up to research scrutiny and has never been peer-reviewed and are based on a flawed and erroneous hypothesis in the first place, is perverse to say the least. The Oxford Criteria (Wessely/Sharpe) 1991 along with the Australian Criteria (Lloyd) 1990 only mention fatigue of 6 months with disabling functional impairment, cognitive or neuropsychiatric symptoms. No other symptoms are specified – this is not ME/CFS this is describing a chronic fatigue state – not the illness/condition that this document is supposed to be addressing and providing advice on. The other reason for the unacceptability of the Oxford criteria is that they do not have a psychiatric diagnosis as an excluding condition eg. Depressive illness and anxiety disorders (there are multiple research papers showing that ME/CFS is not depression), Therefore any group comprising of those diagnosed using either of these criteria only need to have chronic fatigue for more than six months. This means that they could have multiple causes and alternative diagnoses, as well as those whose fatigue is due to	– detailed critiques can be found in the full evidence review (Appendix in the full guideline).

						psychiatric conditions. These criteria are totally useless as a diagnostic tool for ME/CFS, and all research based on groups selected using either of these diagnostic criteria is flawed, and the results are unsuitable for extrapolation to the ME/CFS population.	
SH	BRAME Blue Ribbon for the Awareness of ME	107	FULL	111-112	27-4	The Canadian clinical criteria are the only clinical diagnostic criteria available. All others are for research purposes only. Those who fit these criteria are those, who we believe, truly have the illness of ME/CFS. These criteria have been acknowledged to create an homogeneous group, which is vital as they identify the true illness ME/CFS. The core neurological, immune and neuroendocrine manifestations are central to the illness and are not optional. The Canadian criteria also allow clinics/GPs to treat everyone as they allow those who do not fulfil the criteria to be given the diagnosis of Idiopathic Chronic Fatigue Syndrome. This alternative group can be diagnosed, managed and continually assessed, as they may go on to develop ME/CFS, or they may naturally improve, or may develop/be diagnosed with alternative illnesses.	The evidence review concluded that no current case definitions are established as being superior to the others. The Canadian criteria are based on expert opinion, and not research evidence.
SH	BRAME Blue Ribbon for the Awareness of ME	108	FULL	112	16-18	5.3.2.2 Summary of evidence: ME AND ME/CFS ARE NOT 'TYPES' OF CHRONIC FATIGUE!! Chronic Fatigue is listed by WHO under psychiatric conditions, whereas ME and ME/CFS are listed under ICD10-G93.3 as neurological illnesses alongside PVFS. This guideline is for ME and	Noted and deleted.

						ME/CFS not chronic fatigue states therefore all research relating to chronic fatigue should be removed.	
SH	BRAME Blue Ribbon for the Awareness of ME	109	FULL	112	12-30	The York review was based on a flawed remit, as it did not allow for research into the true illness ME/CFS, of which there is copious good quality strong evidence to be looked at – perhaps that is why you came up with so many 'weak and inconsistent' studies.	The York review was conducted using recognised and validated methods in accordance with NICE methodology. Details of the methods are reported in the full guideline.
SH	BRAME Blue Ribbon for the Awareness of ME	110	FULL	114	11-Table	Costs attached to false diagnoses: there is no mention here of the financial and social costs that are incurred from misdiagnosis, and subsequent management of these conditions, if thorough exclusionary/exploratory testing is not done to start with. The correct use of the Canadian diagnostic criteria, along with proper testing, would lead to correct diagnoses being made sooner, making it more cost effective and less distressing for the patient.	Any implications from correct and false diagnosis relate here to the diagnosis of CFS/ME (instead of diagnosis of other conditions).
SH	BRAME Blue Ribbon for the Awareness of ME	111	FULL	114 115	16-18 Table 1	Why is the cost per hour for a hospital consultant/specialist not included in this table, as we know it is considerably less than for a GP who costs £143ph? GPs are often ill-informed and misunderstanding of ME/CFS. Specialist clinics following a bio-medical approach, using a well trained multi-disciplinary team, headed up by a consultant would be more cost-effective and far more helpful for the patients.	Thank you. This section has been revised.

SH	BRAME Blue Ribbon for the Awareness of ME	112	FULL	124	5.3. 5.1	Recommendations: For the mild/moderately affected 4 months is too soon for making a diagnosis as all diagnostic criteria say that symptoms must be present in adults for 6 months before a diagnosis can be made. This does not mean that a provisional diagnosis of ME/CFS cannot be made, and appropriate advice and management given, before 6 months.	The GDG considered the time frames to be appropriate.
SH	BRAME Blue Ribbon for the Awareness of ME	113	FULL	124	5.3. 5.3	Some patients may make some, or, for a minority, considerable improvement, it is well recognised that there is no cure for ME/CFS, as repeatedly stated throughout the CMO report, yet strangely this vital information is not present in the guidelines. A very small minority may go into long remission – but it must be stressed that this is a relapsing condition, so no-one recovers – and certainly not FULLy. There is no mention that some patients may deteriorate, and that for some it may be fatal.	Noted and this recommendation has been revised.
SH	BRAME Blue Ribbon for the Awareness of ME	114	FULL	124	5-7	Amazed by this statement, as the Canadian Clinical Criteria would enable clinicians to make a definitive diagnosis of ME/CFS, and they also have helpful, informative and constructive advice for managing the condition. We note that you identify that the research case definitions are not necessarily helpful in clinical practice and yet ignore the clinical criteria.	The evidence review concluded that no current case definitions are established as being superior to the others. The Canadian criteria are based on expert opinion, and not research evidence.

SH	BRAME Blue Ribbon for the Awareness of ME	115	FULL	124	12-16	This is a guideline for ME/CFS not for a range of conditions with chronic fatigue, and the Canadian Guidelines would enable clinicians to make a reliable and accurate diagnosis of ME/CFS. As the NICEevidence has shown, studies comparing other broader diagnostic criteria, led to a very large and heterogeneous group, creating more confusion for medical professionals and patients alike regarding diagnosis and management.	The diagnosis recommendations have been revised. The evidence review concluded that no current case definitions are established as being superior to the others. The Canadian criteria are based on expert opinion, and not research evidence.
SH	BRAME Blue Ribbon for the Awareness of ME	116	FULL	125	2-7	Good health care professionals should always be vigilant and observant in monitoring their patients condition and symptoms, and be ready to reconsider a diagnosis or be aware of a co-morbid condition.	Noted. These are covered in the recommendations on review.
SH	BRAME Blue Ribbon for the Awareness of ME	117	FULL	125	18-22	The statement 'health care professionals should be aware of some of the symptoms frequently presented to raise awareness' is meaningless. What is a guideline like this for, if it is not to give health care professionals the information and skills they need to help them to diagnose and manage an illness? Health care professionals should be aware of all the core symptoms, and the range of other symptoms, to enable them to make a diagnosis, offer symptom management and support. There is no mention of empathy with the patient. It is even more essential for good, quality and accurate information to be in a guideline for an illness like ME/CFS, where there are such strongly controversial views. The	We have recommended that the reality and impact of the condition and symptoms should be acknowledged in order to address such concerns.

						patient experience of a clinical consultation is that their GP, far too often, totally disbelieves in ME/CFS, or takes the psychiatric/psychological approach to the illness, instead of offering understanding of the overwhelming complex and debilitating illness that the patients endure 24/7.	
SH	BRAME Blue Ribbon for the Awareness of ME	118	FULL	126	1-3	Spatial disorientation is recognised as being a problem for many moderate and most severely affected ME/CFS patients.	Noted but is not characteristic.
SH	BRAME Blue Ribbon for the Awareness of ME	119	FULL	126	14	5.4.1 Referral to Specialist CFS/ME Care We know of one long standing ME/CFS clinic, which takes the bio-medical approach, that has completed surveys of its patients over the years. It has shown that the patients have found the clinic, and the understanding and knowledgeable consultant, an absolute lifeline over the years to help them understand and manage their illness.	Thank you for this information.
SH	BRAME Blue Ribbon for the Awareness of ME	120	FULL	133	16-19	5.5 A Conceptual Framework If the wealth of biomedical and patient evidence had been thoroughly looked at by the GDG there would have been a substantial understanding of the reality of the illness ME/CFS. It is of great concern to the patient population, and those clinicians and researchers who are truly understanding of this chronic and debilitating illness, that “a view held by a few individuals on the GDG was that CFS/ME could not be identified or	The views of a few members of the GDG did not dominate the guideline. Great care was taken during development to ensure all views were identified and a balanced guideline produced. The framework has been revised to take account of the comments received through the consultation. We hope that the revised version helps patients and professionals

						managed unless a broader view was taken". If they had no real understanding of the illness ME/CFS as listed by WHO, why were they invited to be on the GDG? If it was a 'few members' then why was their view able to dominate the format and content of the guideline? ME/CFS is not chronic fatigue – it has been stated that "*the disabling weakness and exhaustion a patient with ME/CFS experiences is so profound that 'fatigue' is an insult*". ME/CFS is not a behavioural disorder, a psychiatric illness, somatic/functional disorder, an illness belief, depression or anxiety disorder. By taking such a broad view, and by introducing diagnostic criteria, like those created within this guideline, which are just one symptom away from the unacceptable and discredited Oxford Criteria, is of no help to anyone. They create a 'dustbin of illnesses' which leaves patients misdiagnosed and mismanaged, with potentially fatal consequences. By accommodating this broad brush approach, NICEhas failed, in this guideline, to offer an constructive advice or information to those medical professionals who truly wish to understand ME/CFS in order to help their patients and are in danger of doing grievous damage to ME/CFS patients. There is nothing here to give doctors any view of the reality of the illness apart from the patient	work together to improve care and services, despite the differences in the views people hold about the nature of the condition. In considering the explanation for CFS/ME, we have followed the report of the Gibson Inquiry, which accepts that there is insufficient evidence to fully substantiate any of the current theories of causation, and that more high quality biomedical research is needed. Specifically, the GDG does not state that MM/CFS is a behavioural disorder, a psychiatric illness, a somatic/functional disorder, an illness belief, depression or anxiety disorder.

						testimonials.	
SH	BRAME Blue Ribbon for the Awareness of ME	121	FULL	133-134		Is this deliberate here to only mention CFS or an oversight? If this section refers to ME/CFS, even though we still need much more research into the aetiology and pathogenesis of ME/CFS, there is a wealth of good biomedical evidence and research showing abnormalities, along with surveys of thousands of patients to give invaluable information on the reality of this illness and the patient experience of ME/CFS. Much of this information has been forwarded to NICE by ourselves and other ME groups and researchers.	This was an error, and has been corrected. It should have been CFS/ME. The GDG accepts the Gibson Inquiry's conclusion that no current theory on the causes of CFS/ME is, as yet, supported by sufficient evidence, and that further biomedical research is necessary.
SH	BRAME Blue Ribbon for the Awareness of ME	122	FULL	133	27-28	To state there is a 'lack of an objective definition of CFS as a discrete disease entity' is misleading if this is also referring to ME or ME/CFS.	The text has been revised.
SH	BRAME Blue Ribbon for the Awareness of ME	123	FULL	133-134		Adoption of the Canadian Clinical Guidelines by NICEwould have really helped medical professionals, not only to have the information they need to make a more precise and accurate diagnosis of ME/CFS, but would also give them constructive information and skills to help manage their patient's chronic illness.	We hope the revised guideline is an advance. Whilst the GDG felt the Canadian guidelines had virtues, they also thought there were weaknesses which we had tried to overcome.
SH	BRAME Blue Ribbon for the Awareness of ME	124	FULL	134	5-6	'Entrenchment and polarisation of viewpoints about a physical or psychological origin of CFS'. ME/CFS is a physical illness, but whilst psychiatrists, particularly of the 'Wessely school', continue to influence, at the highest level, their views on ME/CFS being a	The guideline accepts the Gibson Inquiry's conclusions on the current evidence about the cause of CFS/ME and the need for more biomedical research.

						mental/behavioural disorder, neurasthenia or illness beliefs. In a recent book on Clinical Medicine: 5th edition: Kumar and Clark 2004 psychiatrists White and Clare, in their section on psychological medicine, list CFS/ME under functional or psychosomatic disorders – medically unexplained symptoms, and deem CFS/ME to be a somatoform disorder. Compare this to the Canadian Clinical Guidelines which patients know to be the reality of this overwhelming, complex, debilitating and chronic illness ME/CFS, and you can not fail to comprehend why there is such a strong difference of opinions. By taking the behavioural approach to managing this illness, instead of addressing the real physical illness affecting the central nervous system, immunological and neuroendocrine systems, which for the severely affected becomes a multi-system, multi-organ illness, these NICEguidelines are not going to improve the situation for patients.	The guideline seeks to promote access to interventions that may help alleviate some symptoms as well as encourage more research to identify the cause.
SH	BRAME Blue Ribbon for the Awareness of ME	125	FULL	135	6-20	Any doctor should aim to have a good therapeutic relationship with their patient, and acknowledge their symptoms, suffering and disability and the impact that has on their lives. When patients visit their doctor, they need information and advice. For example 'is it safe for me to have a vaccination?' or 'what type of anaesthetic	Noted and this is a principle of care (see also the Introduction to the NICE guideline). Also please see the Understanding NICE Guidance for suggested questions that patients may wish to ask their doctor or

						can you recommend, if any, for my dentist to use?' Patients will have a wealth of questions to ask their doctor about their complex medical condition, and these may seem unusual questions to ask, but if you truly understand ME/CFS, then they are very important, in order to avoid adverse and possible severe reactions. Definition and concept of this illness through a biopsychosocial model shows no concept of ME/CFS, is of no real help to patients, and as is shown in patient evidence, is found by the majority to be unhelpful or harmful.	healthcare practitioner. The GDG accepts the Gibson Inquiry's conclusion that no current theory on the causes of CFS/ME is, as yet, supported by sufficient evidence, and that further biomedical research is necessary.
SH	British Paediatric Mental Health Group of the Royal College of Paediatrics and Child Health	2	FULL	122		Diagnosis in children. This is given a definite time frame of 3 months. Why? The RCPCH document chose not to give a definite time frame, rather using the definition of 'severe persistent fatigue not explained by other disorders'. We recognise that it probably takes about 3 months to	The 3-month time frame was recommended in the CMO report and is used in many of the papers. The GDG supported this time-frame.

						work through the system but do not agree with a restrictive time frame.	
SH	British Paediatric Mental Health Group of the Royal College of Paediatrics and Child Health	3	FULL	130		The graphs of the consensus documents are confusing if there have been disagreements at various stages of the consultation process.	Noted, but we have included such detail to allow transparency.
SH	British Paediatric Mental Health Group of the Royal College of Paediatrics and Child Health	4	FULL	132		Why do all children with mild CFS/ME need referral to specialist care after 4-6 months. As I read it from the table, it is appropriate to refer those who wish for a referral or who are not doing so well, but in the recommendations of the guideline it comes out as a 'should'. Many General paediatricians are competent to oversee the management of these children, leaving specialist care for those who really need this scarce resource.	The recommendation has been changed and an alteration has been made to the flow chart.
SH	Cambridgeshire Neurological Alliance	32	FULL	104	All 5.2.8	"Primary healthcare professionals should be familiar with the presenting features of CFS/ME" ➢ The reality is that they are not. There are still horror stories of GPs/others mocking, or just ignoring the person's remarks, or just appears evasive and/or quite rude.	The aim of the recommendation is to encourage training in this area to avoid this happening in future.
SH	Cambridgeshire Neurological Alliance	33	FULL	106	All	The five bullet points listed are often seen in the severe CFS/ME stages and must be seen as part of the CFS/ME symptom list	Noted and this is recognised, but are also listed here as 'red flags' where additional investigation may be needed at any stage of the illness.
SH	Cambridgeshire	34	FULL	107	All	➢ The head-up tilt test should be carried	Issue 1 – Tilt test: The GDG

	Neurological Alliance			Page 125 Page 126 Page 126 Page 126 Page 126 Page 127 Page 128 Page 132 Page	25. All 1. 4. 7. 5.4 All 5.4.4 All All And 3.	out and that would prove the level of disability ➢ Serology testing should be done as many people who have had tick bites, were in fact diagnosed with CFS/ME ➢ Foliate levels can be added as well NICE should recognised that extreme weight loss is also a feature of M.E. and can be due to the hormone disruption impact, severe confusion (i.e. not remembering to eat), unable to self-care, through level of disability, or severe allergies and food	did not find sufficient evidence that this was helpful in diagnosis. We have noted only that they are not to be used routinely, but that clinical indications should guide investigations Issue 2 – Borreliosis: The statistics on borreliosis from the National Reference Laboratory (England & Wales) in Southampton are that about 600 cases of borreliosis are diagnosed annually, of which only two to three have brain involvement. The lab has tested several hundred CFS patients using a validated and sensitive serological test and has found only one positive. This patient had evidence of prior infection - but the patient had had a tick bite and a feverish illness i.e. 'an indicative history'. Therefore, routine testing is not warranted. Issue 3 – Folate levels: The GDG did not find sufficient evidence that this was helpful in diagnosis as a routine test, but may be done if indicated. Issue 4: This section is with regard to excluding other

				133		intolerances.	conditions, for which extreme weight loss may be a symptom. The concern of the GDG is that many potentially life threatening conditions are not identified as the symptoms the patient experiences are attributed to the CFS/ME.
SH	CFS/ME Clinical Network Coordinating Centre	5	FULL	107		Should the EBV/infectious mononucleosis be in the routinely INCLUDED section?	This is a list of tests which should not be done routinely.
SH	Chronic Fatigue Research Unit at King's College London	5	FULL	91	5.2.5, 2	Page 91 (5.2.5,2) draws attention to the conclusions of the Hickie et al 2006 BMJ paper on the predictors of post infective fatigue. There is no mention of our larger UK primary care based prospective study of the predictors of post infective fatigue in the larger cohort study carried out in UK primary care (Wessely S, Chalder T et al. Post Infectious Fatigue: A Prospective Study in Primary Care. Lancet 1995;345:1333-1338) which identified the role of pre exposure depression on the development of post infectious fatigue. That study showed a different pattern of predictors between acute and chronic post infectious fatigue, a finding replicated in the subsequent albeit smaller King's EBV primary care study. The latter concluded that "In the univariate analysis, increased baseline levels of immune activation were associated with and predictive of fatigue at 3 months. Cortisol levels were not	We have removed the recommendation on post-viral management. Regarding the evidence for post-infectious fatigue, that is outside the scope of this guideline. Note also we have clarified management in the early stages of the condition.

						associated with, or predictive of fatigue. Using multivariate models of clinical and psycho-social baseline factors, severity of symptoms and illness perceptions were found to best predict fatigue 3 months later. At 6 months, fatigue was best predicted by female gender and illness perceptions, and at 12 months by female gender and a symptoms-disability factor" (Candy et al. Predictors of fatigue following the onset of infectious mononucleosis. Psychological Medicine 2003;33:847-853). That study is of particular interest since it concluded with a small randomised trial that showed that a single session of activity counselling decreased subsequent fatigue Given that it is accepted that EBV is an established risk factor for the development of CFS, then we believe that this finding is of clinical relevance – we note also that the ME Association in their submission , already published on the internet, appeal for more guidance on what to do in the early stages of illness, this might also speak to that issue (Candy et al A randomised controlled trial of a psycho-educational intervention to aid recovery in infectious mononucleosis. Journal of Psychosomatic Research 2004;57:89-94). NICEmight also note another new paper from New Zealand that is a prospective study of chronic fatigue and CFS after infection – in that paper EBV was a risk factor for chronic fatigue at 3 months, but not for CFS at 6 months- on the other hand depression and anxiety were associated with the onset of both (Moss-	

						Morris R, Spence M. To "lump" or to "split" the functional somatic syndromes: Can infectious and emotional factors differentiate between the onset of chronic fatigue syndrome and irritable bowel syndrome? Psychosomatic Medicine 2006;68:463-469. 9).	
SH	Chronic Fatigue Research Unit at King's College London	10	FULL	134	14-16	Page 134, lines 14 – 16: "CFS has been described as part of a broader condition that includes a range of disorders including fibromyalgia, irritable bowel syndrome…." True, and this will be well received by many doctors, since it reflects their views, and emphasises the way in which we can increase our knowledge of one "syndrome" by drawing on relevant information from another. The considerable literature now on fibromyalgia and its management, the literature on chronic pain, and so on and so forth, is directly relevant to many CFS patients in whom Generalised or muscle pain can be such a prominent feature. We think that this section could be strengthened by firstly making it clear that the statement "has been described" is actually rather more evidence based – there are far too many primary studies to cite, but useful quantitative reviews are found in Aaron L, Burke M, Buchwald D. Overlapping Conditions Among Patients with Chronic Fatigue Syndrome, Fibromyalgia, and Temporomandibular Disorder. Arch Intern Med 2000;160:221-227 and elsewhere, and General reviews in Barsky A, Borus J. Functional somatic syndromes. Annals of	Thank you for these references. The cause of CFS/ME was outside the scope of the guideline, and it is not possible at this stage to review all the evidence on this issue. The GDG is aware of the Gibson Inquiry report and generally accepts the conclusions.

						Internal Medicine 1999;130:910-921. Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354:936-939. and there are also many systematic reviews of treatments	
SH	College of Occupational Therapists	36	FULL	116	7	*"All treatments are offered allowing the person with the CFS/ME to refuse without compromising the future therapeutic relationship".* This is an ideal principle and one that we'd all like to assume but I'm concerned that it might be unworkable in reality. There are times when a patient's preoccupations etc may severely interfere with them making progress, snookering opportunities for the therapist to assist them with moving forward with any type of treatment. (In some of these circumstances we cannot continue to offer intervention at that time but would certainly be pleased to offer intervention without prejudice at a later stage if the person has progressed). Please could we have more clarity here?	The view of the GDG is that this an abiding principle.
SH	College of Occupational Therapists	41	FULL	88	25	"*disease*" is CFS a disease? A better word may be 'illness' or 'syndrome'.	Noted and consistent language has been applied throughout.
SH	College of Occupational Therapists	42	FULL	89	1, 2	Sentence appears out of context.	Thank you for pointing this out. This has been revised.
SH	College of Occupational Therapists	43	FULL	104		Only one other symptom in addition to fatigue. Are we now saying that all patients have chronic fatigue rather than chronic fatigue syndrome? In clinical experience there is a difference between those with a	We have given guidance on broad criteria to alert the clinician to the possibility of CFS/ME, not for use as

						primary fatigue state, which is always likely to impact on mental functioning as well, and those who have a distinct range of symptoms with a number of features, as described in current criteria. There does not seem to be sufficient evidence presented to contravene current practice and clinical experience that there is a distinct syndrome.	diagnostic criteria specifically. This has been clarified in the guideline.
SH	College of Occupational Therapists	44	FULL	105	3rd box	Words "adult or" missing only, refers to child.	Noted and revised.
SH	College of Occupational Therapists	45	FULL	111	4, 5	Multiple authors – Sharpe et al – not just Wessely & Sharpe.	Noted and revised.
SH	College of Occupational Therapists	46	FULL	113	5	Is the *International CFS Study Group* the Canadian definition? If so, it needs to be referenced for cross-referencing.	Reference added.
SH	College of Occupational Therapists	47	FULL	125	25	Perhaps the possibility of anorexia nervosa and other eating disorders should be specifically mentioned in relation to weight loss.	The GDG considered that the cause of the weight loss was then to be explored, rather than suggesting causes in this guideline.
SH	College of Occupational Therapists	48	FULL	125	28	Add 'food intolerances and bowel problems.'	Noted, but this refers to difficulty eating as a key concern for the GDG. We have recognised elsewhere the symptoms of food intolerances and bowel problems.
SH	College of Occupational Therapists	49	FULL	127	7 / 8, 11/12, 13	Ethically, statement 2 is sound in terms of respecting an individual's choice. However, clients need to be aware that resources are limited and interventions are based on	Noted.

						evidence, as stated elsewhere in this document. So, in essence, the therapeutic relationship may be compromised if the patient refuses an intervention because there may be no other intervention on offer and the therapeutic relationship ends. We must be honest from the outset as to what our services can offer and not raise unrealistic expectations. Statements 4 and 5 emphasise this.	
SH	College of Occupational Therapists	50	FULL	134	1	There would be a consequent adverse impact on both the therapeutic relationship and healing process.	We hope the revised text addresses this issue.
SH	College of Occupational Therapists	51	FULL	134	11	Doctor / healthcare professional.	This has been revised.
SH	Department of Health, Peninsula Medical School	21	FULL	88 -89	1- ..8	See above comments on p36, line 27. While the content of this section is largely apposite, it is unhelpful to start by saying it can be a problem! It should start by empowering clinicians to be more confident in the pattern recognition process that enables diagnosis. The problems can follow. The diagnosis depends on recognition of the characteristic set of symptoms, appropriately characterised in type/range and by what factors affect them. NB it is important to explore the nature of the tiredness/fatigue just as we do pain, because the patient will then be able to clarify how different this experience is from everyday fatigue or fatigue associated with some other conditions (eg depression). The presence of malaise, worsened by	Noted and revised.

						exercise/activity is important as is cognitive change. Notably this has been reinforced by a recent study showing the symptoms that can help differentiate CFS/ME from depression (*Hawk C et al. Int J Behav Med 2006. 13: 244-251*). It is important to emphasise that a positive provisional diagnosis is most likely to be achieved by setting aside sufficient time to characterise the history upon which diagnosis depends, and to recognise characteristic features, such as delayed setbacks after over-activity. There should also be reference to the undoubted therapeutic benefit of the narrative history, as well as its valued role in diagnosis.	
SH	Department of Health, Peninsula Medical School	22	FULL	89	1, 7	"Red Flags" must be explained either here, or in the glossary of terms or both. Not everyone will know what these are.	Thank you for pointing this out. This has been revised.
SH	Department of Health, Peninsula Medical School	23	FULL	95 95 107 109	Table 9c Table 9c Box I. 2 5-6	Here and throughout all text: The term is Creatine KInase. Creatinine is different. I am not sure if this is the reason for the confused statements on this test in the later sections (see below). At p 95, 9c, the statement is that CK is agreed as an appropriate test, but later and in the summary of recommendations it is stated as only agreed for children, but without any explanation for why and how this conclusion was reached. The recommendation is bizarre. One of the differential diagnoses for CFS/ME (adults and children) with prominent muscular pain or weakness is a primary muscle disorder	Noted and clarified for adults and children. We have revised the term.

						(various myopathies) or a multi-system disorder affecting muscle (eg poly-/dermato-myositis, polymyalgia rheumatica, vasculitis). CK is a valuable screening marker for such muscle disorders, and is simply and cheaply done.	
SH	Department of Health, Peninsula Medical School	24	FULL	111	9-10	See comments above (P 36 line 12) re CDC. And spelling is “Centers”	Thank you. This has been revised.
SH	Department of Health, Peninsula Medical School	25	FULL	111-112	27-… -4 Sections 5.3.2 .2/3	It may be worth pointing out that the Canadian definition has not (to my knowledge) been tested or validated as a set of criteria, in view of its popularity in some quarters.	Noted.
SH	Department of Health, Peninsula Medical School	26	FULL	114 - 115	16-.. -5	The text and the tabulation imply that the health professionals mentioned are all equally capable of making a diagnosis. Yet, apart from a hospital physician (not mentioned in the table – see below), most of these other professionals, although capable of contributing to treatment and assessment, are not trained or skilled to make diagnosis, especially not in the setting of complex differential diagnosis and co-morbidity. This section needs to be substantially re-thought and rewritten to reflect the actual roles, training and capability of different health professionals.	Thank you for this comment. This section has been revised.
SH	Department of Health, Peninsula Medical School	27	FULL	115	Table	Hospital consultant physician must be added, as this is probably the most common, and most expensive, health care professional, to whom patients are referred	Thank you. This section has been revised.

						for diagnosis.	
SH	Department of Health, Peninsula Medical School	28	FULL	124	1: Box	Recommendations: Strongly agreed.	Thank you.
SH	Department of Health, Peninsula Medical School	29	FULL	125-126	23- … -6	Are these the only "red flags" referred to above (89: 1,7)? What about suicidal ideation; extreme agitation/anxiety, for example, severe angina-like chest pain, niceness of breath on exertion, and numerous other symptoms that could signify other disease? It is important to be clear on what grounds any particular differential diagnoses are specifically promoted to be red flags as opposed to differential diagnostic clues. Whilst NICEwill not wish to write a medical textbook, it is important that its specific mention of "red flag" conditions are justified by some explicit criterion, and be explained to avoid diversion of attention away from the FULL range of differential diagnoses.	Noted, and the recommendation on this and the process of diagnosis have been revised,
SH	Department of Health, Peninsula Medical School	30	FULL	126	21	Add: co-morbidities that render diagnosis and/or treatment more complex. This, in my wide clinical experience, is the most important discriminant for referral to specialist care apart from severity.	Noted and revised.
SH	Department of Health, Peninsula Medical School	31	FULL	132	5.4.5	See also comments above on p 27 algorithm. There is a serious problem with the phrasing of these three recommendations. Despite the first recommendation, the other two are written in a way to imply/encourage specialist referral rather than saying that, if referral is needed, these are the timings. The need for	We have revised the process of diagnosis and management to clarify which interventions can be delivered in a generalist setting, and which interventions need specialised input.

						referral to a specialist unit is covered in the earlier text, but this needs to be restated or explicitly cross-referred to, so that primary care clinicians are enabled to care for patients within their competence and expertise.	
SH	Department of Health, Peninsula Medical School	32	FULL	133	24-25	This statement ("no objective abnormalities") is very misleading. The research literature on the pathophysiology and manifestations of this illness, using a wide variety of techniques (eg blood changes, CNS imaging changes), shows that there are very many objective changes associated with the illness, some of which may be highly pertinent to the experience of illness (eg cytokine levels, fMRI changes). That is different from the use of "objective tests" in clinical diagnosis, which I think is what is being conflated here, and for which none have been shown to have the necessary specificity or positive predictive value.. This sentence needs to be rephrased, as it is currently manifestly incompatible with a substantial research literature.	This is now clarified in the text.
SH	Department of Health, Peninsula Medical School	33	FULL	133-5	Section 5.5	This is really valuable and Generally well stated. My specific comments below do not undermine the value that I attach for this, and the need for its essence to be sufficiently replicated in the NICEversion.	Thank you.

SH	Department of Health, Peninsula Medical School	34	FULL	133	27	A case definition can be "objective", as can a clinical diagnosis by a skilled clinician, even in the absence of "objective tests". I think the word needed here is "validated". Moreover, it is the very fact that a skilled and experienced clinician can convey a high level of diagnostic certainty that can make this transaction a powerful tool for re-enablement. If a primary care physician is unable to have that confidence to convey that level of conviction, then that is a basis for specialist referral.	The text has been amended.
SH	Department of Health, Peninsula Medical School	35	FULL	134-5	25 - .. -5	Agreed. However, the term "medically unexplained syndrome" merits a similar statement to that given on 135, lines 2-4. The fact that medicine cannot currently explain something neither makes it any less valid, nor a singular entity. It is simply a statement of the limitations of contemporary medicine and science, and has absolutely no relevance as a nosological entity in clinical discourse.	We hope the revised wording helps.
SH	Invest in ME	103	FULL	88	1	- *Making a diagnosis of CFS/ME* "5.1 Introduction CFS/ME (Chronic Fatigue Syndrome/Myalgic Encephalomyelitis or Myalgic Encephalopathy) is a condition for which causation is uncertain and diagnostic criteria variable. " IiME Comment: It is not encephalopathy – see WHO ICD 10 G93.3.	The title of the guideline was amended to 'Chronic fatigue syndrome/myalgic encephalomyelitis (encephalopathy)' in response to the scope consultation with stakeholders.
SH	Invest in ME	104	FULL	88	9	• The range of presenting symptoms is	Noted and this sentence has

					onwards	wide, and fatigue and pain are not always the prominent features. IiME Comment: So why is fatigue so heavily emphasised and used to influence elsewhere in this document?	been revised.
SH	Invest in ME	105	FULL	88	11onwards	• Patients may have been investigated extensively, but fruitlessly, for varied physical symptoms and may feel frustrated by the lack of help they have received from the medical profession by the time the diagnosis is made. IiME Comment: The lack of a proper medical examination and lack of funding by MRC for biomedical research needs to be emphasized as a cause also.	The guideline advises a full medical examination and makes research recommendations.
SH	Invest in ME	107	FULL	88	*23 onwards*	'Red flags' in the history and examination indicate the need for urgent specialised investigation. IiME Comment: They also indicate the urgent need for biomedical research to find a diagnostic test for ME.	This is beyond the scope of the guideline.
SH	Invest in ME	108	FULL	89	13 onwards	- 5.2.2.1 There is insufficient evidence to show that potential diagnostic tests for CFS/ME are useful diagnostically for adults and children. 1 IiME Comment: Potential diagnostic tests will be useful in allowing a patient to become prepared early with a diagnosis of ME. 2 Specific diagnostic tests reviewed	Issue 1: This comment refers to an evidence statement which is a statement that synthesises the evidence findings. The GDG discussed the evidence and agreed this

						are: − the head up tilt test(2/3) − five laboratory blood tests (fibrinogen, prothrombin fragment 1+2, thrombin-anti-thrombin complexes, soluble fibrin monomer (SFM) and platelet activation (CD62P, ADP)) (3) − auditory brainstem responses (3) − electrodermal conductivity (3). IiME Comment: These tests may, however, identify subgroups of CFS/ME.	statement. Issue 2: No evidence was found to support this. If evidence arises, it will be considered in the revision of the guideline.
SH	Invest in ME	109	FULL	90	1 onwards	- *5.2.4 Evidence Statements* *5.2.4.1* Clear risk factors for CFS/ME have not been identified. (2-) *5.2.4.2* There is low grade or limited evidence for a wide range of risk factors including: − sick certification after viral illness, IiME Comment: What about the viral illness itself? − presence of fatigue at time of viral illness, IiME Comment: Is this implying that the fatigue is the causative factor rather than the viral illness? − lower physical functioning, IiME Comment: This must be really low grade evidence if it exists? − higher pain and fatigue scores at	This is an evidence statement which is a statement that synthesises the evidence findings. However, because of the lack of utility of this evidence statement, this has been deleted.

						baseline, older age (adults and children), IiME Comment: We fail to see what evidence this can refer to. − exhaustion, − being female, − low educational level, IiME Comment: Well, this puts the end to the idea of “yuppie flu”!!!! Are NICEreally stating that people of lesser education are now the suspects for ME? − visits to the GP, IiME Comment: This we find ridiculous! Are NICEstating that people who need to visit their GP are more inclined to get ME? Maybe the frequency of visits might have something to do with being disbelieved? It might have something to do with symptoms persisting despite ‘standard’ treatment? Is NICEattempting to portray ME patients as hypochondriacs? − longstanding limiting medical condition aged 10 years, − higher social class in childhood, IiME Comment: And yet lower educational level earlier! − psychological distress prior to presentation, IiME Comment: Where is the evidence for this? It does NICEno credit to list these ‘risk	

						factors' without supplying evidence. − presence of infectious mononucleosis, − positive Monospot tests at time of onset, − time in bed at onset, − exercise power, − mood disorder. (-2) IiME Comment: We do not believe this is worthy of a document purporting to assist diagnosis or treatment of ME. It is widely accepted that ME follows viral or bacterial infections, vaccinations, chemical exposure. Yet these risk factors are not mentioned at all. There is no mention of the pressure on returning to work or school prematurely after infection as a cause for long term ME. What is low grade is the research funding and epidemiological studies. *5.2.4.3* Clear risk factors for development of CFS/ME in children and young people have not been identified (2-) IiME Comment: How about pressure to return to school too early?	
SH	Invest in ME	110	FULL	91	18-23	- 5.2.5.2 *Additional Clinical Evidence* No new evidence was found in the update searches. However, a recent paper in the BMJ concluded that 'prolonged fatigue states	We have removed the recommendation on post-viral management.

						after infections are common and disabling' and that post-infective fatigue syndrome was predicted 'largely by the severity of the acute illness, rather than by demographic, psychological, or microbiological factors'. This strengthened the recommendation regarding post viral management. IiME Comment: What about research from Dr. Vance Spence and oxidative stress? This is due, perhaps, to the make up of the NICE group which seems to have nobody qualified to analyse this data.	
SH	Invest in ME	111	FULL	91	25	- *5.2.6 Health Economics Evidence Summary* The investigations needed to rule out other significant disease before making a positive diagnosis of CFS have a number of components which are of importance from an economic perspective. IiME Comment: Are we still discussing ME or is it just now CFS? These are very lax standards of precision in this document.	Noted with thanks, this has been changed.
SH	Invest in ME	112	FULL	92	*12-17*	"Any approach which produces the same outcome for less healthcare provider time will improve the cost-effectiveness of the overall process." IiME Comment: This last sentence is so risky as it will inevitably lead to short-cuts, lack of precision in diagnosis and almost inevitable degradation in treatment.	For the evaluation of cost-effectiveness, both costs and consequences of an intervention are examined. Therefore, the quoted paragraph has to be viewed in context of the prior section. It can be assumed that patients accrue disutility over time while they go through multiple investigative

							procedures until a final diagnosis is made. This means that the longer this period is, the greater the quality of life loss in absolute terms. Necessary staff time is directly linked to the costs of a test, and with the disutility to the patient over time, less time intensive interventions are expected to be more cost-effective. It should be noted that "the same [effectiveness] outcome" means per definition that items such as 'diagnostic precision' will not be compromised by an alternative programme.
SH	Invest in ME	113	FULL	92	18 onwards	"Regarding the role of investigations after a positive diagnosis of CFS has been made, the likelihood of the result of the investigation changing management should be considered, together with the improvement in quality of life that change might bring, and contrasted with the cost of the investigation and the disutility of the investigation to the individual " IiME Comment: Are we still discussing ME or is it just now CFS? These are very lax standards of precision in this document.	Noted with thanks, this has been changed.
SH	Invest in ME	114	FULL	93	1 onwa	*5.2.7 Clinical Scenario Questionnaire to GDG and Wider Group*	In accordance with the methodology for clinical scenarios, the assumptions

					rds	1. The person with the CFS/ME and health care professionals involved in their care will make decisions in partnership. These are directed by the patient's personal preferences and builds on the existing experience and skills of the professional. IiME Comment: Elsewhere it is the patient who is in control yet here it is partnership. It should be consistent throughout these guidelines that the patient is always in control. Decisions cannot be based on existing experience of the 'professional' if they are biased or lacking in appropriate knowledge. This very much depends on the healthcare professional associated with the patient. 2. All treatments are offered allowing the person with the CFS/ME to refuse without compromising the further therapeutic relationship. IiME Comment: Yes – this is extremely important 4. Treatment is provided by the NHS in the context of availability of adequate numbers of competent, appropriately trained health care professionals. IiME Comment: This is important but who decides 'appropriately trained'?	that form the basis for answering the questions must be explicit. So that respondents have a common understanding of the factors which influence the appropriateness of treatment. These statements were agreed as assumptions for the questionnaire. They are not guideline recommendations. A fuller explanation is in the methodology chapter.
SH	Invest in ME	116	FULL	*105*		*"similar symptoms and signs as CFS/ME"* IiME Comment: The biomedical community have listed a number of contraindicative conditions that need to be considered in	Issue 1 – Signs and symptoms : Noted with thanks.

						isolating a diagnosis of ME These could be proposed for inclusion here to replace the existing text. "Primary healthcare professionals should listen careFULLy to parents' and/or carers' concerns and be willing to reassess their initial opinion, or to seek a second opinion from a 'colleague if a child fails to recover as expected. " IiME Comment: who is 'qualified' and who is a 'colleague'? This is a very interesting formulation of expression, as this could come from the discredited MSBP diagnosis criteria, and is obviously biased towards the psychosocial model. Biomedical experience of ME professionals confirm that it is quite a common occurrence that patients do not recover in the traditionally anticipated manner. However, this does not indicate psychological intervention, rather a lack of understanding of the aetiology and treatment attempted. Surely a referral to a paediatrician with expertise in ME should be made to ensure that ME is correctly assessed, rather than a General paediatrician? Shouldn't a referral be made more rapidly than "within 6 weeks"? "As with other potentially chronic conditions, before progressing to a diagnosis of CFS/ME, medical examination and	Issue 2 – Second opinion:The wording is taken from the Referral for Suspected Cancer guideline. As with

						assessment of mental health (both targeted according to the presenting symptoms) should be carried out. " IiME Comment: Why mental health – is this applicable to all other illnesses – such as cancer, MS, IBS? This is quite shocking. Is it usual to have psychiatric assessments of patients presenting with "*potentially chronic conditions*"? This, again, indicates bias towards the psychosocial model.	CFS/ME, cancer is rare in children and is not the first thing that may be suspected. This aims to encourage healthcare professionals to listen to parents/carers, 'think outside the box' and to seek a relevant second opinion. It would be difficult to dictate from whom the opinion would be sought as this would depend on the symptoms. We have revised the recommendation on mental health…
SH	Invest in ME	117	FULL	*106*		"In the absence of a definite diagnosis and/or while waiting for referral, advice and symptom management should not be delayed until a diagnosis is made." IiME Comment: This statement again goes in direct contravention of the biomedical model, where treatment requires a specific diagnosis. "When an acute infection is followed by excessive fatigue, the adult or child should receive advice on how to promote recovery. The advice should focus on sleep management, risks of prolonged bed rest (for example, deterioration in muscle function), and a gradual return to a normal daily routine. " IiME Comment: Surely the promotion of	Issue 1: The view of the GDG was that symptoms should be managed while waiting for a diagnosis. Issue 2: This recommendation has been removed.

						adequate rest is more important. The testimonies in this document alone detail the risk of returning to activity too soon. You are not listening to the patients. How about the risks of GET and CBT and other psychological therapies? The benefits of adequate rest need to be emphasised along with adequate supplies of current, accurate information about ME and the research which is underway. "Investigations should be tailored to the history, and signs and symptoms of the adult or child, taking into account other possible diagnoses. " IiME Comment: What does this mean? It is so loose that it is an irrelevant comment. "Before progressing to a diagnosis of CFS/ME, investigations should be carried out to exclude other diagnoses that would explain the symptoms. Such tests could include the following, but clinical judgment should be used. • Urinalysis for protein, blood, glucose. • FULL blood count. • Assessment of blood ferritin levels (children only). • Urea & electrolytes. • Liver function tests. • Thyroid function tests. • Erythrocyte sedimentation rate / plasma	Issue 3: The GDG considered this to be an appropriate recommendation.

						viscosity. • C-reactive protein. • Random blood glucose. • Serum creatinine. • Screening blood tests for gluten sensitivity. • Serum calcium. • Creatinine kinase (children only). " IiME Comment: What is the physical biological/biomedical basis for defining these clinical tests in relation to the aetiology of ME? This list needs to be modified, at a minimum. Prof Puri has identified raised levels of Choline along with other chemicals in the brain blood interface in ME patients, and Drs Kerr and Gow have identified modified gene expressions unique to ME patients. If we look at the gene array we do find some abnormalities, but if patients with ME/CFS, exercise then we find a lot more abnormalities. The standard NHS blood and thyroid function tests have been shown not to address specific expressions in ME patients and, therefore, cannot provide reliable results. There is still debate about specific thyroid function tests being implicated in ME, e.g. maladjustment of T3 and T4 levels that do not provide the expected results.	Issue 4: No evidence was found for the use of these tests as diagnostic tools. If evidence arises, it will be considered in the revision of the guideline.
SH	Invest in ME	119	FULL	107	*3-6*	5.2.9 Deriving Recommendations The GDG decided that certain	The GDG has given general guidance but tests must be

						investigations should be carried out to rule out other diseases and conditions, but it was impossible to recommend a definitive, comprehensive list IiME Comment: which surely shows a failing in these guidelines. We need to have a list, which can be added to as more research becomes available. These guidelines already rule out necessary testing of known mis-diagnoses.	based on the presenting symptoms. The GDG discussed this but it would be impossible to be inclusive re-writing a medical textbook..
SH	Invest in ME	121	FULL	110	*1*	*- 5.3 Arriving at a Diagnosis* *5.3.1.1* Evidence to substantiate existing case definitions of CFS or ME is limited. No studies have established the superiority of one case definition over another IiME Comment: Why are the Canadian Guidelines Criteria not referenced here, since they are becoming more widely accepted around the world by the biomedical community of ME experts, rather than inventing a further set of criteria that are not agreed outside the psychosocial model practitioners? *5.3.1.2* Community based studies have indicated that patients meeting CDC 1994 criteria form a more heterogeneous group than patients meeting CDC 1988 criteria (2-) IiME Comment: So shouldn't Canadian guidelines ("even more stringent" according to NICE) now be used ?	We have added a synthesis of criteria used in other guidelines (from the New Zealand Guidelines Group) for information. We have also revised the recommendations on diagnosis for clarification.

SH	Invest in ME	122	FULL	110	7 onwards	*- 5.3.2 Clinical Evidence Summary* The definition of CFS/ME is based upon its classification as a 'syndrome,' that is, a pathological condition characterized by its symptoms rather than its cause. The systematic review conducted by the Centre for Reviews and Dissemination (CRD) at the University of York forms the primary evidence base for adult-onset CSF/ME in this guideline IiME Comment: Isn't this then putting the whole guidelines document at risk as that York review was limited and unrepresentative?	The York review was conducted using recognised and validated methods in accordance with NICE methodology. Details of the methods are reported in the full guideline.
SH	Invest in ME	123	FULL	111	*4-8*	The Oxford Criteria of CFS/ME, developed in 1991 by British psychiatrists Simon Wessely and Michael Sharpe defined CFS/ME as a "syndrome in which fatigue has been present for at least six months, during which time it has been present more than 50 per cent of the time." Other symptoms may also be present such as myalgia, mood and sleep disturbance. [7] . IiME Comment: These are psychiatrists and cannot represent a pathological illness. The Oxford criteria are far too broad to be of any use.	Have revised this statement.
SH	Invest in ME	124	FULL	111	*27*	The 2003 Canadian definition is more stringent and was developed by an international CFS clinical team. IiME Comment: So why not recommend the use of the Canadian Guidelines if they are	The evidence review concluded that no current case definitions are established as being superior to the others. The Canadian criteria are based on expert

						more stringent.	opinion, and not research evidence.
SH	Invest in ME	125	FULL	113	*17 onwards*	*Health Economics Evidence Summary* IiME Comment: The economics of diagnosis are of little interest. Accurate diagnosis is the requirement and will likely lead in the long term to economies. We believe it is a false economy to attempt to quantify at the outset which line of diagnosis is to be used based on this ROC curve model.	There are necessary decisions to make when it comes to diagnosis and the all consequences to the NHS and its patients need to be included in this process. Please see Nicola Crichton's article (J Clin Nur 2002;11:134) for an introduction to ROC curves.
SH	Invest in ME	126	FULL	116	*4 onwards*	1. The person with the CFS/ME and health care professionals involved in their care will make decisions in partnership. These are directed by the patient's personal preferences and builds on the existing experience and skills of the professional. IiME Comment: Patient must be in control, not just partnership. Will this model then support a patient who refuses CBT and GET, in the knowledge that these therapies are either unhelpful or harmful, when insurance companies demand that they be used? 2. All treatments are offered allowing the person with the CFS/ME to refuse without compromising the further therapeutic relationship. IiME Comment: Agreed. We welcome this. 3. There is a good rapport in which the patient and their families/carers feel	Issue 1: We have recommended throughout the need for partnership, working with individuals as they prefer. It should also be noted that this relationship may change over time as people become more expert in self-management if appropriate. Issue 2: Thank you.

						believed and validated. IiME Comment: Do NICEapply similar comments to other biological illnesses – cancer, MS, HIV/AIDS? Do these patients have to be 'believed' and 'validated'? Isn't this indicative of the current environment where ME patients are treated as having a somatoform condition? 4. Treatment is provided by the NHS in the context of availability of adequate numbers of competent, appropriately trained health care professionals. IiME Comment: Who decides which 'professionals' are competently trained. These should be specified.	Issue 3: We have recommended this to address concerns that people are not being believed, and have also recommended that the reality and impact of the condition and symptoms should be acknowledged. Issue 4: Details of training are outside the scope of a clinical guideline. However, it is anticipated that appropriate professional bodies will ensure that healthcare professionals are adequately trained.
SH	Invest in ME	127	FULL	124	*1*	- *5.3.5 Recommendations* 5.3.5.1 A diagnosis of CFS/ME in an adult should be made after symptoms have persisted for 4 months, and after other likely causes of the symptoms have been ruled out IiME Comment What are the agreed criteria for diagnosis? Shouldn't the international Canadian Guidelines be used for such a diagnosis, and what is the reason for the	Issues 1 and 2: The diagnosis recommendations have been revised to clarify. Regarding the time frames, these are guides to allow for appropriate investigation and to ensure that people are not left without a diagnosis after a prolonged period. However, where a diagnosis <u>can</u> be made earlier, then there is no

						proposed 4 months delay? This again flouts accepted international wisdom that early diagnosis and intervention can help prevent the onset of severe ME and provide evidence for refinement of diagnostic tools. *5.3.5.2* The diagnosis of a child should be made by a General paediatrician after symptoms have persisted for 3 months and other likely causes of the symptoms have been ruled out IiME Comment Again, a paediatrician with expertise in ME would, surely, be more appropriate. Also, why wait 3 months for a diagnosis, as a different time period from an adult? Early diagnosis is even more important for children. *5.3.5.3* When a diagnosis is made, a prognosis of cautious optimism should be conveyed. With appropriate management, most children and adults, but not all, will have some improvement and some will recover fully. IiME Comment: What is the scientific basis for this statement? Why single out this illness from others. Where is the basis for this statement? 'Some' adults, 'some' children, 'some' will and 'some' won't. Define or quantify 'some'. Otherwise this is a totally pointless statement. Patients want honesty – even children – so it is better to be realistic and factual rather than woolly and unspecific Has there ever been any scientific research	requirement to wait for the time points stated. Issue 3: Noted and revised to reflect Centres for Disease Control and Prevention data on prognosis

						published in the international community to base such a prosaic statement for cautious optimism. Has there been a scientific or rigorous assessment of the outcomes of ME patients? This paragraph/statement raises a number of major questions that need to be answered before the statement could be accepted, such as: how many patients were involved; what was the patient selection criteria; what were the diagnostic tools used to confirm the cohort was purely suffering ME; were there other medical or clinical influences; over what period of time did the study follow individual patients progress; what happened to the severe ME sufferers; what were the demographics; what were the statistical analysis results; what appropriate management techniques were trialled; what were the statistical samples of age and gender; what definition of "most" was employed, e.g. simple majority of all participants over/under a defined age; what percentage recovered FULLy; how was "some improvement defined"; who performed the research; was more than one medical research centre involved in the research; was the research approved by the Medical Ethics Committee; what clinical and research qualifications did the researchers possess; where were the study results published; who were the independent academic referees who assessed the academic and scientific rigorousness; and, who funded the study to be conducted? If any of the above questions can not be answered with adequate academic probity,	

						then the statement must be removed.	
SH	Invest in ME	128	FULL	124	*5*	*- 5.3.6 Deriving Recommendations* Diagnostic Criteria The GDG reviewed the current diagnostic criteria, but did not find any one of them particularly helpful in managing the condition or in making a definitive diagnosis. IiME Comment: This cannot be correct. The Canadian guidelines give specific expertise on diagnosis. Other specialists (Dr. Byron Hyde) also have good diagnostic criteria.	The evidence review concluded that no current case definitions are established as being superior to the others. The Canadian criteria are based on expert opinion, and not research evidence.
SH	Invest in ME	129	FULL	124	*7*	The case definitions used in research papers are not necessarily helpful in clinical practice, especially in a condition whose symptoms evolve gradually and where early recognition and treatment is probably beneficial. IiME Comment: Acute onset ME is not gradual. Most ME cases are acute onset.	This section has been revised.
SH	Invest in ME	130	FULL	124	*12*	The GDG was concerned that the application of narrow diagnostic criteria may make it less likely that advice and treatment is given early in the course of the illness. On the other hand, the GDG were also concerned that if broader criteria were used, people would be falsely diagnosed and other serious conditions missed. IiME Comment: Exactly - which is why the Oxford criteria are unfit for ME. Why does NICEcontinue using these criteria and not come out in favour of the Canadian	The diagnosis recommendations have been revised. The evidence review concluded that no current case definitions are established as being superior to the others. The Canadian criteria are based on expert opinion, and not research

						guidelines which are more stringent? There is no point in having Generalised and inaccurate criteria – such as the Oxford – if it means including other conditions due to the range allowed. This document is supposed to be for a neurological illness.	evidence.
SH	Invest in ME	131	FULL	125	*12*	- *Making a diagnosis* However, the GDG decided that a diagnosis was crucial to the patient and their families in understanding their symptoms and receiving appropriate treatment. It must however, be considered a working diagnosis and regularly reviewed IiME Comment: Shouldn't it be based on a thorough medical examination? Patients should be treated as individuals and not be the object of labelling. CFS/ME should not be seen as a dead end diagnosis where all investigations stop and patients are only called in for note taking.	Noted and revised (see also the recommendations on assessment and investigation).
SH	Invest in ME	132	FULL	125	*18*	Signs and Symptoms There was strong agreement that persistent, debilitating, post exertional fatigue characterised the condition IiME Comment: So why is GET recommended?	The recommendations are based on evidence for such interventions; however, patient preference and need is paramount throughout.
SH	Invest in ME	133	FULL	132	*1*	5.4.5.1 IiME Comment: [*Referral to specialised care* …] A referral of a patient diagnosed with ME should follow agreed diagnostic criteria that have been developed by gaining an	As noted throughout, management should be agreed with the patient and should be guided by the patient's preferences and

						understanding of the aetiology of the illness. Is there a “fingerprint test” that can differentiate Chronic Fatigue states from the neurological condition defined by the WHO ICD-10 93.3 definition? If not referral should be based on “cautious best practice approach”, noting that patients suffering with severe ME may be damaged by the application of GET and that there is no proof that CBT can assist such conditions. In fact, the “drop-out” rate of severe ME patients from the CNNC centres would suggest that CBT provides no positive outcomes. The CNNC should be able to provide statistics for their operation. However, it is noted that without scientifically rigorous statistical analysis this response statement is purely anecdotal, like much of the content of the proposed NICEguidelines. [*Referral* …] In addition to previous comments about timescale delays for referrals, what criteria are to be used to select the “moderate” or “severe” ME symptoms to instigate accelerated or immediate referral action? This statement seems to contradict a previously stated (and challenged) need for a diagnosis after 4 months for an adult and 3 months for a child.	needs. Regarding timeframes, definitions of severity can be found at the beginning of the guidelines, and earlier referral/diagnosis can be made if appropriate, for example for people with severe/disabling symptoms.

SH	Invest in ME	134	FULL	132	1 onwards	5.4.5.3 "The GDG considered that when seen in the early stages of illness, it is reasonable to observe adult patients for a few weeks before specialist referral as some patients will improve spontaneously. The view of the GDG is that no adult should wait for more than 6 months for a referral. " IiME Comment: In the early stages of illness it is important to identify viral or bacterial causes and treat them early with relevant antimicrobials. What are the statistics relating to this (wonderful event of) spontaneous improvement? From which clinical study are the published and peer-reviewed results available? The Guideline Development Group and the Independent Guideline Review Panel established with the National Collaborating Centre should have reported the significant findings to support this statement. Without the scientific basis to support this statement, this statement should be removed or reworded to - "Some patients who are not found to have ME will improve spontaneously".	However, patients may present with symptoms which then improve spontaneously, in which case they probably did not have CFS/ME. We refer to symptoms improving, not spontaneous remission of CFS/ME.
SH	Invest in ME	135	FULL	133	*7 onwards*	"Referral to a multi-disciplinary team specialising in CFS/ME The GDG decided that a referral should be made following a diagnosis. However, this may be a provisional diagnosis rather than a certainty. The view of the GDG was that 3-6 weeks following the onset of symptoms	The statistics on borreliosis from the National Reference Laboratory (England & Wales) in Southampton are that about 600 cases of borreliosis are diagnosed annually, of which only two to three have brain involvement.

						was Generally too short a time but that 6 months is too long. The GDG decided that 3-4 months following the onset of symptoms, once exclusion tests were completed and following a provisional diagnosis, was Generally the appropriate time to refer patients to a multi-disciplinary team specialising in CFS/ME. However, this needed to be based on the individual, as people with severe symptoms needed to be referred immediately. " IiME Comment: Infectious agents (such as Mycoplasma pneuomoniae), which are implicated in ME, may not be picked up by the test recommended to be performed by a GP. It is no point in waiting 3-4 months before prescribing antibiotics. Lyme Disease needs to be treated early so the diagnostic test (preferably the more precise US or Euro version) needs to be made. It is not only patients with severe symptoms who need to be treated early.	The lab has tested several hundred CFS patients using a validated and sensitive serological test and has found only one positive. This patient had evidence of prior infection - but the patient had had a tick bite and a feverish illness i.e. 'an indicative history'. Therefore, routine testing is not warranted.
SH	Invest in ME	136	FULL	133	*16 onwards*	5.5 A Conceptual Framework There is little understanding of the nature of the disease and there were differing views on the GDG about this with lengthy discussions. A view held by a few individuals on the GDG was that CFS/ME could not be identified or managed unless a broader view was taken. This perspective is put forward below. IiME Comment: Views by ME support	The framework has been revised. We recognise that there are different views on the nature of the disease, including whether CFS and ME are distinct entities. We accept the Gibson Inquiry's view that the origins and nature of CFS/ME are poorly understood and that more high quality biomedical

						groups show that ME must be seen as a distinct and separate illness from CFS. This is part of the problem with healthcare staff and others – by broadening the view inevitably the requirements for diagnosing and treating ME patients will be diluted.	research is required. We have revised the framework in an attempt to account for the different views and level of knowledge in a way that encourages professionals and patients to work together to improve care and services.
SH	Invest in ME	137	FULL	133	*20 onwards*	A conceptual framework for patients and health professionals when making a diagnosis of Chronic Fatigue Syndrome IiME Comment: Are we now talking only of CFS? There is a complete lack of precision in this terminology !!! "A diagnosis of Chronic Fatigue Syndrome (CFS) is made on clinical grounds alone after the exclusion of conventional disease processes that could account for the wide-ranging symptoms that are usually experienced by patients with CFS. As there are no objective abnormalities to account for the illness experienced and the associated disability suffered in CFS, additional distress for patients, their families and the wider social network commonly occurs. Importantly, the lack of an objective definition of CFS as a discrete disease entity can jeopardise the therapeutic relationship between patient and healthcare professional with a consequent adverse impact on the healing process. The relationship between the individual with CFS, their families and health professional can be further stressed by disagreements	This has now been clarified.

						about the origins of CFS. “ IiME Comment: Are we now talking only of CFS? Complete lack of precision in this terminology !!! Appalling precision in these guidelines.	The terminology has been clarified.
SH	Invest in ME	138	FULL	134	*5 onwards*	“Entrenchment and polarisation of viewpoints about a physical or psychological origin of CFS undermines relationships that support recovery” IiME Comment: so much evidence exists to support the biological viewpoint that this should not be here at all. ME patients are concerned about treatment for ME patients – not CFS “Another consequence of the unclear definition and aetiology of CFS is the difficulty experienced by patients and healthcare professionals in distinguishing CFS from several overlapping conditions such as fibromyalgia and irritable bowel syndrome. “ IiME Comment: This is ludicrous – ME has clearly distinct symptoms which proper medical examination will show. “Differing beliefs about definition and cause of CFS can extend from the patient and the doctor to family members and the wider	The GDG accepts the Gibson Inquiry’s conclusion that no current theory on the causes of CFS/ME is, as yet, supported by sufficient evidence, and that further biomedical research is necessary. The text has been revised. The GDG was conscious that some patients still experience

						community resulting in dissatisfied, disabled patients and frustrated doctors. “ IiME Comment: It also results in bigoted and biased doctors “The patient journey can become an ordeal with unnecessary distress, added costs and waste for the health economy, the patient and their family. CFS has been described as part of a broader condition that includes a range of related disorders including fibromyalgia, irritable bowel syndrome, chronic pain, pelvic pain, temporomandibular joint dysfunction and atypical facial pain. “ IiME Comment: Are we talking about CFS or ME? ME has also been described as a multi-system order involving immunological, endocrinological, cardiovascular and gastroenterological…..	delay in diagnosis. This section now includes statements intended to reduce this problem. See our comment above about acceptance of the Gibson Inquiry’s conclusions.
SH	Invest in ME	139	FULL	134	*25 onwards*	“Terminology used by doctors such as ‘functional syndrome’ and ‘medically unexplained symptoms’ are part of common usage in clinical practice today. The terms have arisen to describe non-conventional diseases and are intended to validate CFS and overlapping conditions to help improve patient care and research into the disorder. Although the term ‘functional’ has been	This section has been revised. We seek to acknowledge that different people hold different views on causation, and sometimes these views are strongly held. Since we do not know what the cause of CFS/ME is, the GDG cannot accept any of

						found to be more acceptable with patients than terms such as 'psychosomatic' or 'medically unexplained', some terminology has become derogatory with use. " IiME Comment: Are we talking about CFS or ME? This shows the hypocrisy with current healthcare in the UK toward ME. The reason that some terms have become derogatory relates to the lack of guidelines to healthcare staff to see the biomedical evidence behind ME and to obfuscate the issue by insisting on treating ME with psychological therapies. "*The terms have arisen to describe non-conventional diseases and are intended to validate CFS and overlapping conditions to help improve patient care and research into the disorder*". The term ME has been in the WHO ICD category as a neurological illness for a long time. NICEcould have taken the initiative and used the WHO term. Instead it does nothing but perpetuate the myths here.	the current theories, but must instead encourage more basic research and encourage those who hold strong views to take a more tolerant, open-minded attitude to ensure that patients who may benefit from various interventions do have access to those interventions.
SH	Invest in ME	140	FULL	135	*2 - 5*	"For some patients and health professionals, the functional concept and all associated terminology are deemed unacceptable. The 'mental or physical' condition debate predominates in the clinical encounter undermining the doctor patient relationship. "	We hope the revised version of this section of the guideline will lead to improvements in this regard.

						IiME Comment: These NICEguidelines are doing little to prevent this from continuing.	
SH	Invest in ME	141	FULL	135	*6 onwards*	"Outcomes are likely to improve if the diagnosis of CFS is communicated more successFULLy through a collaborative approach between the patient and doctor leading to a therapeutic relationship. " IiME Comment: Are we talking about CFS or ME? "This requires doctors to take an active approach to provide accurate information and to discuss key issues with patients on an ongoing basis to achieve better outcomes. " IiME Comment: It also requires the doctor to be aware of current and past biomedical research. If an effective therapeutic relationship is to develop, doctors must acknowledge that, despite the current lack of understanding of underlying causes of CFS (IiME Comment: Are we talking about CFS or ME?), the symptoms are real and the suffering and associated disability is genuine. The ideas, concerns and expectations of the patient, carers, families and the doctor should be explored for differences and similarities. Appropriate and agreeable terminology and understanding is important when making a diagnosis and establishing a therapeutic relationship. The definition and concept of CFS (IiME Comment: Are we talking about CFS or ME?) through a biopsychosocial	It should have been CFS/ME, as throughout the guideline. Noted and healthcare practitioners should be aware of the relevant research to their practice. We agree that the clinician should acknowledge that the suffering and disability are genuine and hope the revised text is helpful. Please see the Diagnosis chapter for a further discussion of these additional

						model acknowledges the role of both external and internal influences on the development of and recovery from CFS (IiME Comment: Are we talking about CFS or ME?). The biopsychosocial model negates the duality of mind or body and a significant cause of conflict between the patient and healthcare professional. IiME Comment : The failure to explain the biopsychosocial theory on which NICErecommendations for treatment are based; This is caused by bodies such as NICEperpetuating these myths in the face of evidence and patients' experiences, supported by overwhelming biomedical evidence, proclaiming that Wessely-style theories are nonsense. What is the science behind biopsychosocial approach. As with any other chronic disorder the patients attitude to his or her illness experience and disability, the understanding of the nature of the condition and its likely course over time together with the relationship between patient and doctor are likely to have a significant impact on long term outcomes. IiME Comment: This document purports to discuss CFS/ME – but the number of times CFS alone is mentioned shows poor editing, analysis and devalues the contents. This chapter is named MAKING a DIAGNOSIS	issues.

						of CFS/ME – CFS is mentioned alone many times. CFS is not the same as ME!	
SH	Invest in ME	142	FULL	135	*25*	*References* IiME Comment: The references below are related to psychiatric papers and should have no place in discussion about neurological ME. Unless there is a separate agenda with the NICEdocument?Why not list references from Spence, Hooper, Hyde, Carruthers, Jason, Cheney, Peterson, De Meirleir, Myhill, Kerr, Puri etc.	There is no separate agenda. We hope the revised text is helpful.
SH	LocalME	79	FULL	105		Diagnostic Recommendations This is a curious paragraph in a number of respects: ME is a neurological illness (ref. to WHO classification) – so why would patients with neurological signs be excluded from diagnosis? Cardiovascular abnormalities have been found in patients with ME (ref. 'Human Tragedy and the Heart of the Matter', vascular research by ME Research UK). Surely anxiety and depression indicate anxiety and depression – rather than acting as markers for some 'serious underlying pathology'. Of course anxiety and depression should be treated in their own right if present. More Generally, the implication is that a diagnosis of ME/ICD CFS does not in itself indicate a likelihood of 'serious underlying pathology'. Even if 'serious' is intended to be read as 'life threatening', this does not	We have revised the recommendations on the other symptoms that are to be investigated urgently to be more specific.

						always hold true: fatalities, although rare, do occur (ref. Carruthers et al, 2003, p34, and the documented deaths of [X, X, X]).	
SH	LocalME	80	FULL	126	1	Spatial disorientation CAN be an alarming symptom of CFS/ME.	Noted but is not characteristic.
SH	NHS Direct		FULL	126	1	Spatial disorientation CAN be an alarming symptom of CFS/ME.	Noted but is not characteristic.
SH	Royal College of General Practitioners Wales	4	FULL	135	14	After FULL-stop add: This process includes being genuinely willing to discuss in an informed way the explanatory models of the illness that are being adopted by the patient or carer. See page 36-7 for most likely variations. This process may raise the possibility of a FULL review of the primary diagnosis.	This section has been heavily revised. We hope this point is now made.
SH	Royal College of Nursing	32	FULL	104	1	Diagnosis to be considered if fatigue plus one additional symptom – It does not clarify the symptom presentation later when making the diagnosis	We have given guidance on broad criteria to alert the clinician to the possibility of CFS/ME, not for use as diagnostic criteria specifically. This has been clarified in the guideline.
SH	Royal College of Nursing	33	FULL	133	15	Not sure that this conceptual framework is helpful nor does it help clarify what CFS/ME is	We have revised the framework, and drawn on the report of the Gibson Inquiry in thinking about what CFS/ME is/are. We hope that the revised version will help patients and professionals work together to manage the condition.

SH	Royal College of Paediatrics and Child Health	39	FULL	110		5.3.1.5 We wonder why this statement is added here. It does not seem to answer the key clinical questions and is based (as far as we can tell) on a paper (ref 42, Smith 2003) that has been considered of poor validity and lower evidence level. We are concerned that doctors reading this guideline might interpret this guideline as that anxiety and depression are primary causes of CFS/ME for which, as far as we are aware, there is no evidence of.	This comment refers to an evidence statement which is a statement that synthesises the evidence findings. The GDG discussed the evidence and agreed this statement. However, as noted, the study had been graded as 2-, so the issues around quality are implicit, and therefore no recommendations have been made based on this statement.
SH	Royal College of Paediatrics and Child Health	40	FULL	122	1	Diagnosis in children. This is given a definite time frame of 3 months. Why? The RCPCH document chose not to give a definite time frame, rather using the definition of 'severe persistent fatigue not explained by other disorders'. We recognise that it probably takes about 3 months to work through the system but do not agree with a restrictive time frame.	The 3-month time frame was recommended in the CMO report and is used in many of the papers. The GDG supported this time-frame.
SH	Royal College of Paediatrics and Child Health	41	FULL	132		Why do all children with mild CFS/ME need to be offered referral to specialist care after 4-6 months. As I read it from the table, it is appropriate to refer those who wish for a referral or who are not doing so well, but in the recommendations of the guideline it comes out as a 'should'. Many General paediatricians are competent to oversee the management of these children, leaving specialist care for those who really need this scarce resource.	The recommendation has been changed and an alteration has been made to the flow chart.

SH	Sheffield South West Primary Care Trust	3	FULL	105		Recommendations (5.2.8) Regarding red flags. Need to clarify that anxiety and depression can be secondary to having a long term medical condition such as CFS/ME and may not always need to be considered as a red flag. In fact it may be an indication for referral to a specialist CFS/ME service.	We have clarified the details of these recommendations, and other related ones to address this.
SH	St Bartholomew's Hospital Chronic Fatigue Services	43	FULL	88	9	If neither pain nor fatigue are prominent, this calls into question the diagnosis of CFS/ME. Alternative diagnoses, such as sleep and mood disorders, are more likely explanations of prominent sleep and cognitive complaints.	Noted and this sentence has been revised.
SH	St Bartholomew's Hospital Chronic Fatigue Services	44	FULL	104	5.2.8	"Recurrent flu-like symptoms" No symptom can be described by an analogy. Muscle and joint pains are separate symptoms already mentioned, so these "symptoms" are both ill-defined and redundant. They should be omitted. • "dizziness, nausea and palpitations." These symptoms are not part of any research criteria or replicated empirical studies of CFS/ME. Their inclusion will dissuade doctors from properly investigating these symptoms, which is both poor and potentially dangerous clinical care. These symptoms should be omitted.	The section on symptoms has been revised.
SH	St Bartholomew's Hospital Chronic Fatigue Services	45	FULL	111	4	The Oxford criteria were not developed by two psychiatrists, not even those as eminent as mentioned in the guideline. They were developed using the Delphic	Noted and revised.

						technique by some 27 CFS/ME doctors and scientists, only 7 of whom were psychiatrists (Sharpe MC, Archard LC, Banatvala JE, Borysiewicz LK, Clare AW, David A, Edwards RHT, Hawton KEH, Lambert HP, Lane RJM, McDonald EM, Mowbray JF, Pearson DJ, Peto TEA, Preedy VR, Smith AP, Smith DG, Taylor DJ, Tyrrell DAJ, Wessely S, White PD. A report - chronic fatigue syndrome: guidelines for research. Journal of the Royal Society of Medicine 1991:84;118-21.)	
SH	St Bartholomew's Hospital Chronic Fatigue Services	46	FULL	132	5.4.5.1 and 5.4.5.2	Point made above: Severity of disability is more important than severity of symptoms; yet you do not mention this. We suggest substituting “disability” for “symptoms”	We have revised the language used in the recommendations. We have used CFS/ME alone, so as to include both symptoms and disability.
SH	St Bartholomew's Hospital Chronic Fatigue Services	47	FULL	133	15 +	Conceptual framework: We warmly welcome this very helpful explanation of models of understanding, which we think important to include.	Thank you for this comment. We have attempted to improve the framework further to take account of other comments received.
SH	The British Psychological Society	37	FULL	88	9	If fatigue is not always a prominent feature, why diagnose CFS? This is inconsistent with all other criteria. If fatigue and pain are not prominent features, what are?	Noted and this sentence has been revised.
SH	The British Psychological Society	38	FULL	88	General	This does identify those with ME who experience muscle fatiguability following minimal exertion plus a delay in the recovery of muscle power after exertion ends. The guidelines are very broad. It’s like not differentiating between tension	The evidence reviewed in this guideline does not allow us to distinguish between these groups when making recommendations. However, we have stressed

						headaches, migraines and cluster headaches. There is now enough evidence to at least separate ME/post viral fatigue and stress-related CFS (TATT). Lumping everyone together is contrary to the way that doctors approach other conditions.	the need to consider both preferences and needs of the individual throughout the recommendations.
SH	The British Psychological Society	39	FULL	91	19	Here the draft recognises the post-viral group and the lack of association between psychological predictors and chronicity. It underlines the need to include alternatives to CBT/GET or GA. Counselling may be more appropriate for patients who have realistic attributions but require additional support to help them deal with the burden of illness.	We have removed the recommendation on post-viral management. Throughout we have noted the need to tailor management options to the needs and preferences of the individual. No evidence on counselling was identified.
SH	The British Psychological Society	40	FULL	132	1 (box)	We agree with point 5.4.5.1 that referrals to specialised care should be based on a consideration of the person's needs and symptoms, illness duration and severity, and in partnership. It may therefore not be necessary, and it may even be counter-productive, to give time-scales for referral (5.4.5.2). Instead, each case should be considered on its merits, and account should be taken of the likely outcome of referral. The guidelines should be wary of creating an expectation in patients for referral to specialised care where no suitable services exist.	We agree that each case should be considered on its merits, but the view of the GDG was that some time scales would be helpful. A definition of specialist services is given. These may vary in different localities.
SH	The British Psychological Society	41	FULL	134	14	There have been studies evaluating the concept of functional somatic syndromes, e.g. Moss-Morris and Spence (2006).	This section has been revised. We seek to acknowledge that different

						Doctors should be able to tell the difference between CFS, IBS and facial pain and there's no rationale for treating them all the same. Doctors do not treat all cases of IBS in the same way. Some patients respond to dietary changes, some to anti-spasmodics, some to hypnosis etc (OHCM 2004, 249). In relation to facial pains, the history is important and some patients will be offered drugs, others may be sent for dental treatment to correct malocclusion etc. Differences matter. It's a moot point whether this concept contributes to our understanding of CFS and unless arguments against it are included for balance, it should be removed. Patients may well regard the link with facial pain and IBS as evidence of the trivialisation of their condition. See Komaroff et al (1996). This section gives the impression that the authors assume CFS to be a single entity, barely distinguishable from other disorders. It takes no account of the findings of ongoing disease in subgroups.	people hold different views on causation, and sometimes these views are strongly held. Since we do not know what the cause of CFS/ME is, the GDG cannot accept any of the current theories, but must instead encourage more basic research and encourage those who hold strong views to take a more tolerant, open-minded attitude to ensure that patients who may benefit from various interventions do have access to those interventions.
SH	The British Psychological Society	42	FULL	135	19	The biopsychosocial model is one of several ways of studying CFS but there are problems. In the literature, the model as it relates to CFS does not recognise the possibility that ongoing symptoms may be due to a persistent disease process (viruses, an abnormal immune response etc). Even somatic symptoms are explained in terms of stress and inactivity (clearly shown in Burgess 2006). Chronicity is attributed to inactivity, stress, abnormal	We do not debate the cause of CFS/ME in depth; our aim is to show that there are widely divergent, sometimes strongly held opinions on causation, but that these views must not be allowed to prevent patients gaining access to the support, care and interventions that can

						perception of symptoms and maladaptive beliefs. It comes across as highly reductionistic (Song and Jason 2005). In the case of CFS, this model is essentially a psychosomatic model. "The biopsychosocial model negates the duality of mind or body and a significant cause of conflict between the patient and healthcare professional." Given the descriptions in the literature, this is not the case in relation to CFS at the moment.	help them.
SH	University of Manchester	4	FULL	132	1 (box)	We agree with point 5.4.5.1 that referrals to specialised care should be based on a consideration of the person's needs and symptoms, illness duration and severity, and in partnership. We would therefore suggest that it is not necessary, and may be counter-productive, to give time-scales for referral (5.4.5.2). Instead, each case should be considered on its merits, and account should be taken of the likely outcome of referral. The guidelines should be wary of creating an expectation in patients for referral to specialised care where no suitable services exist.	We agree that each case should be considered on its merits, but the view of the GDG was that some time scales would be helpful. A definition of specialist services is given. These may vary in different localities.
SH	Welsh Association of ME & CFS Support	62	FULL	89	6	This seems confusing	Thank you for pointing this out. This has been revised.
SH	Welsh Association of ME & CFS Support	63	FULL	90		The evidence base, low grade or otherwise, for the statements in section 5.2.4.2. are poor and of limited value. They are also offensive.	This is an evidence statement which is a statement tha tsynthesises the evidence findings. However, because of the lack of utility of this

							evidence statement, this has been deleted.
SH	Welsh Association of ME & CFS Support	64	FULL	92	18	The changing of terminology between CFS/ME and CFS is confusing and makes one wonder if we are dealing with two different conditions.	Noted with thanks, this has been changed.
SH	Welsh Association of ME & CFS Support	65	FULL	93	4 - 5	Decisions made in partnership - surely the final decision is the patient's and the partnership refers to the exchange of information between practitioner and patient.	In accordance with the methodology for clinical scenarios, the assumptions that form the basis for answering the questions must be explicit. So that respondents have a common understanding of the factors which influence the appropriateness of treatment. . These statements were agreed as assumptions for the questionnaire. They are not guideline recommendations. A fuller explanation is in the methodology chapter.
SH	Welsh Association of ME & CFS Support	66	FULL	94		Some of the blood tests etc for both adults and children are needed to exclude some conditions which can be treated. E.g Lyme disease,	This table documents the questions and responses to the questionnaire for transparency. They cannot be changed now.
SH	Welsh Association of ME & CFS Support	67	FULL	104		5.2.8. Confusing list of symptoms which need a great deal of improvement to enable doctors to recognise a symptom pattern of CFS/ME if they are not given a comprehensive listing of those symptoms	We have given guidance on broad criteria to alert the clinician to the possibility of CFS/ME, not for use as diagnostic criteria specifically.

						with guidance on how common such symptoms are?	This has been clarified in the guideline.
SH	Welsh Association of ME & CFS Support	68	FULL	105		After 'pathology' A list of possible alternative diagnoses should be included here.	The GDG discussed this but it would be impossible to be inclusive without rewriting a medical textbook..
SH	Welsh Association of ME & CFS Support	69	FULL	105		Assuming recovery in children. Some children will not recover and this should not be seen as an opportunity for blame to be attached to either the child or their parents/carers.	This is not referring to recovery from CFS/ME.
SH	Welsh Association of ME & CFS Support	70	FULL	105		Is it normal for an assessment of mental health to be carried out before diagnosing with other chronic neurological conditions?	We have recommended that a mental health assessment be targeted to symptoms, so is not an obligatory assessment, but is targeted as appropriate.
SH	Welsh Association of ME & CFS Support	71	FULL	106		Where is the evidence for this statement on muscle function? What you are suggesting could be detrimental to the patient and their recovery.	These tests are excluding other diagnoses.
SH	Welsh Association of ME & CFS Support	72	FULL	106		The addition of a test for allergies to foods should be included here with a careful clinical history taken of possible markers for lactose intolerance	We have noted the need for expert dietician input as appropriate, and where such allergies are suspected, tests should be undertaken. As noted in the guideline, we have concentrated on the management of CFS/ME, with appropriate symptom management.
SH	Welsh Association of ME	73	FULL	107		We would suggest all patients are routinely	The statistics on borreliosis

	& CFS Support					tested for Lyme disease.	from the National Reference Laboratory (England & Wales) in Southampton are that about 600 cases of borreliosis are diagnosed annually, of which only two to three have brain involvement. The lab has tested several hundred CFS patients using a validated and sensitive serological test and has found only one positive. This patient had evidence of prior infection - but the patient had had a tick bite and a feverish illness i.e. 'an indicative history'. Therefore, routine testing is not warranted.
SH	Welsh Association of ME & CFS Support	74	FULL	107		We would suggest testing for virus activity could lead to appropriate treatment for patients.	This is addressed as testing is recommended where there is an indicative history.
SH	Welsh Association of ME & CFS Support	75	FULL	112	5 - 9	Too wide a definition	This is a quote from the RCPCH guidelines.
SH	Welsh Association of ME & CFS Support	76	FULL	112	28	We would suggest that it is post exertional fatigue which is a cardinal feature and not just fatigue.	We refer here to fatigue as a general symptom, with specific descriptions of fatigue in the recommendations.
SH	Welsh Association of ME & CFS Support	77	FULL	116	4 – 5	Decisions made in partnership - surely the final decision is the patient's and the partnership refers to the exchange of information between practitioner and patient.	This is reporting the agreed assumptions for the questionnaire and cannot be changed now.

SH	Welsh Association of ME & CFS Support	78	FULL	124		5.3.5.3. This could be at the cost of social and other situations	We are not sure how this relates to the recommendation?
SH	Welsh Association of ME & CFS Support	79	FULL	125	20 - 22	Needs clarifying as badly worded.	Noted and revised.
SH	Welsh Association of ME & CFS Support	80	FULL	126	7 - 11	What happens when there are no competent doctors?	NICE guidelines set the standards. It is the responsibility of local implementation teams to ensure that the care outlined is available.
SH	Welsh Association of ME & CFS Support	81	FULL	127	11 - 12	When there are no competent healthcare professionals - what happens to the person with CFS/ME?	NICE guidelines set the standards. It is the responsibility of local implementation teams to ensure that the care outlined is available.
SH	Welsh Association of ME & CFS Support	82	FULL	133	1 – 2	Needs to have the Welsh specific information too.	This is a reference to a document.
SH	Welsh Association of ME & CFS Support	83	FULL	133	12 - 13	Needs to have the Welsh specific information too.	This advice would apply to Wales.
SH	Welsh Association of ME & CFS Support	84	FULL	133	20 – 21	Consistency of terminology. Or is another condition being discussed here?	This has been clarified.
SH	Welsh Association of ME & CFS Support	85	FULL	134	3	Terminology	We hope the corrections have addressed this problem.
SH	Welsh Association of ME & CFS Support	86	FULL	135	18	Insulting. Implies all in the head.	This is not the view of the GDG, as the revised wording should make clear.
SH	West Midlands Consortium	74	FULL	126	1	Disagree. Spatial disorientation can be an alarming symptom of CFS/ME.	Noted but is not characteristic.