Appendix Two: Literature Review

This appendix outlines the main themes which were identified from the literature review.

Nomenclature and definitions

Although guideline statements for CFS/ME across the world are invariably developed with due regard to consensus, the vast amount of commentary, reports and reviews in the public arena express a critical response. Much of this focuses on details of recommendations but there is also considerable tension expressed over the underlying theory of CFS/ME. Despite substantial agreement on some of the major features of diagnosis, management and services, no one document satisfies those who believe the condition to have a biological basis, on the one hand, and those who view it as fundamentally psychological, on the other. Viewpoints remain polarised and fuel the controversy over CFS/ME that is perpetuated in response to each new attempt to determine best practice.

Terms used to name the condition/illness do not escape challenge. It is difficult to disentangle the naming issue from that of definition. Where the term CFS implies broad and inclusive criteria for a wide range of fatigue conditions, ME is more keenly focussed on specific neurological symptoms. Symptoms of depressive illness and some of those specific to ME are often conflated, but the fatigue experienced in each case does not necessarily respond to treatment in the same way. Some of the key symptoms of ME have been described as closer to multiple sclerosis (ME) than to clinical depression: MRI and SPECT scans show abnormalities in the blood flow to the brain of people with CFS that is similar but not identical to patients with depression and other studies show that ME patients have abnormal levels of neurotransmitters.[1,2] Without consistent diagnostic criteria, effectiveness in treatments for ME cannot be generalised from studies of CFS per se.

1 Jason, L., Richman, J, Friedberg, F., Wagner, L., Taylor, R. & Jordan, K (1997) 'Politics, Science, and the Emergence of a New Disease: The Case of Chronic Fatigue Syndrome' American Psychologist Vol.52, No.9, 973-983.

In acknowledgement of this debate, we offer a brief outline of the definitions reviewed in the preparation of this document [See table 1].

In 1969 WHO classified ME as a neurological disease and this is still enshrined in the ICD-10 code G93.3 where it is classed as a disorder of the brain. The early CDC case definition developed in the US in 1988 used the term CFS but this was conceived as something different to ME and was never intended to replace it. In the UK, psychiatrists developed their own criteria that omitted the minor symptoms of the American CDC creating a less strict definition and effectively resulting in a more heterogeneous population. Published in 1991 and known as the Oxford criteria, this has been criticised continually for its focus on fatigue and comparative lack of consideration of other physical symptoms. Nevertheless it was readily adopted by an increasingly confused medical profession. The US CDC definition of CFS was revised in 1994 to adopt a broader definition and emphasised fatigue as the key symptom. As a result, it too became more inclusive of psychiatric illnesses and excluded neurological symptoms. Regarded as the 'international' or 'Fukuda' definition of CFS and adopted as the standard criteria for research purposes, it was further revised in 2003 to clarify inherent ambiguities in the 1994 version. Given this confusion over definition, prevalence rates are unreliable. With no agreed standard diagnostic criteria, in 2001, rates in Britain were said to vary by a factor of eight.[3]

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2 Schwartz RB, Garada BM, Komaroff AL, et al (1994). "Detection of intracranial abnormalities in patients with chronic fatigue syndrome: comparison of MR imaging and SPECT". AJR. American journal of roentgenology 162 (4): 935–41; Abu-Judeh HH, Levine S, Kumar M, et al (1998). "Comparison of SPET brain perfusion and 18F-FDG brain metabolism in patients with chronic fatigue syndrome". Nuclear medicine communications 19 (11): 1065–71; MacHale SM, Lawfie SM, Cavanagh JT, et al (2000). "Cerebral perfusion in chronic fatigue syndrome and depression". The British Journal of Psychiatry : the journal of mental science 176: 550–6; Fischler B, D'Haenen H, Cluydts R, et al (1996). "Comparison of 99m Tc HMPAO SPECT scan between chronic fatigue syndrome, major depression and healthy controls: an exploratory study of clinical correlates of regional cerebral blood flow". Neuropsychobiology 34 (4): 175–83; Demitrack MA, Gold PW, Dale JK, Krahn DD, Kling MA, Straus SE (1992). "Plasma and cerebrospinal fluid monoamine metabolism in patients with chronic fatigue syndrome: preliminary findings". Biol. Psychiatry 32 (12): 1065–77; Badawy AA, Morgan CJ, Llewelyn MB, Albuquerque SR, Farmer A (2005). "Heterogeneity of serum tryptophan concentration and availability to the brain in patients with the chronic fatigue syndrome". J. Psychopharmacol. (Oxford) 19 (4): 385-391 cited in 'Chronic Fatigue Syndrome'.

Two further sets of criteria emerged in the 1990s: the Australian criteria (1990) and the London criteria published in the National Task Force Report (1994). These differed from the American and Oxford definitions by placing more weight on neurological criteria. At this stage, the National Task Force acknowledged that commonly used criteria for CFS did not necessarily include those for ME and so coined the term CFS/ME in an attempt to include all cases. In 2003 the Canadian (Carruthers) definition was developed. This is favoured by many sufferers of CFS/ME because it emphasises neurological symptoms and does not support a psychological/psychiatric theory of the disease. It was also endorsed by the Scottish Cross Party Group on ME [4] and in the Gibson Report, published in the UK in 2006. From the outset the Canadian consensus document refers to the 'compelling research evidence of physiological and biochemical abnormalities identifying ME/CFS as a distinct, biological, clinical disorder.'[5] 'Patients meeting the Canadian criteria were more physically ill, had greater physical functional impairment, greater fatigue/weakness, and more neurocognitive, neurological and cardiopulmonary abnormalities and had more impairments that significantly differentiated them from the psychiatric comparison group than did patients meeting the Fukuda criteria'.

The Gibson Report (UK, 2006) acknowledged the CFS – ME distinction. As it was beyond the remit of the group to join the international debate on nomenclature the group chose to adopt CFS/ME as its working terminology. In terms of defining criteria it cited both the CDC CFS toolkit and the Canadian Criteria in preference to the Oxford Criteria.

A Scottish Short Life Working Group, in 2002, had taken the same approach as the Gibson Report to the use of CFS/ME. It favoured an early provisional diagnosis that, with the exception of 6 months persistence, conformed largely

3 'What is ME? What is CFS? Information for clinicians and lawyers' December 2001

4 In their Legacy Paper (2007), the Scottish Cross Party Group on ME proposed the adoption of the Canadian criteria in Scotland believing it to provide 'a clear and sound understanding of the clinical presentation and biomedical basis of M.E./strictly defined CFS' instead of the UK NICE Guidelines.

5 Carruthers, B. & van de Sande, M.I., (2005) Myalgic Encephalomyelitis/Chronic Fatigue syndrome: A Clinical Case Definition and Guidelines for Medical Practitioners. An Overview of the Canadian Consensus Document.

to the US CDC 1994 definitional criteria. In 2007 a Scottish Cross Party Group used the term ME (as defined by WHO ICD) and favoured the adoption of the Canadian Criteria.

Clinical Guidelines

A search of literature, including the major reports and guidelines from the past six years, was undertaken to identify areas of consensus. A summary table of key points and/or recommendations [see table 2] was produced. The table relies on a limited range of sources. For an overview of the international perspective a paper by the New Zealand Guidelines Group provided a clear comparison of approaches to CFS/ME across Australia, Canada, the US and the UK[6]. This was supported further by reference to a Health Technology Assessment review of evidence prepared by the Norwegian Knowledge Centre for the Health Services (2006)[7]. Reference is also made to the Scottish Short Life Working Group (2002)[8], the Action for ME scoping report (2007)[9], an advisory report to the Minister of Health, Welfare & Sport in the Netherlands (2005)[10] and the NICE Guidelines (2007)[11].

The UK Independent Working Group on CFS/ME set up in 1998 was a response to a prevailing scepticism over CFS/ME as a bona fide illness and confusion over the best way to define, manage and provide appropriate services. Crucially, the working group's *Report to the Chief Medical Officer* (known as the CMO's report) published in 2002, stated unequivocally that

6 New Zealand Guidelines Group (2004): Analysis of Chronic Fatigue Syndrome Guidelines. Report to the Ministry of Health.

7 Norwegian Knowledge Centre for the Health Services (2006). A Review of the Scientific Literature for the Diagnosis and Treatment of Chronic Fatigue Syndrome/Myalgic Encephalopathy. Oslo: Norwegian Knowledge Centre for the Health Services.

8 Short Life Working Group (2002).Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) Outline for Development of Services for CFS/ME in Scotland: Report of the Scottish Short Life Working Group. Scottish Executive, December 2002.

9 Action for ME (2007). Scotland CFS/ME Scoping Exercise Report. Bristol, Action for ME, 2007.

10 Gezonheidsraad. Health Council of the Netherlands (2005) Chronic Fatigue Syndrome. Advisory Report to the Minister of Health, Welfare & Sport.

11 NICE (2007). NICE clinical guideline 53 Chronic fatigue syndrome / myalgic encephalomyelitis (or encephalopathy): diagnosis and management of CFS/ME in adults and children.

CFS/ME was a real illness and that, despite its challenging nature, should be treated as any other chronic condition. The *Report* set out recommendations in terms of treatment and care, health service planning, education and awareness, as well as for a programme of research. Lack of understanding of CFS/ME had led to pejorative judgements of parents and so the CMO's report recommended a specialist approach to children suspected of having the condition calling for professionals with specialist knowledge of CFS/ME to be available to child protection cases where necessary.

The report was generally well-received and the government endorsed its view that health professionals should accept and treat CFS/ME as a chronic illness. It also acknowledged the recommendation for improvement in the knowledge and skills required to provide appropriate care and treatment, and the need for further research. Following the report, the government invited the MRC to develop a strategy 'for advancing biomedical and health services research'. This strategy was published in 2003 but to harsh criticism on the basis that it was underpinned by a belief in CFS/ME as essentially psychosomatic.

Shortly after the publication of the CMO's report, the government announced a budget of £8.5m towards 'a stepped development' in CFS/ME services under the direction of Dr Anthony Pinching, Associate Dean of Cornwall Peninsula Medical School and former Deputy Chair of the Working Group. This funded the CFS/ME Service Investment Programme that saw the establishment of eight specialist service centres across England & Wales.

In 2002 Scotland published the findings of its own Short Life Working Group looking at how the recommendations of the CMO's report could be implemented in Scotland. In most respects Scotland reflected the status quo reported for England & Wales, particularly in terms of prevalence and the need for research. A rapid survey indicated that across Scotland, NHS services for CFS/ME were ad hoc and relied largely on the interests of individual clinicians. With no clear strategic plan in place, it was recommended that NHS boards undertake health needs assessments and develop plans for service development. In line with the CMO's report, a

patient-centred, tiered structure was recommended, to be delivered by multi-disciplinary and multi-agency teams with specialist services for complex cases and particular groups such as children and young people, housebound/bedbound patients as well as those living in remote or rural areas. It was envisaged that CFS/ME could be managed, as other chronic illnesses, within the primary care setting supported by specialist services and the services delivered in Dorset were suggested as an exemplar. It was also acknowledged that a managed clinical network might be useful to help integrate services across Scottish NHS boundaries. The planning of services was to be underpinned by ongoing research and provide the necessary skills training for health care professionals. Voluntary sector interest groups, who contributed to the working group discussions, also highlighted the need for improved information for patients and carers.

There was broad consensus within the two reports. They shaped subsequent service planning in the UK and helped inform practitioners but neither constituted formal guidelines for clinicians. Guidelines proved difficult to develop and it was 2007 before draft guidelines for England & Wales were produced by the National Institute of Clinical Guidelines (NICE). No guideline document has yet addressed the Scottish situation specifically. During the long gestation period of the NICE guidelines the prevailing international view was under constant shift.

In May of 2002 the Royal Australasian College of Physicians published *Clinical Practice Guidelines* that were informed by a review of the scientific evidence and a substantial consultation process that included the views of clinicians, patients and patient support groups. Deemed to be unclear, these first guidelines were superseded by a more succinct report in 2004. By this time, a further set of guidelines had been published in Canada. The Canadian guidelines noted the critical response to the earlier UK and Australian documents; focussing particularly on the narrowness of both the group selection and the evidence base used. As a counter to this, the Canadian group took a wider perspective by inviting input from experts in CFS/ME across the world and accepting a lower level of evidence on which to

base their recommendations, thereby allowing discussion of management and treatment strategies that, although regarded as less robust, nevertheless attracted a strong consensus view among patients and practitioners. In contrast to the US CDC (1994) criteria for CFS/ME that underpinned the Australian and UK documents, and that were devised principally for research purposes, a key feature of the Canadian criteria was the development of a consensus-based clinical case definition to help with diagnosis in the clinical situation. Less emphasis was put on fatigue as the principal characteristic of CFS/ME, it required a wider range of accompanying physical symptoms and in the suggested differential diagnosis it selected out more alternative conditions. As a result, it defined CFS/ME more specifically by including non-fatigue symptoms that are less attributable to psychological causes. The Canadian document presented an alternative for the clinical setting that quickly became widely accepted and preferred by many patient groups. The revised Australian guidelines (2004) adopted this approach and provided a tick list for practitioners based on the Canadian criteria. By building physical symptoms into the defining criteria of CFS/ME the Canadian case definition represented something of a paradigm shift in the recognition of CFS/ME but it was not one that was embraced universally. Despite its publication more than one year later, an Advisory Report to the Minister of Health, Welfare and Sport of the Netherlands in 2005, made no reference to the Canadian document and cited the CDC '94 as the working criteria for CFS/ME. At the same time, the US CDC was developing a CFS Toolkit that reflected much of the ethos of the Canadian consensus within a revised CDC definition.

In 2006 a UK enquiry group set up to spark further debate and encourage scientific research into CFS/ME, reiterated some of the issues raises in the CMO's report and supported in Scotland by the Short Life working Group. Known as the Gibson Enquiry, it confirmed that recommendations had not been implemented. It noted that while the international community showed more sympathy for a biomedical point of view, the UK continued to rely on evidence rooted in a psychological perspective. For many, this was reflected in the NICE guidelines published in 2007. While the guidelines supported most of the recommendations of the earlier CMOs report and those now

commonly acknowledged internationally, they were challenged on the basis of the research trials used to underpin key recommendations regarding the management of activity levels and exercise. .

Despite vociferous criticism, each of the documents mentioned has contributed to broader consensus on many of the key CFS/ME issues. Explicit evidence-based, international consensus was noted in the seven areas outlined below.

1. Case definition criteria weak

Despite ongoing discussion over many years it is still difficult to identify unanimous agreement on which symptoms are necessary and sufficient to a diagnosis of CFS/ME: evidence to substantiate any case definition or set of criteria is weak.[12]

2. Epidemiology

With reference to CFS/ME epidemiology, it is acknowledged that data is limited. Based on available data and in an international context, the New Zealand Guidelines Group (NZGG) (2004) found it to be more prevalent in females, to affect all socio-economic groups and, with regard to children, to affect those as young as 5, with a common onset age range of between 13 and 15 years. They also found that although most people with CFS/ME improve over time, some remain long-term disabled and that the outcome tends to be better for children and adolescents.

3. Aetiology

The NZGG note the aetiology of CFS/ME as unclear but that it is frequently found to follow an infection. Exacerbating factors included exertion, sleep disturbance and stress. [13]

12 Mulrew, C.D., Ramirez, G., Cornell, J.E. & Allsup, K. (2001) 'Defining and managing chronic fatigue syndrome' Evidence Rep Technology Assessment Summer (42): 1-4 cited in NICE Guidelines (2007), p.155; NZGG (2004). Available URL: http://www.nzgg.org.nz/guidelines/0084/040518_matrix.pdf

13 NZGG (2004) http://www.nzgg.org.nz/guidelines/0084/040518_matrix.pdf

4. Diagnosis

Studies of CFS/ME use a variety of diagnostic criteria making comparisons difficult.[14] The NZGG (2004) included a comparative summary outlining areas of agreement across Australia, US, Canada and the UK regarding CFS.[15] A wide range of symptoms were detailed: the common features across each of the countries appears in Figure 1 below.

Fig 1

Key characteristic	Plus some of the following:…	…for example:
Unexplained and persistent fatigue	Post-exertional malaise/fatigue:	-inappropriate loss of physical and mental stamina with long recovery period
	Sleep disturbance:	-early morning waking; insomnia; hypersomnia; unrefreshing sleep; disturbed sleep/wake cycle
	Pain:	-muscle and/or joint pain; significant headaches of new type, patter or severity; painful lymph nodes; sore throat
	Cognitive impairment:	-confusion; difficulty thinking; inability to concentrate; impairment of short-term memory; word-finding difficulty; inability to plan/organise thoughts; spatial disorientation
	Idiopathic chronic fatigue:	-if alternative causes for fatigue have been ruled out, but criteria for CFS are not met. Treat as CFS.

This international comparison noted agreement that the fatigue should be unexplained and persistent but there was variance on the duration of fatigue before a diagnosis is made, ranging from 6 weeks (for clinical purposes) to 6 months (for research purposes). In 2002 a Scottish Short Life Working Group

14 A Review of the Scientific Literature for the Diagnosis and Treatment of Chronic Fatigue Syndrome/Myalgic Encephalopathy(2006) Oslo: Norwegian Knowledge Centre for the Health Services

15 Before the production of the comparative summary matrix a caution was noted: "a comparative summary is not a guideline and is, in effect, producing a set of recommendations with no explanation of inconsistent recommendations and a poorly evaluated evidence-base. The strength and relative importance of recommendations will not be identified, and the local applicability of procedures and treatment and management strategies detailed will not have been considered or informed by local knowledge and expertise. New Zealand Guidelines Group (2006) Analysis of Chronic Fatigue Syndrome Guidelines. Report to the Ministry of Health

(SSLWG) in the UK noted international consensus on the presence of symptoms for at least six months before a diagnosis is established.[16] This was reduced to 4 months (in adults) and 3 months (in children) in the NICE Guidelines of 2007 although there was agreement across the SSLWG and NICE that, in order to prevent delay, a provisional diagnosis could be made after 6 weeks (4 weeks in children & adolescents) of symptom persistence. The importance of having a positive diagnosis rather than one based on exclusion was agreed in the NZGG comparison document.

Diagnostic testing strategies were found to be influenced more by particular perspectives on CFS/ME rather than evidence of effectiveness.[17] International comparison showed differences in the range of tests recommended but common agreement on routine testing included the following: full blood count; thyroid stimulating hormone; biochemistry profile; serum electrolysis and urinalysis. Additional tests in common included those for hepatitis B & C, thyroid function test and any others suggested by individual symptoms or history.

5. Specialist referral

International consensus was also noted in relation to referral with each country acknowledging the possibility that referral may be necessary as part of the diagnostic workup and that specialist input may need to be multidisciplinary. NICE Guidelines noted no evidence for the benefits of specialist referral but the consensus methodology employed by the guidelines development process resulted in a recommendation that decisions re specialist referral are made in conjunction with the patient, with due consideration for that person's condition and the local services available, and should be offered immediately to those with sever symptoms.[18] The SSLWG emphasised the role of the specialist in pain management and there was general agreement from all sources that children diagnosed with CFS/ME

16 Scottish Short Life Working Group (2002) Chronic Fatigue syndrome / Myalgic Encephalomyelitis. Outline for Development of Services for CFS/ME in Scotland. Report of the Short Life Working Group

17 NZGG (2004). Available URL: http://www.nzgg.org.nz/guidelines/0084/040518_matrix.pdf

18 NICE (2007), pp.177, 183

should be referred to a paediatrician known to have an interest in the condition.[19]

6. Information and training

Evidence suggests the need for more and better information and/or training for healthcare workers, patients and carers particularly in relation to employment/education and welfare benefits. [NICE; SSLWG; Action for ME (AfME)] From the international perspective, information and training are viewed as part of the shared management of the condition. [NZGG]

7. Management & treatment plans

There was international agreement that treatment plans should be individualised. This is reflected in the recommendations of the SSLWG , (AfME) and NICE.

Management plans should acknowledge variation in the abilities of any one person with CFS/ME on a day-to-day basis. They should aim to increase the person's function without increasing symptoms.

Exercise

There was international agreement that too much exercise can exacerbate symptoms and that limited exercise should only be introduced with caution. Views on graded exercise programmes varied. Although it was acknowledged that a degree of exercise relating directly to each individual's level of energy and/or pain may be beneficial, the international summary included a cautionary note that graded exercise programmes had recently been identified as harmful. A Norwegian evidence review noted a lack of information on the effect of graded exercise therapy on depression or quality of life. NICE guidelines recommend GET for people with mild to moderate CFS/ME citing multiple RCT evidence of 'significant improvements in measures of fatigue and physical function'. Recommendations relating to exercise programmes are contentious with some reports noting a preference for 'pacing' over GET,

19 SSLWG (2002) p.14; Department of Health (2004) National Service Framework for Children cited in NICE

while NICE consider GET the most cost-effective option and warn of insufficient evidence in relation to pacing.[20] [21] In Scotland, a significant proportion of people with ME (32%) who participated in the AfME survey said that GET made them worse while 30% said Graded Activity made them worse.[22]

Drug treatments

Drug treatments accepted by each country include tricyclic antidepressants, NSAIDs & other analgesics, and muscle relaxants.

Sleep

It may be necessary to refer patients to a sleep specialist in order to exclude primary sleep disorder. In the case of CFS/ME-related sleep difficulties, behavioural therapy should be tried before medication to improve sleep hygiene. Sedating tricyclics are recommended for use.

Assessing consensus

As Table 2 indicates key areas of agreement in the management of CFS/ME. The UK position is drawn from the NICE Guidelines where recommendations are explicit. Other documents are more discursive or presented as a simplified matrix, making comparison difficult. The table suggests broad agreement and, with a couple of exceptions, the issues noted attract support at an international level. Activity management is not considered consistently. For example, the UK position counsels services to be clear about the lack of evidence for benefit or harm with regard to Pacing while others discuss pacing in less formal terms, as part of a more generalised approach to exercise/activity management.

Reflecting a generally held view amongst patient support groups, AfME emphasise patient autonomy and the need for goals to be set by the patient.

(2007); NZGG (2004)

20 NICE Guidelines (2007), 'Summary of submissions from stakeholders', p.95

21 AfME, p.32

While this is not highlighted in the same way in other documents, it is often implicit. It is therefore, fair to comment that patient autonomy per se is not contentious: the nature of autonomous decision-making is a crucial factor in the management of CFS/ME. It might also be suggested that this issue plays a significant part in the polarised controversy over CFS/ME. In the absence of robust and definitive research findings, the patient's perspective may be informed by beliefs about the root cause of their symptoms that stand in sharp contrast to those that underpin the service at his/her disposal. In this situation, the autonomous patient view will continue to challenge the status quo. Services should be designed to operate as effectively as possible within this context and so there may be benefit in considering any guidelines with a degree of flexibility that is negotiated with the individual patient. However, the breadth of agreement on CFS/ME in general also suggests that consensus is relatively strong and forms a central core on which to base a professional response to CFS/ME.

22 In the AfME scoping exercise survey questionnaire definitions of GET and Graded Activity were not detailed but defined by each individual who answered the questions.

Table 1

Table 1 has been prepared with reference to a range of sources outlining diagnostic criteria. The level of detail in descriptions varies and terminology is not standardised. This table is intended to give an overview of the key factors included in the principal sets of criteria. Areas shaded in blue indicate criteria required for diagnosis.

Key criteria **Must be present**	US CDC 1988	Australian (Lloyd) 1990	UK Oxford 1991	US CDC 1994	UK London 1994	Canadian (Carruthers) 2003	Australia 2004	UK NICE 2007
Fatigue	√	√	√	√	√	√	√	√
Definite/new onset – not life long	√		√	√		√		√
Severe & disabling fatigue affecting physical and mental functioning	√		√			√	√	
Should have been present for =>6months and for more than 50% of that time	√	√	√	√	√	=>4months (3months in children)		=>4months (3months in children)
Additional criteria related to fatigue				Plus =>4 symptoms required from following categories				
No improvement with bed rest	√			√				√
Post-exertional or exacerbated by minor exercise		√		√	√	√	√	√
Causes significant disruption of usual, daily activities		√		√				√
Not the result of exercise/exertion				√				√
Prolonged recovery	√				√	√		√
Other Criteria								
	Plus =>6 symptoms required from following categories inc 9 above)		Not required to be present					Plus =>1 symptoms required from following categories
Sleep disturbance [or unrefreshing sleep]	√		√	√		√	√	√
Myalgia	√		√	√		√	√	√
Pain [other than myalgia	√			√		√	√	√

e.g. headaches; lymph nodes; throat]								
[Migratory] arthralgias	√			√		√		√
						Additional symptoms – required in combination		
Neuropsychiatric dysfunction	√	√						
Cognitive dysfunction						√	√	√
New onset short term memory impairment		√		√		√		√
Mood disturbance			√					
Neurological disturbances					√	√		
Variable involvement of cardiac & other bodily systems					√			
Extended relapse course with tendency to chronicity					√			
Marked variability in course of a day					√			
Dizziness/nausea						√	√	√
Orthostatic intolerance						√	√	
palpitations						√		√
Gastro-intestinal symptoms (e.g. irritable bowel)						√	√	

Note: Re UK NICE 2007 - Diagnosis should be reconsidered if the following are not present: post-exertional malaise; cognitive difficulties; sleep disturbance; chronic pain.

Table 2: Key areas of agreement

Key points/recommendations noted in major documents	Supported by	Note
Shared decision making with patient	UK	
CFS/ME symptoms[23] / diagnostic criteria	Various	Evidence to substantiate any case definition/set of criteria is weak. No studies providing basis of case definition[24]
Diagnosis: when symptoms have persisted for 4months (adult) / 3months (child) => 6months(adult)	UK Australia; Canada; Netherlands	Evidence on diagnostic testing is weak. NZGG: agreement on fatigue persistence with >6 months (adult) 3 months (child) being the most common duration given.
Diagnosis: re tests that should be done (n=13)	Various	NZGG indicates agreement for routine tests to include: full blood count; TSH; biochemistry profile and serum electrolysis & urinalysis. Additional tests include: Hep B&C; thyroid function test, and any others suggested by history or symptoms.
Conditions considered in differential diagnosis differs:		Taken from NZGG (2004)
14+ psychiatric disorders	Australia	
12+ psychiatric disorders	UK	
32 including psychiatric disorders	US	
8+ psychiatric disorders and substance abuse	Canada	
Specialist diagnostic testing for adolescents & children	US	

[23] Fatigue that is new onset; is persistent and/or recurrent; is unexplained by other conditions; has resulted in substantial reduction in activity level; is characterised by post-exertion malaise AND one or more of : difficulty with sleeping; muscle and/or joint pain without inflammation; headaches; painful lymph nodes without pathological enlargement; sore throat; cognitive dysfunction; symptoms exacerbated by physical exertion; general malaise of flu-like symptoms; dizziness and/or nausea; or palpitations.
[24] Mulrew, C.D., Ramirez, G., Cornell, J.E. & Allsup, K. (2001) 'Defining and managing chronic fatigue syndrome' *Evidence Rep Technology Assessment* Summer (42): 1-4

Advice on symptom management should not be delayed until diagnosis established	UK	
Information & training patients and carers. [info and support re illness, healthcare, and assistance re work/education]	UK SSLWG (p.8) NZGG: info to patients and carers part of shared management. AfME (p.14)	
Take account of patient's age and previous treatments	UK	
Recognise patient's right to refuse/withdraw from treatment	UK	
Establish supportive/collaborative relationship with patient/carer/family	UK; Australia; Netherlands	
Care co-ordinated for each patient by named health professional	UK	
Diagnostic/therapeutic options to suit individual need	UK NZGG SSLWG	
Management:		
Diet [healthcare professionals should provide general advice re importance of good diet but seek advice from dietician if patient wishes to undertake special diet]	UK	
drug treatment [of the three noted by NZGG NICE cite only tricyclic antidepressants]	UK NZGG: include tricyclic antidepressants; NSAIDS and other analgesics, and muscle relaxants.	NICE (UK) state that no research evidence supports people's experience of greater intolerance to drug treatments including more severe side effects. NZGG: common agreement that people with CFS/ME 'are often susceptible to medication side effects'.
Nausea [Should be managed conventionally]	UK	
Sleep [advise on sleep hygiene]	UK SSLWG NZGG	

Rest [rest periods part of management plan. Should be reviewed regularly]	UK	
Relaxation [help with pain; sleep problems and co-morbid stress/anxiety. Can be incorporated into rest periods]	UK	
Pacing	Canada Australia	Patient confidence in Pacing noted by : SSLWG(p.15) (UK); AfME (p.32) (UK) ; Gibson Enquiry (UK) ; and Netherlands The NICE Guidelines (UK) view is that people should be advised of insufficient research to support benefit/harm of pacing.
Equipment (e.g. wheelchair) recommended if maintains independence and QoL.	UK	
Education (liaise with education services re fitness for school/coll/uni)	UK	
Employment (liaise with employers re fitness for work)	UK	
Complementary therapies/medicines [insufficient evidence to support]	UK SSLWG (p.17)	Lack of empirical trials (SSLWG) US guidance suggests some benefits.
Referral to specialist [should be based on need – decision to refer should be made jointly – should be offered immediately to those with severe CFS/ME symptoms]	UK SSLWG (p.14) NZGG: referral may be necessary as part of diagnostic workup.	Evidence weak. GDG group consensus. NZGG: specialist in put may need to be multidisciplinary.
Referral to paediatrician for children	UK SSLWG (p.14) NZGG	
Specialist care (management & treatment):	UK SSLWG: level of specialist services required in Scotland	
Individualised plan	UK SSLWG (p.11); AfME (p.18) NZGG	

Aim at physical and emotional impact on symptoms	UK NZGG SSLWG	
Patient should be well-informed	UK AfME (p.18) NZGG: info to patients and carers part of shared management	
Patient autonomy	AfME (p.18)	Implied but not emphasised
Goals setting by patient	AfME (p.18)	Implied but not emphasised
CBT (offered to those with mild-moderate) [patient should be in charge of aims of programme] [therapeutic goals should be agreed between patient and health professional]	UK SSLWG (p.15)	Further research required (SSLWG) Netherlands note limited benefit and modifications for some
GET (offered to those with mild-moderate)	UK	Long term data is limited (SSLWG) Netherlands: CBT/GET considered together – non-commital on effectiveness of GET NZGG includes note that graded exercise programmes recently found to be harmful.
Activity management	SSLWG (p.16) UK	UK specifies Activity Management as it is used within the NICE Guideline
Drug therapies		
Pain management: -start with lower doses -multiple non-pharmacological and/or psychological approaches may be helpful -lifestyle management with no mention of psychological approach -efficacy of alternative therapies cited	 UK; SSLWG UK; US; Australia Canada US	
Setbacks/relapses -should be planned for -should be managed	SSLWG (p19) UK	
Review/ongoing management [should be regular and structured]	UK SSLWG	

Patients with severe CFS/ME: - require specialist management - requires community involvement/home visiting	UK SSLWG (p.18)	
Self-monitoring/patient diaries to help management	Canada Australia	