Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) in adults and children

NCCPC The National Collaborating Centre for Primary Care

RCGP Royal College of General Practitioners

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Preface

The publication of this guideline presents an opportunity to improve care for people with CFS/ME. In the past their needs have too often been overlooked, and this situation needs to change.

Several factors have contributed to the neglect of CFS/ME. Firstly, the illness is poorly understood. There is no generally accepted theory about its cause or causes, and the symptoms can be diverse, with wide variations both between individuals and in each person over time. This creates further difficulties when attempting to define CFS/ME for the purpose of making a diagnosis. Secondly, there is only limited epidemiological evidence on the numbers of people who develop CFS/ME and on the natural history of the illness. As a result, the available therapies are few, evidence of effectiveness is limited to people with mild to moderate CFS/ME, and access to expert therapists has often been difficult.

These factors have meant that people with CFS/ME have sometimes been unable to obtain suitable care. The guideline development group were concerned that some patients with severe CFS/ME were housebound and received little or no care or support, while many others with mild or moderate CFS/ME had not been diagnosed or were unable to access potentially effective care. A recent two-year programme to set up demonstration services has shown what can be achieved, and we wish to encourage development of care based on the experience of these schemes.

A further problem created by the lack of adequate research evidence is the sometimes widely divergent and hotly contested beliefs about CFS/ME, including those about its cause, whether it is more than one illness, and which approaches suit which patients. Development of recommendations about the cause of CFS/ME was outside the scope of the guideline.

In developing the guideline, we kept in mind the overall goal of improving care for people with CFS/ME, that is, improving diagnosis, enabling patients to receive therapy appropriate for, and acceptable to them, and providing information and support, with the patient's preferences and views firmly driving decision-making. Rather than aligning ourselves with one or other perspective on CFS/ME, we have sought to provide practical guidance for professionals and patients. We strongly recommend the same practical and pragmatic approach to professionals and patients themselves.

Professor Richard Baker

Chair, Guideline Development Group

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- the following people who were invited to comment on the draft guidelines
    - Annette Barclay
    - Dr. Diane L Cox
    - Jacqui Footman
    - Sylvia Penny
    - Catherine Stillman-Lowe

Abbreviations

BNF	British National Formulary
CBT	cognitive behavioural therapy
CCBT	computerised cognitive behavioural therapy
CDC	Centers for Disease Control
CFS	chronic fatigue syndrome
CGRDU	Clinical Governance Research and Development Unit
CI	confidence interval
CMO	Chief Medical Officer
CMV	cytomegalovirus
CRD	Centre for Reviews and Dissemination
EAS	education and support
EBV	Epstein–Barr virus
ECG	electrocardiogram
EPP	Expert Patient Programme
ESR	erythrocyte sedimentation rate
GAT	graded activity therapy
GDG	Guideline Development Group
GET	graded exercise therapy
GRP	Guideline Review Panel

HCP	healthcare professional
HIV	human immunodeficiency virus
ICER	incremental cost-effectiveness ratio
IPRAS	interpercentile range adjusted for symmetry
MADM	mean absolute deviation from the median
MCV	mean cell volume
ME	myalgic encephalomyelitis or myalgic encephalopathy
MAOI	monoamine oxidase inhibitor
MRI	magnetic resonance imaging
NADH	nicotinamide adenine dinucleotide
NCC-PC	National Collaborating Centre for Primary Care
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NSAID	non-steroidal anti-inflammatory drug
PCT	Primary Care Trust
PVFS	postviral fatigue syndrome
QALY	quality-adjusted life year
QoL	quality of life
RAM	RAND/UCLA appropriateness method
RCGP	Royal College of General Practitioners

RCT	randomised controlled trial
ROC	receiver operating characteristics
SFM	soluble fibrin monomer
SG	support group
SMC	standard medical care
SSRI	selective serotonin reuptake inhibitor

Glossary of terms

Please see also the guidelines manual 2007 - Appendix K: Abbreviations and glossary (www.nice.org.uk) for definitions of general terms used throughout the guideline.

Activity	Any task or series of tasks that a person performs. A task may have physical, emotional, cognitive and social components.
Activity analysis	A process of breaking down activities into their component parts and specific sequences to identify the skills and abilities required to complete them.
Activity cycling	See 'Boom and bust' cycle.
Activity management	A person-centred approach to managing a person's symptoms by using activity. It is goal-directed and uses activity analysis and graded activity to enable people to improve, evaluate, restore and/or maintain their function and well-being in self-care, work and leisure.
Age	• Adult: aged 18 years and older. • Young person: aged between 12 and 17 years. • Child: aged between 5 and 11 years. The age at which care is transferred between child and adult health services varies between 16 and 19 years, depending on the young person and their family's preferences and local circumstances.
Baseline	A sustainable and stable range of functioning that can be maintained without significant symptom exacerbation.
'Boom and bust' cycle	Cycles of fluctuating activity levels and symptoms, which are a common feature of CFS/ME. Boom and bust cycles can happen when a person with CFS/ME is overactive when they are feeling better, which may lead to an increase in symptoms and a decrease in function.
Breathing techniques	Used to reduce respiratory rate, promoting parasympathetic activity and therefore stimulating relaxation. A number of techniques may be used, such as diaphragmatic breathing (using the diaphragm to breathe rather than the rib-cage) and 7/11 breathing (inhaling to a count of 7 and exhaling to a count of 11).
Cognitive behavioural therapy (CBT)	An evidence-based psychological therapy that is used in many health settings, including cardiac rehabilitation and diabetes management. It is a collaborative treatment approach. When it is used for CFS/ME, the aim is to reduce the levels of symptoms, disability and distress associated with the condition. A course of CBT is usually 12–16 sessions. The use of CBT does not assume or imply that symptoms are psychological or 'made up'.
Deconditioning	Loss of physical fitness as the general physiological response to, for example, a prolonged period of inactivity.

Exercise	Any form of physical activity that uses the major muscle groups of the body. Activities of daily living (for example, brushing hair or getting dressed), sitting up in bed and walking about are all exercise in the context of this guideline.
Goal-setting	A collaborative process in which the patient and healthcare professional set reasonable short-term and long-term goals, including discussing the components of the goals and methods to reach them. Goals should be specific, achievable and measurable (that is, describe the patient's behaviour when the goal is reached), set within a definite timeframe and recorded clearly for reference by patient and healthcare professionals in review sessions.
Graded activity	Activities that have been selected, adapted and graded for therapeutic purposes to promote health and well-being.
Graded exercise therapy (GET)	An evidence-based approach to CFS/ME that involves physical assessment, mutually negotiated goal-setting and education. The first step is to set a sustainable baseline of physical activity, then the duration of the activity is gradually increased in a planned way that is tailored to the person. This is followed by an increase in intensity, when the person is able, taking into account their preferences and objectives, current activity and sleep patterns, setbacks/relapses and emotional factors. The objective is to improve the person's CFS/ME symptoms and functioning, aiming towards recovery.
Over–under activity	See 'Boom and bust' cycle.
Pacing	The report of the Chief Medical Officer's working group defined the principles of pacing, and these are supported by people with CFS/ME and patient groups. Many of the principles are included in this guideline's recommendations on CBT, GET and activity management. Examples include spreading activities over the week, breaking tasks down into small manageable parts, interspersing activity with rest and setting appropriate, realistic goals for increasing activity. In this guideline, pacing is defined as energy management, with the aim of maximising cognitive and physical activity, while avoiding setbacks/relapses due to overexertion. The keys to pacing are knowing when to stop and rest by listening to and understanding one's own body, taking a flexible approach and staying within one's limits; different people use different techniques to do this. However, in practice, the term pacing is used differently by different groups of people. One understanding of its meaning is as adaptive pacing therapy, which is facilitated by healthcare professionals, in which people with CFS/ME use an energy management strategy to monitor and plan their activity, with the aim of balancing rest and activity to avoid exacerbations of fatigue and other symptoms. Another understanding is that pacing is a self-management strategy, without specific intervention from a healthcare professional. People with CFS/ME generally support this approach.
Persistent fatigue	Fatigue that lasts for at least 3 or 4 months and substantially outlives its precipitating cause.
Relaxation	A state of reduced physical and mental arousal, characterised by feelings of peace, and release from tension and anxiety. Achieving such a state often requires practice.

Rest periods	Short periods when a person is neither sleeping nor engaged in physical or mental activity. Rest periods are a core component of all management approaches for CFS/ME.
Setback/relapse	An increase in symptoms above the usual daily fluctuations, which may result in a reduction in function for a time.
Severity*	The degree to which CFS/ME affects a person's functioning and daily life . • People with mild CFS/ME are mobile, can care for themselves and can do light domestic tasks with difficulty. Most are still working or in education, but to do this they have probably stopped all leisure and social pursuits. They often take days off, or use the weekend to cope with the rest of the week. • People with moderate CFS/ME have reduced mobility and are restricted in all activities of daily living, although they may have peaks and troughs in their level of symptoms and ability to do activities. They have usually stopped work, school or college and need rest periods, often sleeping in the afternoon for 1 or 2 hours. Their sleep at night is generally poor quality and disturbed. • People with severe CFS/ME are unable to do any activity for themselves, or can carry out minimal daily tasks only (such as face washing, cleaning teeth). They have severe cognitive difficulties and depend on a wheelchair for mobility. They are often unable to leave the house, or have a severe and prolonged after-effect if they do so. They may also spend most of their time in bed, and are often extremely sensitive to light and noise.
Sleep hygiene	Behavioural strategies and environmental adaptations to improve sleep quality.
Specialist	A healthcare professional who has expert knowledge of and skills in a particular clinical area.
Specialist CFS/ME care	A service providing expertise in assessing, diagnosing and advising on the clinical management of CFS/ME, including symptom control and specific interventions. Ideally this is provided by a multidisciplinary team, which may include GPs with a special interest in the condition, neurologists, immunologists, specialists in infectious disease, paediatricians, nurses, clinical psychologists, liaison psychiatrists, dietitians, physiotherapists and occupational therapists.
Stage	There are different stages in the natural course of CFS/ME: acute illness, maintenance or stabilisation, and recovery.

*These definitions are based on the RCPCH guidelines[1], the CMO's report[2], citing Cox and Findley.[3]

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Registered stakeholder organisations

The following list is based on the NICE register of stakeholders as at 4 December 2006 (downloaded March 2007)

- 25% ME Group
- Action Against Allergy
- Action for ME
- Addenbrooke's NHS Trust
- Airedale General Hospital
- Anglesey Local Health Board
- Aquamarine Network
- Assist Trauma Care
- Association for Family Therapy

- Association for Psychoanalytic Psychotherapy in the NHS
- Association of British Neurologists
- Association of NHS Occupational Physicians
- Association of Medical Microbiologists
- Association of the British Pharmaceuticals Industry (ABPI)
- Association of Young People with ME
- Avon and Wiltshire Mental Health Partnership NHS Trust
- Barnsley Acute Trust
- Barnsley PCT
- Barts and The London NHS Trust (Therapy Action Group)
- BASRaT (British Association of Sports Rehabilitators and Trainers)
- Birmingham Heartlands and Solihull NHS Trust
- Blackwater Valley and Hart PCT
- Bolton, Salford and Trafford Mental Health
- BRAME – Blue Ribbon for the Awareness of ME
- Breakspear Medical Group Ltd
- British Association for Community Child Health
- British Association for Counselling and Psychotherapy
- British Association of Sport and Exercise Medicine

- British Association of Drama Therapists
- British Dietetic Association
- British Infection Society
- British National Formulary (BNF)
- British Nuclear Medicine Society
- British Paediatric Mental Health Group of the Royal College of Paediatrics and Child Health
- British Psychological Society
- British Society for Clinical Neurophysiology
- BUPA
- Cambridgeshire and Peterborough MH Partnership NHS Trust
- Carers Together
- CASPE
- Central Liverpool PCT
- Cephalon UK Ltd
- CFS/ME Clinical Network Coordinating Centre, Royal Victoria Infirmary
- CFS/ME Service Investment Programme
- Chartered Society of Physiotherapy
- Cheshire and Wirral Partnership NHS Trust
- Chronic Fatigue Research Unit at King's College London

- CISters
- College of Mental Health Pharmacists
- College of Occupational Therapists
- Commission for Social Care Inspection
- Community Practitioners and Health Visitors Association
- Connecting for Health
- Cornwall Partnership Trust
- Counselling and Psychotherapy Trust
- County Durham & Darlington Priority Services NHS Trust
- David Lewis Centre, The
- Defence Medical Services Directorate (MOD)
- Department of Health
- Department of Health, Peninsula Medical School
- Derbyshire Mental Health Services NHS Trust
- Devon Partnership NHS Trust
- Doctors Support Network
- East Anglia ME Patient Partnership (EAME)
- Eli Lilly and Company Ltd
- Epsom and St. Helier University Trust Chronic Fatigue Service

- Faculty of Occupational Medicine
- Ferring Pharmaceuticals Ltd
- Gedling PCT
- Gibson Parliamentary Inquiry into ME/CFS
- Good Hope Hospital NHS Trust
- Guildford and Waverley PCT
- Hampshire Partnership NHS Trust
- Health Protection Agency
- Healthcare Commission
- Hertfordshire Partnership NHS Trust
- Human Givens Institute
- Invest in ME
- King's College Hospital NHS Trust
- Local ME
- Maidstone and Tunbridge Wells NHS Trust
- Manchester Mental Health and Social Care Trust
- ME Association, The
- ME-letterforce National e-group
- Medicines and Healthcare Products Regulatory Agency

- Mid Staffordshire General Hospitals NHS Trust
- Milton Keynes PCT
- Myalgic Encephalomyelitis Research Group for Education and Support (MERGE)
- National CFS Network Executive Committee
- National CFS/ME Observatory
- National Institute for Mental Health in England (NIMHE)
- National Patient Safety Agency
- National Public Health Service – Wales
- National Tremor Foundation
- National Youth Advocacy Service
- NCCHTA
- Newcastle PCT
- NHS Direct
- NHS Fife
- NHS Plus
- NHS Quality Improvement Scotland
- North Bristol NHS Trust
- North Eastern Derbyshire PCT
- North Glamorgan NHS Trust – Merthyr Tydfil

- North Staffordshire Combined Healthcare NHS Trust
- North Yorkshire and York PCT
- Northern Ireland Campaign for ME/CFS
- Northwest London Hospitals NHS Trust
- Northwest Wales ME/FM Support Group
- Nottinghamshire Healthcare NHS Trust
- Nutrition Society
- One Click
- Oxford Nutrition Ltd
- Oxfordshire and Buckinghamshire Mental Health Care NHS Trust
- Pain Concern
- Peninsula Primary Care Psychology & Counselling Services
- PERIGON (formerly the NHS Modernisation Agency)
- Pottergate Centre for Dissociation and Trauma
- PPG group (paediatric/psychiatric pharmacology group)
- Primary Care Rheumatology Society
- Princess Alexandra Hospital NHS Trust
- Prodigy
- Queen Elizabeth Hospital (Norfolk)

- Queen Elizabeth Hospital NHS Trust (Woolwich)
- Regional Public Health Group – London
- Robert Jones and Agnes Hunt Orthopaedic and District Hospital, The
- Rotherham PCT
- Royal College of General Practitioners
- Royal College of General Practitioners Wales
- Royal College of Nursing (RCN)
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Physicians of London
- Royal College of Psychiatrists
- Royal Liverpool Children's NHS Trust
- Royal National Hospital for Rheumatic Diseases NHS Trust
- Royal Pharmaceutical Society of Great Britain
- Royal Society of Medicine
- Royal West Sussex Trust, The
- Sandwell and West Birmingham Hospitals NHS Trust
- Scottish Intercollegiate Guidelines Network (SIGN)
- Sheffield Children's NHS Trust

- Sheffield South West PCT
- Sigma-tau Spa
- Society for Academic Primary Care
- South and Central Huddersfield PCT
- South London and Maudsley Acute Trust
- South East Sheffield PCT
- South West Alliance for ME (SWAME)
- St Bartholomew's Hospital Chronic Fatigue Services
- Staffordshire Moorlands Primary Care Trust
- Stockport PCT
- Surrey Hampshire Borders NHS Trust
- Survivors Trust, The
- Syncope Trust and Reflex Anoxic Seizures (STARS)
- Syner-Med (PP) Ltd
- UCLH NHS Foundation Trust
- UK Anaemia
- UK Coalition of People Living with HIV and AIDS
- UK Psychiatric Pharmacy Group
- University College London Hospitals NHS Trust

- University of Manchester
- Vale of Aylesbury PCT
- Wareney PCT
- Welsh Assembly Government (formerly National Assembly for Wales)
- Welsh Association of ME & CFS Support
- Wessex Neurological Centre
- West Midlands Groups Consortium
- Young ME Sufferers Trust ,The

Executive summary and recommendations

Aims of the guideline

The guideline covers care provided by healthcare professionals who have direct contact with and make decisions about the care of people with chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) (CFS/ME). It covers care provided in primary and secondary care, and in specialist centres/teams.

The Guideline Development Group (GDG) developed this guideline with the aims of:

- increasing the recognition of CFS/ME
- influencing practice in the 'real world'
- improving access to appropriate services, and supporting consistent service provision
- emphasising the need for multidisciplinary working
- improving care for patients, particularly for those with severe CFS/ME
- providing guidance on 'best practice' for children with CFS/ME
- balancing clinical guidance with flexibility and management tailored to the needs of the patient
- facilitating communication between practitioners and patients, and their families or carers, as appropriate.

Key priorities for implementation

General principles of care

Shared decision-making between the person with CFS/ME and healthcare professionals should take place during diagnosis and all phases of care. The healthcare professional should:

- Acknowledge the reality and impact of the condition and the symptoms.
- Provide information about the range of interventions and management strategies as detailed in this guideline (such as the benefits, risks and likely side effects).
- Provide information on the possible causes, nature and course of CFS/ME.
- Provide information on returning to work or education.
- Take account of the person's age (particularly for children younger than 12 years), the severity of their CFS/ME, their preferences and experiences, and the outcome of previous treatment(s).
- Offer information about local and national self-help groups and support groups for people with CFS/ME and their carers (see also the NHS Expert Patients Programme).

Healthcare professionals should be aware that – like all people receiving care in the NHS – people with CFS/ME have the right to refuse or withdraw from any component of their care plan without this affecting other aspects of their care, or future choices about care.

To facilitate effective management of the condition, healthcare professionals should aim to establish a supportive and collaborative relationship with the person with CFS/ME and their carers. Engagement with the family is particularly important for children and young people, and for people with severe CFS/ME.

Healthcare professionals should provide diagnostic and therapeutic options to people with CFS/ME in ways that are suitable for the individual person. This may include providing domiciliary services (including specialist assessment) or using methods such as telephone or email.

Diagnosis and initial management

Advice on symptom management should not be delayed until a diagnosis is established. This advice should be tailored to the specific symptoms the person has and be aimed at minimising their impact on daily life and activities.

A diagnosis should be made after other possible diagnoses have been excluded and the symptoms have persisted for:

- 4 months in an adult
- 3 months in a child or young person; the diagnosis should be made or confirmed by a paediatrician.

Healthcare professionals should proactively advise about fitness for work and education, and recommend flexible adjustments or adaptations to work or studies to help people with CFS/ME to return to them when they are ready and fit enough. This may include, with the informed consent of the person with CFS/ME, liaising with employers, education providers and support services, such as:

- occupational health services
- disability services through Jobcentre Plus
- schools, home education services and local education authorities
- disability advisers in universities and colleges.

Specialist CFS/ME care

Any decision to refer a person to specialist CFS/ME care should be based on their needs, the type, duration, complexity and severity of their symptoms, and

the presence of comorbidities. The decision should be made jointly by the person with CFS/ME and the healthcare professional.

An individualised, person-centred programme should be offered to people with CFS/ME. The objectives of the programme should be to:

- sustain or gradually extend, if possible, the person's physical, emotional and cognitive capacity
- manage the physical and emotional impact of their symptoms.

Cognitive behavioural therapy and/or graded exercise therapy should be offered to people with mild or moderate CFS/ME and provided to those who choose these approaches, because currently these are the interventions for which there is the clearest research evidence of benefit.

Full list of recommendations

In response to stakeholder comments the GDG changed the order of the recommendations to reflect the CFS/ME care pathway of recognition, diagnosis and management. In particular, the GDG felt it was important to raise awareness of the possibility of CFS/ME early so that symptoms could be managed before a diagnosis was made.

The recommendations are listed below in the order that they appear in the NICE guideline. However, as the GDG reviewed the evidence relating to the key clinical questions according to topic, the recommendations also appear together with the question to which they relate in the relevant chapter or section.

1.1 General principles of care

1.1.1 Shared decision-making

1.1.1.1 Shared decision-making between the person with CFS/ME and healthcare professionals should take place during diagnosis and all phases of care. The healthcare professional should:

- Acknowledge the reality and impact of the condition and the symptoms.
- Provide information about the range of interventions and management strategies as detailed in this guideline (such as the benefits, risks and likely side effects).
- Provide information on the possible causes, nature and course of CFS/ME.
- Provide information on returning to work or education.
- Take account of the person's age (particularly for children younger than 12 years), the severity of their CFS/ME, their preferences and experiences, and the outcome of previous treatment(s).
- Offer information about local and national self-help groups and support groups for people with CFS/ME and their carers (see also the NHS Expert Patients Programme).

1.1.1.2 When providing care for children and young people, healthcare professionals should follow best practice as described in the national service frameworks for children for England or for Wales .

1.1.1.3 Healthcare professionals should be aware that – like all people receiving care in the NHS – people with CFS/ME have the right to refuse or withdraw from any component of their care plan without this affecting other aspects of their care, or future choices about care.

1.1.1.4 Healthcare professionals should recognise that the person with CFS/ME is in charge of the aims and goals of the overall management plan. The pace of progression throughout the course of any intervention should be mutually agreed.

1.1.1.5 Healthcare professionals should provide diagnostic and therapeutic options to people with CFS/ME in ways that are suitable for the individual person. This may include providing domiciliary services (including specialist assessment) or using methods such as telephone or email.

1.1.2 Support and information

1.1.2.1 To facilitate effective management of the condition, healthcare professionals should aim to establish a supportive and collaborative relationship with the person with CFS/ME and their carers. Engagement with the family is particularly important for children and young people, and for people with severe CFS/ME.

1.1.2.2 A named healthcare professional should be responsible for coordinating care for each person with CFS/ME.

1.1.2.3 Healthcare professionals should provide accurate information to people at all stages of CFS/ME, starting from when a diagnosis is first being considered. This should be tailored to the person's circumstances, including the stage and duration of the condition, symptoms experienced and relevant personal and social factors.

1.1.2.4 Information should be available in a variety of formats if appropriate (printed copy, electronic and audio), which people with CFS/ME and their carers can refer to at home and in the clinical setting.

1.1.3 Provision of care

1.1.3.1 Healthcare professionals responsible for caring for people with CFS/ME should have appropriate skills and expertise in the condition.

1.1.3.2 Every person diagnosed with CFS/ME should be offered:

- information about the illness (see section 1.1.2)
- acceptance and understanding
- assistance negotiating the healthcare, benefits and social care systems
- assistance with occupational activities including work and education if appropriate (see section 1.4.5).

1.1.3.3 An individualised management plan should be developed with the person with CFS/ME, and their carers if appropriate. The plan should be reviewed and changes documented at each contact. It should include:

- relevant symptoms and history
- plans for care and treatment, including managing setbacks/relapses
- information and support needs
- any education, training or employment support needs
- details of the healthcare professionals involved in care and their contact details.

1.2 Presentation

1.2.1 Presenting symptoms suspicious of CFS/ME

1.2.1.1 CFS/ME is recognised on clinical grounds alone. Primary healthcare professionals should be familiar with and be able to identify the characteristic features of CFS/ME.

1.2.1.2 Healthcare professionals should consider the possibility of CFS/ME if a person has:

- fatigue with all of the following features:

~ new or had a specific onset (that is, it is not lifelong)

~ persistent and/or recurrent

~ unexplained by other conditions

~ has resulted in a substantial reduction in activity level

~ characterised by post-exertional malaise and/or fatigue (typically delayed, for example by at least 24 hours, with slow recovery over several days)

and

- one or more of the following symptoms:

~ difficulty with sleeping, such as insomnia, hypersomnia, unrefreshing sleep, a disturbed sleep–wake cycle

~ muscle and/or joint pain that is multi-site and without evidence of inflammation

~ headaches

~ painful lymph nodes without pathological enlargement

~ sore throat

~ cognitive dysfunction, such as difficulty thinking, inability to concentrate, impairment of short-term memory, and difficulties with word-finding, planning/organising thoughts and information processing

~ physical or mental exertion makes symptoms worse

~ general malaise or ‘flu-like’ symptoms

~ dizziness and/or nausea

~ palpitations in the absence of identified cardiac pathology.

1.2.1.3 Healthcare professionals should be aware that the symptoms of CFS/ME fluctuate in severity and may change in nature over time.

1.2.1.4 Signs and symptoms that can be caused by other serious conditions (‘red flags’) should not be attributed to CFS/ME without consideration of alternative diagnoses or comorbidities. In particular, the following features should be investigated :

- localising/focal neurological signs
- signs and symptoms of inflammatory arthritis or connective tissue disease
- signs and symptoms of cardiorespiratory disease
- significant weight loss
- sleep apnoea
- clinically significant lymphadenopathy.

1.2.2 History, examinations and investigations

1.2.2.1 A full history (including exacerbating and alleviating factors, sleep disturbance and intercurrent stressors) should be taken, and a physical examination and assessment of psychological wellbeing should be carried out.

1.2.2.2 A child or young person who has symptoms suggestive of CFS/ME should be referred to a paediatrician for assessment to exclude other diagnoses within 6 weeks of presentation.

1.2.2.3 The following tests should usually be done:

- urinalysis for protein, blood and glucose
- full blood count
- urea and electrolytes
- liver function
- thyroid function
- erythrocyte sedimentation rate or plasma viscosity
- C-reactive protein
- random blood glucose
- serum creatinine
- screening blood tests for gluten sensitivity
- serum calcium
- creatine kinase
- assessment of serum ferritin levels (children and young people only).

Clinical judgement should be used when deciding on additional investigations to exclude other diagnoses.

1.2.2.4 Tests for serum ferritin in adults should not be carried out unless a full blood count and other haematological indices suggest iron deficiency.

1.2.2.5 Tests for vitamin B12 deficiency and folate levels should not be carried out unless a full blood count and mean cell volume show a macrocytosis.

1.2.2.6 The following tests should not be done routinely to aid diagnosis:

- the head-up tilt test
- auditory brainstem responses
- electrodermal conductivity.

1.2.2.7 Serological testing should not be carried out unless the history is indicative of an infection. Depending on the history, tests for the following infections may be appropriate:

- chronic bacterial infections, such as borreliosis
- chronic viral infections, such as HIV or hepatitis B or C
- acute viral infections, such as infectious mononucleosis (use heterophile antibody tests)
- latent infections, such as toxoplasmosis, Epstein–Barr virus or cytomegalovirus.

1.2.3 Advice on symptom management before diagnosis

1.2.3.1 Advice on symptom management should not be delayed until a diagnosis is established. This advice should be tailored to the specific symptoms the person has, and be aimed at minimising their impact on daily life and activities.

1.2.4 Re-assessment before diagnosis

1.2.4.1 If symptoms do not resolve as expected in a person initially suspected of having a self-limiting condition, primary healthcare professionals should listen carefully to the person's and their family and/or carers' concerns and be prepared to reassess their initial opinion.

1.2.4.2 If considering the possibility of CFS/ME or another serious alternative condition, primary healthcare professionals should consider discussion with a specialist if there is uncertainty about the interpretation of signs and symptoms and whether a referral is needed. This may also enable the primary healthcare professional to communicate their concerns and a sense of urgency to secondary healthcare professionals if symptoms are unusual.

1.3 Diagnosis

1.3.1 Making a diagnosis

1.3.1.1 A diagnosis should be made after other possible diagnoses have been excluded and the symptoms have persisted for:

- 4 months in an adult
- 3 months in a child or young person; the diagnosis should be made or confirmed by a paediatrician.

1.3.1.2 When a diagnosis of CFS/ME is made, healthcare professionals should provide honest, realistic information about CFS/ME and encourage cautious optimism.

- Most people with CFS/ME will improve over time and some people will recover and be able to resume work and normal activities.
- However, others will continue to experience symptoms or relapse and some people with severe CFS/ME may remain housebound.
- The prognosis in children and young people is more optimistic.

1.3.1.3 The diagnosis of CFS/ME should be reconsidered if none of the following key features are present:

- post-exertional fatigue or malaise

- cognitive difficulties
- sleep disturbance
- chronic pain.

1.4 General management strategies after diagnosis

1.4.1 Symptom management

1.4.1.1 There is no known pharmacological treatment or cure for CFS/ME. However, symptoms of CFS/ME should be managed as in usual clinical practice.

1.4.1.2 No research evidence was found to support the experience of some people with CFS/ME that they are more intolerant of drug treatment and have more severe adverse/side effects. However, if people with CFS/ME have concerns, healthcare professionals may consider starting drug treatment for CFS/ME symptoms at a lower dose than in usual clinical practice. The dose may be increased gradually, in agreement with the patient.

1.4.1.3 Drug treatment for children and young people with CFS/ME should be started by a paediatrician. However, prescribing may be continued in primary care, depending on the preferences of the patient and their carers, and local circumstances.

1.4.1.4 If a person experiences nausea as part of CFS/ME, this should be managed conventionally, including giving advice on eating little and often, snacking on dry starchy foods and sipping fluids. The use of anti-emetic drugs should be considered only if the nausea is severe.

1.4.1.5 Although exclusion diets are not generally recommended for managing CFS/ME, many people find them helpful in managing symptoms, including bowel symptoms. If a person with CFS/ME undertakes an exclusion diet or dietary manipulation, healthcare professionals should seek advice from a dietitian because of the risk of malnutrition.

1.4.2 Function and quality-of-life management

Sleep management

1.4.2.1 Healthcare professionals should provide tailored sleep management advice that includes:

- Explaining the role and effect of disordered sleep or sleep dysfunction in CFS/ME.
- Identifying the common changes in sleep patterns seen in CFS/ME that may exacerbate fatigue symptoms (such as insomnia, hypersomnia, sleep reversal, altered sleep–wake cycle and non-refreshing sleep).
- Providing general advice on good sleep hygiene .
- Introducing changes to sleep patterns gradually.
- Regular review.

1.4.2.2 If sleep management strategies do not improve the person's sleep and rest, the possibility of an underlying sleep disorder or dysfunction should be considered, and interventions provided if needed.

1.4.2.3 Sleep management strategies should not include encouraging daytime sleeping and naps. People with CFS/ME should be advised that excessive sleep does not generally improve physical or mental functioning, and excessive periods of daytime sleep or frequent napping may further disrupt the sleep–wake cycle.

Rest periods

1.4.2.4 Rest periods are a component of all management strategies for CFS/ME. Healthcare professionals should advise people with CFS/ME on the role of rest, how to introduce rest periods into their daily routine, and the frequency and length appropriate for each person. This may include:

- Limiting the length of rest periods to 30 minutes at a time.
- Introducing 'low level' physical and cognitive activities (depending on the severity of symptoms).
- Using relaxation techniques (see recommendation 1.4.2.6).

1.4.2.5 Healthcare professionals should review the use of rest periods regularly as part of the patient's management plan.

Relaxation

1.4.2.6 Relaxation techniques appropriate to the person with CFS/ME should be offered for the management of pain, sleep problems and comorbid stress or anxiety. There are a number of different relaxation techniques (such as guided visualisation or breathing techniques) that can be incorporated into rest periods.

Pacing

1.4.2.7 People with CFS/ME have reported pacing to be helpful in self-managing CFS/ME. However, healthcare professionals should advise people with CFS/ME that, at present, there is insufficient research evidence on the benefits or harm of pacing.

1.4.3 Diet

See also recommendations on managing nausea (1.4.1.4) and bowel symptoms (1.4.1.5), and use of supplements (1.4.7.2–4).

1.4.3.1 Healthcare professionals should emphasise the importance of a well-balanced diet in line with 'The balance of good health' . They should work with the person with CFS/ME to develop strategies to minimise complications that may be caused by nausea, swallowing problems, sore throat or difficulties with buying, preparing and eating food.

1.4.3.2 Healthcare professionals should emphasise the importance of eating regularly, and including slow-release starchy foods in meals and snacks. The physiological consequences of not doing so should be explained to the person with CFS/ME.

1.4.4 Equipment to maintain independence

1.4.4.1 For people with moderate or severe CFS/ME, providing or recommending equipment and adaptations (such as a wheelchair, blue badge or stairlift) should be considered as part of an overall management plan, taking into account the risks and benefits for the individual patient. This may help them to maintain their independence and improve their quality of life.

1.4.5 Education and employment

1.4.5.1 Having to stop their work or education is generally detrimental to people's health and well-being. Therefore, the ability of a person with CFS/ME to continue in education or work should be addressed early and reviewed regularly.

1.4.5.2 Healthcare professionals should proactively advise about fitness for work and education, and recommend flexible adjustments or adaptations to work or studies to help people with CFS/ME to return to them when they are ready and fit enough. This may include, with the informed consent of the person with CFS/ME, liaising with employers, education providers and support services, such as:

- occupational health services
- disability services through Jobcentre Plus

- schools, home education services and local education authorities
- disability advisers in universities and colleges.

1.4.5.3 For people with CFS/ME who are able to continue in or return to education or employment, healthcare professionals should ensure, with the person's informed consent, that employers, occupational health or education institutions have information on the condition and the agreed management plan.

Education

1.4.5.4 Healthcare professionals should follow the guidance from the Department for Children, Schools and Families on education for children and young people with medical needs, or equivalent statutory guidance.

1.4.5.5 Healthcare professionals should work closely with social care and education services to ensure a common understanding of the goals of the person with CFS/ME. The use of a flexible approach should be discussed, including home tuition and use of equipment that allows a gradual reintegration into education.

1.4.5.6 Time in education should not be used as a sole marker of progress of CFS/ME, and education should not be the only activity a person undertakes. There should be a balance between time spent attending school or college and doing homework, and time spent on home and social activities.

Employment

1.4.5.7 If possible, and with the informed consent of the person with CFS/ME, healthcare professionals should discuss employment issues with occupational health professionals, who will communicate with the person's manager or human resources representative. If there is no access to occupational health services, the responsible clinician should liaise with the employer directly .

1.4.6 Strategies that should not be used for CFS/ME

1.4.6.1 The following drugs should not be used for the treatment of CFS/ME:

- monoamine oxidase inhibitors
- glucocorticoids (such as hydrocortisone)
- mineralocorticoids (such as fludrocortisone)
- dexamphetamine
- methylphenidate
- thyroxine
- antiviral agents.

1.4.6.2 The following strategies should not be offered to people with CFS/ME:

- Advice to undertake unsupervised, or unstructured, vigorous exercise (such as simply ‘go to the gym’ or ‘exercise more’) because this may worsen symptoms.
- Specialist management programmes (see section 1.6) delivered by practitioners with no experience in the condition.

1.4.6.3 Although there is considerable support from patients (particularly people with severe CFS/ME) for the following strategies, healthcare professionals should be aware that there is no controlled trial evidence of benefit:

- Encouraging maintenance of activity levels at substantially less than full capacity to reserve energy for the body to heal itself (sometimes known as the envelope theory).

- Encouraging complete rest (cognitive, physical and emotional) during a setback/relapse.

1.4.6.4 Strategies for managing CFS/ME should not include:

- Prolonged or complete rest or extended periods of daytime rest in response to a slight increase in symptoms.

- An imposed rigid schedule of activity and rest.

1.4.7 Complementary and supplementary therapies

1.4.7.1 There is insufficient evidence that complementary therapies are effective treatments for CFS/ME and therefore their use is not recommended. However, some people with CFS/ME choose to use some of these therapies for symptom control, and find them helpful.

1.4.7.2 There is insufficient evidence for the use of supplements – such as vitamin B12, vitamin C, co enzyme Q10, magnesium, NADH (nicotinamide adenine dinucleotide) or multivitamins and minerals – for people with CFS/ME, and therefore they should not be prescribed for treating the symptoms of the condition. However, some people with CFS/ME have reported finding these helpful as a part of a self-management strategy for their symptoms.

1.4.7.3 People with CFS/ME who are using supplements should be advised not to exceed the safe levels recommended by the Food Standards Agency .

1.4.7.4 Some people with CFS/ME need supplements because of a restricted dietary intake or nutritional deficiencies. Healthcare professionals should seek advice from a dietitian about any concerns.

1.5 Referral to specialist CFS/ME care

1.5.1.1 Any decision to refer a person to specialist CFS/ME care should be based on their needs, the type, duration, complexity and severity of their

symptoms, and the presence of comorbidities. The decision should be made jointly by the person with CFS/ME and the healthcare professional.

1.5.1.2 Referral to specialist CFS/ME care should be offered:

- within 6 months of presentation to people with mild CFS/ME
- within 3–4 months of presentation to people with moderate CFS/ME symptoms
- immediately to people with severe CFS/ME symptoms.

1.6 Specialist CFS/ME care

1.6.1.1 After a patient is referred to specialist care, an initial assessment should be done to confirm the diagnosis.

1.6.1.2 If general management strategies (see section 1.4) are helpful for a person with CFS/ME, these should be continued after referral to specialist CFS/ME care.

1.6.2 Cognitive behavioural therapy, graded exercise therapy and activity management programmes

Choosing and planning treatment

1.6.2.1 An individualised, person-centred programme should be offered

to people with CFS/ME. The objectives of the programme should be to:

- sustain or gradually extend, if possible, the person's physical, emotional and cognitive capacity
- manage the physical and emotional impact of their symptoms.

1.6.2.2 The rationale and content of the different programmes, including their potential benefits and risks, should be fully explained to the person with

CFS/ME. Healthcare professionals should explain that no single strategy will be successful for all patients, or during all stages of the condition.

1.6.2.3 Healthcare professionals should recognise that the person with CFS/ME is in charge of the aims of the programme. The choice of the programme, its components, and progression throughout the programme should be mutually agreed and based on:

- the person's age, preferences and needs
- the person's skills and abilities in managing their condition, and their goals (such as improvement or treatment of deterioration of symptoms, prevention of relapse or maintenance)
- the severity and complexity of symptoms
- physical and cognitive functioning.

1.6.2.4 Cognitive behavioural therapy (CBT) and/or graded exercise therapy (GET) should be offered to people with mild or moderate CFS/ME and provided to those who choose these approaches, because currently these are the interventions for which there is the clearest research evidence of benefit.

1.6.2.5 If a full CBT or GET programme is inappropriate or not available, components of CBT or GET should be offered, either individually or more effectively in combination with:

- activity management strategies (see 1.6.2.22)
- sleep management (see 1.4.2.1–3)
- relaxation techniques (see 1.4.2.6).

1.6.2.6 The choice of programme, its components and progression through it should be reviewed regularly, taking into account the goals and abilities of the person with CFS/ME, and other approaches agreed as necessary.

1.6.2.7 Healthcare professionals should advise people with CFS/ME to contact them if they experience an increase in symptoms that lasts for longer than a few days after starting the specialist programme, or if symptoms are severe or distressing.

Cognitive behavioural therapy (CBT)

1.6.2.8 A course of CBT should be delivered only by a healthcare professional with appropriate training in CBT and experience in CFS/ME, under clinical supervision. The therapist should adhere closely to empirically grounded therapy protocols.

1.6.2.9 CBT should be offered on a one-to-one basis if possible.

1.6.2.10 CBT for a person with CFS/ME should be planned according to the usual principles of CBT, and should include:

- Acknowledging and validating the person's symptoms and condition.
- Explaining the CBT approach in CFS/ME, such as the relationship between thoughts, feelings, behaviours and symptoms, and the distinction between causal and perpetuating factors.
- Discussing the person's attitudes and expectations.
- Developing a supportive and collaborative therapeutic relationship.
- Developing a shared formulation and understanding of factors that affect CFS/ME symptoms.
- Agreeing therapeutic goals.
- Tailoring treatment to the person's needs and level of functioning.
- Recording and analysing patterns of activity and rest, and thoughts, feelings and behaviours (self-monitoring).

- Establishing a stable and maintainable activity level (baseline) followed by a gradual and mutually agreed increase in activity.

- Challenging thoughts and expectations that may affect symptom improvement and outcomes.

- Addressing complex adjustment to diagnosis and acceptance of current functional limitations.

- Developing awareness of thoughts, expectations or beliefs and defining fatigue-related cognitions and behaviour.

- Identifying perpetuating factors that may maintain or exacerbate CFS/ME symptoms to increase the person's self-efficacy (sense of control over symptoms).

- Addressing any over-vigilance to symptoms and related checking or reassurance-seeking behaviours by providing physiological explanations of symptoms and using refocusing/distraction techniques.

- Problem solving using activity management and homework tasks to test out alternative thoughts or beliefs, such as undertaking pleasure and mastery tasks (tasks that are enjoyable and give a sense of accomplishment).

- Building on existing assertion and communication skills to set appropriate limits on activity.

- Managing sleep problems, for example by addressing any unhelpful beliefs about sleep, behavioural approaches to sleep disturbance, stress management, and/or relaxation training (see recommendations 1.4.2.1–6).

- Treating any associated or comorbid anxiety, depression or mood disorder according to NICE clinical guidelines on these conditions (see section 6).

- Offering information on managing setbacks/relapses (see section 1.7).

Graded exercise therapy (GET)

1.6.2.11 GET should be delivered only by a suitably trained GET therapist with experience in CFS/ME, under appropriate clinical supervision.

1.6.2.12 GET should be offered on a one-to-one basis if possible.

1.6.2.13 People with mild or moderate CFS/ME should be offered GET that includes planned increases in the duration of physical activity. The intensity should then be increased when appropriate, leading to aerobic exercise (that is, exercise that increases the pulse rate).

1.6.2.14 GET should be based on the person's current level of activities (such as physical activity, daily routines, sleep patterns and frequency of setbacks/relapses) and emotional factors, vocational or educational factors and individual goals (details of these may be obtained from an activity diary). The programme should also include sleep and relaxation strategies (see recommendations 1.4.2.1–6).

1.6.2.15 When planning GET, the healthcare professional should:

- Undertake an activity analysis to ensure that the person with CFS/ME is not in a 'boom and bust' cycle before they increase the time spent in exercise.

- Discuss with the person the ultimate goals that are important and relevant to them. This might be, for example, a twice-daily short walk to the shops, a return to a previous active hobby such as cycling or gardening, or, for people with severe CFS/ME, sitting up in bed to eat a meal.

- Recognise that it can take weeks, months or even years to achieve goals, and ensure that this is taken into account in the therapy structure (for example, by setting short- and medium-term goals).

- Explain symptoms and the benefits of exercise in a physiological context.

1.6.2.16 When starting GET, the healthcare professional should:

- Assess the person's current daily activities to determine their baseline.

- Agree with them a level of additional low-intensity exercise that is sustainable, independent of daily fluctuations in symptoms, and does not lead to 'boom and bust' cycles. This may be sitting up in bed or brushing hair, for example, for people with severe CFS/ME, or gentle stretches or a slow walk.

- Encourage them to undertake this exercise for at least 5 days out of 7, or build up to this level if and when possible.

- Advise them that this level of exercise may mildly increase symptoms for a few days (for example, a mild to moderate increase in stiffness and fatigue), explain why this may occur and discuss strategies to mitigate it.

- Offer information on the management of setbacks/relapses (see section 1.7).

Progressing with GET

1.6.2.17 When the low-intensity exercise can be sustained for 5 days out of 7 (usually accompanied by a reduction in perceived exertion), the duration should be reviewed and increased, if appropriate, by up to 20%. For example, a 5-minute walk becomes 6 minutes, or a person with severe CFS/ME sits up in bed for a longer period, or walks to another room more often. The aim is to reach 30 minutes of low-intensity exercise.

1.6.2.18 When the duration of low-intensity exercise has reached 30 minutes, the intensity of the exercise may be increased gradually up to an aerobic heart rate zone, as assessed individually by a healthcare professional. A rate of 50–70% maximum heart rate is recommended.

1.6.2.19 Exercise intensity should be measured using a heart rate monitor, so that the person knows they are within their target heart rate zone.

1.6.2.20 If agreed GET goals are met, exercise duration and intensity may be increased further if appropriate, if other daily activities can also be sustained, and in agreement with the person with CFS/ME.

Maintaining exercise

1.6.2.21 After completing a GET programme, the healthcare professional and the person with CFS/ME should continue working together to develop and build on strategies to maintain exercise. Support should be available, if needed, to enable the person to reinforce the learning and lifestyle changes made and continue GET beyond discharge.

Activity management

1.6.2.22 Activity management is a goal-oriented and person-centred approach tailored to the needs of the person with CFS/ME. It should include:

- Understanding that activities have physical, emotional and cognitive components, and identifying these components.

- Keeping a diary that records cognitive and physical activity, daytime rest and sleep. This will help to set baseline levels of activity (a stable and sustainable range of functioning), identify patterns of over- and underactivity, and develop an activity/exercise strategy.

- Establishing a baseline; specific activities may need to be increased or decreased while this is happening.

- Gradually increasing activity above the baseline in agreement with the person.

- Planning daily activities to allow for a balance and variety of different types of activity, rest and sleep. This may include making a weekly activity schedule.

- Spreading out difficult or demanding tasks over the day or week.

- Splitting activities into small achievable tasks according to the person's level of ability/functioning, followed by gradual increases in the complexity of the tasks.

- Monitoring, regulating and planning activities to avoid a 'boom and bust' cycle.

- Goal setting, planning and prioritising activities.

- Explaining the role of rest in CFS/ME and helping the person work out how to build in rest periods and achieve a productive day (see recommendations 1.4.2.1–6).

- Regularly reviewing activity levels and goals.

- Offering information on the management of setbacks/relapses (see section 1.7).

1.6.3 Pharmacological interventions for symptom control

1.6.3.1 If chronic pain is a predominant feature, healthcare professionals should consider referral to a pain management clinic.

1.6.3.2 Prescribing of low-dose tricyclic antidepressants, specifically amitriptyline, should be considered for people with CFS/ME who have poor sleep or pain. Tricyclic antidepressants should not be offered to people who are already taking selective serotonin reuptake inhibitors (SSRIs) because of the potential for serious adverse interactions.

1.6.3.3 Melatonin may be considered for children and young people with CFS/ME who have sleep difficulties, but only under specialist supervision because it is not licensed in the UK.

1.7 Management of setbacks/relapses

1.7.1 Preparing for a setback/relapse

1.7.1.1 People with CFS/ME should be advised that setbacks/relapses are to be expected as part of CFS/ME.

1.7.1.2 Healthcare professionals and people with CFS/ME should develop a plan for managing setbacks/relapses, so that skills, strategies, resources and support are readily available and accessible when needed. This plan may be shared with the person's carers, if they agree.

1.7.2 During a setback/relapse

1.7.2.1 Setbacks/relapses may be triggered by factors such as unexpected/unplanned activities, poor sleep, infection or stress. Healthcare professionals, in discussion with the person with CFS/ME, should try to identify the cause(s) of a setback/relapse, but it should be recognised that this may not always be possible.

1.7.2.2 When managing a setback/relapse, the management plan should be reviewed. Healthcare professionals should discuss and agree an appropriate course of action with the person with CFS/ME, taking into account:

- the person's experience
- possible causes of the setback/relapse, if known
- the nature of the symptoms
- the severity and duration of the setback/relapse
- the current management plan.

1.7.2.3 When managing setbacks, healthcare professionals should put strategies into place that:

- Include relaxation and breathing techniques.
- Maintain activity and exercise levels if possible, by alternating activities with breaks and pacing activities, as appropriate.
- Involve talking to families and carers, if appropriate.
- Recognise distressing thoughts about setbacks/relapses such as 'this means I'll never get better', but encourage optimism.
- Involve reconsidering and revising the levels and types of symptom control.

1.7.2.4 In some setbacks/relapses, it may be necessary to reduce, or even stop, some activities and increase the frequency and/or duration of rest periods to stabilise symptoms and re-establish a baseline activity level. This should be discussed and agreed with the person with CFS/ME.

1.7.2.5 People with CFS/ME should be advised to minimise daytime sleep periods. However, healthcare professionals should recognise that this is not always possible, depending on the severity of a person's symptoms and the setback.

1.7.3 After a setback/relapse

1.7.3.1 After a setback/relapse, healthcare professionals should review the person's activity levels to re-establish a baseline and review the management plan. A gradual return, when possible, to previous exercise and functional routines should be encouraged. Activity should be increased gradually.

1.7.3.2 Healthcare professionals should advise on:

- Slowly decreasing the frequency and duration of rest periods.

- Continuing the use of relaxation techniques, even when the person with CFS/ME is beginning to feel better.

1.7.3.3 After a setback, healthcare professionals and people with CFS/ME should review the experience to determine, if possible, whether triggers can be managed in the future, and put strategies in place to do this.

1.8 Review and ongoing management

1.8.1.1 Regular, structured review should be undertaken for all people with CFS/ME. The review should include, if appropriate:

- Assessing improvement or deterioration in symptoms.
- Assessing any adverse or unwanted effects of therapy.
- Ongoing investigations.
- Considering the need to repeat investigations (for children and young people, repeating investigations should be considered if there is no improvement after 1 year).
- Reviewing the diagnosis, especially if signs and symptoms change (see recommendation 1.2.1.4).
- Considering referral to specialist CFS/ME care.
- Reviewing equipment needs.
- Assessing any additional support needs (see sections 1.1 and 1.4).

1.8.1.2 The timing of the reviews should depend on the severity and complexity of symptoms, the effectiveness of any interventions, and the needs of the person with CFS/ME.

1.9 Key principles of care for people with severe CFS/ME

1.9.1 General principles of care

1.9.1.1 Management of severe CFS/ME is difficult and complex and healthcare professionals should recognise that specialist expertise is needed when planning and providing care for people with severe CFS/ME.

1.9.1.2 Diagnosis, investigations, management and follow-up care for people with severe CFS/ME should be supervised or supported by a specialist in CFS/ME.

1.9.1.3 People with severe CFS/ME may need to use community services at times. These services may include nursing, occupational therapy, dietetics, respite care, psychology and physiotherapy (see the 'National service framework for long-term conditions'). The input of different professionals should be coordinated by a named professional.

1.9.1.4 People with severe CFS/ME should be offered a summary record of every consultation because of their cognitive difficulties.

1.9.1.5 Most people with CFS/ME will not need hospital admission. However, there may be circumstances when a planned admission should be considered. The decision to admit should be made with the person with CFS/ME and their family, and be based on an informed consideration of the benefits and disadvantages. For example, a planned admission may be useful if assessment of a management plan and investigations would require frequent visits to the hospital.

1.9.2 Rest

1.9.2.1 When making decisions about prolonged bed rest, healthcare professionals should seek advice from a specialist experienced in the care of people with severe CFS/ME. The significant physical and psychological risks associated with prolonged bed rest should be taken into account.

1.9.2.2 Healthcare professionals working with people with severe CFS/ME who are in bed most (or all) of the time, should explain the associated risks (such as postural hypotension, deep venous thrombosis, osteoporosis, pressure sores and deconditioning) and monitor these.

1.9.3 Management approaches

1.9.3.1 People with severe CFS/ME should be offered an individually tailored activity management programme (see recommendation 1.6.2.22) as the core therapeutic strategy, which may:

- be delivered at home, or using telephone or email if appropriate
- incorporate the elements of recommendation 1.6.2.22 and draw on the principles of CBT and GET (see recommendations 1.6.2.1–21).

1.9.3.2 An activity management programme should be reviewed regularly and frequently.

Clinical care pathways

There is a care pathway for CFS/ME on page 6 of the quick reference guide at www.nice.org.uk/CG053.

Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. Details of the criteria used when making these research recommendations can be found in the Guidelines Manual 2006 (www.nice.org.uk/guidelinesmanual). The research recommendations were chosen to prioritise those areas that would most directly inform future guidelines.

The aetiology of CFS/ME was outside the scope of the guideline and therefore a systematic search of the area was not carried out. For that reason, the GDG has not made a research recommendation about the causes of CFS/ME, but it recognises that research in this area would be very helpful.

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. Additional research recommendations discussed in the GDG have been documented in the appropriate sections throughout the guideline.

Extrapolating use of intervention strategies

Are intervention strategies that have been shown to be effective in mildly to moderately affected adults also effective in children and in people (adults and children) with severe CFS/ME?

Why this is important

There is limited evidence for the use or effectiveness of strategies recommended in this guideline in these two patient groups. Population data suggest that these groups constitute a significant percentage of the population with CFS/ME. Some patient experience suggests that some of these interventions may be harmful and/or not effective.

Delivery of standard methods of care

Are there more efficient ways of delivering standard methods of care? For example, what is the most efficient way of delivering domiciliary care for people with CFS/ME?

Why this is important

Randomised controlled trials, with adequate power, are needed to compare different methods of delivering standard methods of care, and whether outcomes differ depending on whether they are delivered in primary or secondary care. Subgroup analysis may clarify which approach is most efficient (that is, cost effective without decreasing efficacy) in different groups of people with CFS/ME (for example, people who are severely affected).

Prevalence and course of the illness

What is the prevalence and incidence of CFS/ME in different populations? What is the natural course of the illness?

Why this is important

Reliable information on the prevalence and incidence of this condition is needed to plan services. This will require well-constructed epidemiological studies across different populations to collect longitudinal data to predict outcome, and to calculate the economic impact of loss of work or education.

We recommend that these questions are answered using a mixture of:

- cross-sectional population studies, including people with different levels of disease severity from all ethnic groups and social classes
- longitudinal cohorts of people with CFS/ME, and population cohorts to assess the incidence and prognosis of CFS/ME in a previously normal cohort.

Measuring outcome

What is the best way of measuring outcome in research studies?

Why this is important

There is a lack of studies in this area. Knowing what is important to people with CFS/ME is crucial for designing future studies. It is not known how best to measure improvement scientifically for people with CFS/ME, and how much of an improvement is significant. More information is needed on functional outcomes such as return to work or education, return to normal family life or social activities, or increased self-esteem, to inform future estimates of the cost effectiveness of treatment.

Structure of the guideline documentation

An outline of the guideline documentation can be seen in the Contents listing (above).

Chapters 1 and 2 provide details of the background and the methods used to develop the guideline. Chapter 3 reports the experience of people with CFS/ME.

Chapters 4 to 7 cover specific clinical topics and include the guideline recommendations and a summary of the evidence. The recommendations are also presented in full in the executive summary. Each clinical chapter includes the key clinical question(s), the recommendations, a summary review of the evidence base (including the health economics evidence), with the detailed evidence review and tables being annexed, and a summary of how the recommendations were derived. A summary of the consensus development is also included, with details of the consensus development in the appendices. Important general methodological and clinical issues are flagged as appropriate.

Development of the guideline

Clinical context

In 2004, the then National Institute of Clinical Excellence commissioned the National Collaborating Centre for Primary Care (NCC-PC) to develop a clinical guideline on chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) (CFS/ME) for use in the National Health Service (NHS) in England and Wales. This followed referral of the topic by the Department of Health (DH) and the Welsh Assembly Government. A scope for the guideline was agreed (see below) and this defined exactly what this guideline would (and would not) examine, and what the guideline developers would consider.

The guideline provides recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

Who is the guideline for?

The guideline covers care provided by healthcare professionals who have direct contact with and make decisions about the care of people with CFS/ME. It covers care provided in primary and secondary care, and in specialist centres/teams.

The guideline is also relevant to the work, but does not address the practice, of those working in:

- occupational health services
- social services
- educational services
- the voluntary sector.

Scope

Population

Groups that are covered

The guideline addresses the diagnosis, treatment and management of CFS/ME in children aged 5 years and upwards (including young people in transition to adulthood) and adults who are mildly, moderately or severely affected by the condition.

Groups that are not covered

The guideline does not address the management of people for whom CFS/ME has been excluded as a diagnosis.

Clinical management

The guideline covers the clinical management of patients given a diagnosis of CFS/ME.

As the management of CFS/ME depends on a correct diagnosis, the guideline includes recommendations about the process of assessment leading to a diagnosis. This includes:

- clinical case definition
- appropriate timing for diagnosis
- the appropriate use of laboratory tests, imaging or other tests.

The guideline addresses the following types of interventions, including, where good evidence exists, different approaches applicable to different groups (for example, according to age, gender, ethnicity, or the severity or duration of symptoms), and respecting the patient's (and where appropriate carer's) views:

- symptom management strategies

- rehabilitation strategies
- support for patients and carers.

Also, specific interventions covered by the guideline include:

- self management strategies
- return to education and/or employment
- pharmacological therapies
- physical therapies (including graded exercise therapy)
- life-style management (including pacing, graded activity)
- psychological therapies (including cognitive behaviour therapy)
- nutrition
- complementary therapies.

The guideline also makes recommendations on:

- criteria for referral to appropriate specialist services for children, young people and adults
- the provision of advice by healthcare professionals on home tuition or return to school
- the provision of advice by healthcare professionals on return to work
- information needs of healthcare professionals, patients and carers and other professionals involved in care.

The guideline does not address:

- the management of co-morbidities

- highly specialised procedures and procedures that have been investigated only in pilot/exploratory studies
- service provision or models of care.

Plans for guideline revision

NICE clinical guidelines are updated as needed, so that recommendations take into account important new information. The emergence of new evidence will be checked 2 to 4 years after publication of the guideline to decide whether all, or part, of the guideline should be updated. If important new evidence is published at other times, a more rapid update of some recommendations may be considered.

1 Introduction to chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy)

1.1 Introduction

Chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (or encephalopathy) (ME) is a relatively common illness. The physical symptoms can be as disabling as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, congestive heart failure and other chronic conditions. CFS/ME places a substantial burden on people with the condition, their families and carers, and hence on society.

Many different potential aetiologies for CFS/ME – including neurological, endocrine, immunological, genetic, psychiatric and infectious – have been investigated, but the diverse nature of the symptoms can not yet be fully explained. The World Health Organization (WHO) classifies CFS/ME as a neurological illness (G93.3), and some members of the Guideline Development Group (GDG) felt that, until research further identifies its aetiology and pathogenesis, the guideline should recognise this classification. Others felt that to do so did not reflect the nature of the illness, and risked restricting research into the causes, mechanisms and future treatments for CFS/ME.

In 1998, the Chief Medical Officer for England convened an Independent Working Group which reported in 2002.[4] In the report, the Working Group stated that CFS/ME is a genuine illness, and that health and social care professionals should therefore recognise it as such. The CMO working group called for a consensus to be reached on terminology and definition, and while awaiting this, suggested that the composite term CFS/ME is used and that it is considered as one condition or a spectrum of disease for the purpose of the report. This is the approach also adopted in this guideline. As a result of the report,[4] the Medical Research Council was commissioned to develop a research strategy, and has made research on CFS/ME a priority.

1.2 Clinical need for the guideline

CFS/ME comprises a range of symptoms that includes fatigue, malaise, headaches, sleep disturbances, difficulties with concentration and muscle pain. A person's symptoms may fluctuate in intensity and severity, and there is also great variability in the symptoms different people experience. CFS/ME is characterised by debilitating fatigue that is unlike everyday fatigue and can be triggered by minimal activity. This raises especially complex issues in adults and children with severe CFS/ME.

CFS/ME, like other chronic conditions for which the causes and disease processes are not yet fully understood, poses significant problems for healthcare professionals. It can cause profound, prolonged illness and disability, which has a substantial impact on people with CFS/ME and their carers. Uncertainties about diagnosis and management, and a lack of clinical guidance for healthcare professionals, have exacerbated this impact.

1.3 Aetiology

Currently, the aetiology of CFS/ME remains unknown, although several factors have been suggested, including immunological, genetic, viral, neuroendocrine and psychological.[5] Indeed, there is growing evidence that the condition is heterogeneous, and may not have a single or simple aetiology. It may be best regarded as a spectrum of illness that is triggered by a variety of factors in people who have an underlying predisposition. This is the view of aetiology taken by the GDG, pending the findings of ongoing research.

1.4 Diagnosis

The clinical practice guidelines on chronic fatigue syndrome developed by the Royal Australian College of Physicians define CFS as 'a descriptive term used to define a recognisable pattern of symptoms that cannot be attributed to any alternative condition'.[6] There is ongoing debate about the most appropriate

diagnostic criteria to be applied. Please see Chapter 5 for a full discussion of diagnosis.

Because of the potential educational and social disruption, it has been generally agreed that for children and adolescents 6 months of fatigue before diagnosis is too long. For this reason fatigue durations of 8 weeks[7] and 3 months[8] have been proposed.[1] The Royal College of Paediatrics and Child Health guideline stated that a patient who is referred with debilitating fatigue for assessment should be given an initial opinion of 'generalised fatigue'.

At present, there are no physical signs that identify CFS/ME specifically. In addition, there are no diagnostic laboratory tests or other diagnostic criteria that can, as yet, confirm a diagnosis of CFS/ME,[9] although research is ongoing. The diagnosis of CFS/ME is therefore made on the basis of a recognisable pattern of characteristic symptoms, and on the exclusion of other known causes.

A positive diagnosis of CFS/ME should be made after other known causes for the symptoms have been excluded and where the symptoms are causing functional impairment.[1]

1.5 Management

Early research into CFS/ME focused on possible causes, diagnostic criteria and natural history of the illness, with research into the treatment or management of the condition increasing only in recent years. Results are now available from a number of studies that have assessed the effectiveness of interventions used in the treatment or management of CFS/ME or have considered the support and information needs of healthcare professionals, patients and carers.

Guidelines on the management of CFS/ME have been published in Canada, the USA and Australia; in the UK, the Royal College of Paediatrics and Child Health published guidelines on the management of CFS/ME in children and young people in December 2004.[1;6;10;11] An evidence-based report on the diagnosis and management of CFS/ME was also adopted in the Netherlands.[12]

The approach taken in this guideline is that of managing CFS/ME as a condition. Detailed guidance about the management of every potential symptom has not been included since the management of symptoms should follow established principles. For example, the principles of pain management should be applied in managing pain in someone with CFS/ME.

1.6 Prognosis

The CMO's report concluded that the natural course of CFS/ME is such that:

- most patients will show some degree of improvement over time, especially with treatment
- a substantial number of patients will pursue a fluctuating course with periods of relative remission and relapse, and
- a significant minority become severely, and perhaps permanently, disabled.[4]

Overall, there is considerable variation reported in both the severity and the duration of symptoms. The US Centers for Disease Control (CDC) cited a review of published studies reporting recovery rates of 8–63% (median 40%), with full recovery being rare (5–10% achieving total remission).[9]

1.7 Epidemiology

1.7.1 Incidence and prevalence

Overall, the evidence suggests a population prevalence of at least 0.2–0.4%,[4] which means that a general practice with a population of 10,000 patients is likely to have up to 40 patients with CFS/ME, half of whom will need input from specialist CFS/ME services. However, there is a lack of epidemiological data for the UK, which means that population estimates are based on extrapolations from other countries. The estimated annual prevalence is approximately 4000 cases per million of the population.[13]

The CDC reported that:

- people of every age, gender, ethnicity and socioeconomic group can have CFS/ME
- CFS/ME affects women at four times the rate of men
- it is most common in people aged in their 40s and 50s
- although CFS/ME is much less common in children than in adults, children can develop the illness, particularly during adolescence.[9]

1.8 Existing service provision

CFS/ME can cause profound, prolonged illness and disability. Uncertainties about diagnosis and management, and lack of clinical guidance for healthcare professionals have created problems in the care of people with CFS/ME, including lack of access to appropriate care.

The 2002 CFS/ME Working Group Report highlighted that the provision of services specifically tailored for patients with CFS/ME in England is limited, and may be non-existent in some areas. Specialist CFS/ME services for children and young people, including inpatient facilities, are limited across the UK. Referrals from primary care have been to one or more of several specialties, such as general medicine, immunology, neurology, haematology, rheumatology and psychiatry. The CFS/ME Working Group Report suggested that the lack of locally based specialist CFS/ME services could pose a problem 'to both patients who need a service and to commissioners of health services who wish to reduce the cost of out of area treatments'.[4]

The 2004–2006 CFS/ME Service Investment Programme, which was set up to address major gaps in service provision across England, has led to the phased establishment of 13 clinical network coordinating centres, 36 local teams for adults' services and 11 specialist CFS/ME care teams for children and young people. The new CFS/ME services now cover 65% of the population of England whilst some of the remaining 35% of the population are covered by the pre-

existing services. Within the first 2 years of the project, 11,040 adult patients were seen and enrolled into treatment programmes. The children and young people teams have seen 669 children and have established multiagency arrangements for treatment and support.[14] However, the initial set-up phase of the Investment Programme has now ended and the extension and even the continuance of some of these services is at risk, even though the NHS has been given the necessary funding to continue them. Questions therefore remain about access to appropriate care for all who need it.

2 Methodology

2.1 Introduction

This chapter describes the methods used to generate the GDG's recommendations for the diagnosis and management of CFS/ME in adults and children.

The methods were based on those of the National Institute for Health and Clinical Excellence (NICE) in: National Institute for Health and Clinical Excellence (April 2006) 'The guidelines manual'. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual. *The Guideline Development Process – an overview for stakeholders, the public and the NHS* describes how organisations can become involved in the development of a guideline.

Consensus development methods were used in addition to the usual guideline development processes, and these are also detailed below.

2.2 The developers

The National Collaborating Centre for Primary Care (NCC-PC) is based at the Royal College of General Practitioners and has an academic partner, the Clinical Governance Research and Development Unit (CGRDU), based in the Department of Health Sciences at the University of Leicester. Its other partner organisations are the Royal Pharmaceutical Society of Great Britain and the Community Practitioners' and Health Visitors' Association. The Collaborating Centre was set up in 2000, to undertake commissions from NICE to develop clinical guidelines for the National Health Service (NHS) in England and Wales.

This guideline was developed by the NCC-PC and supported by an evidence review carried out by the University of York. The NCC-PC Methods team consisted of a project lead, project manager/researcher and health economist. The evidence review was commissioned from the Centre for Reviews and

Dissemination at the University of York (see Appendix 1), and was an update review based on a previous systematic review on the diagnosis, treatment and management of CFS/ME in adults and children.[5] The NCC-PC health economist undertook a review and subsequent modelling of the available health economics evidence, and details can be seen in the appropriate chapters.

2.3 The Guideline Development Group (GDG)

The Guideline Development Group (GDG) was deliberately convened to have a sufficiently large and broad membership to reflect the wider expertise amongst the various specialties to which people with CFS/ME may be referred. It chiefly comprised consumer representatives and healthcare professionals with daily, clinical experience of treating CFS/ME, rather than purely academic expertise. Nominations for GDG members were invited from various stakeholder organisations and members were selected to ensure appropriate representation. Nominations were also received for co-opted experts. Each nominee was expected to serve as an individual expert in their own right and not as a representative of their nominating organisation, although they were encouraged to keep their nominating organisation informed of the process. Co-optees contributed to aspects of the guideline development by attending up to two meetings at the invitation of the group members and reviewing papers as appropriate, but they were not full members of the GDG.

The GDG met on 18 occasions, at approximately 4–6-weekly intervals over 24 months, to review the evidence identified, to comment on its quality and completeness, and to develop recommendations for practice, based on the available evidence and using formal consensus techniques.

2.4 Developing key clinical questions

The first stage in the development of the guideline was to narrow the scope into a series of key clinical questions. The key clinical questions formed the basis for subsequent evidence reviews and helped the GDG to develop recommendations.

The key clinical questions were developed by the GDG with assistance from the Methods team, including the team from York University who did the searching and reviewing. The project team then refined the questions into specific research questions to aid literature searching, appraisal and synthesis. The GDG reviewed, commented on and refined the protocol (see Appendix 1) that directed the searching and reviewing.

The following key clinical questions were addressed,

- Question 1 (two parts): What are the existing case definitions for CFS/ME in adults and children? What evidence exists to substantiate or validate these case definitions?

- Question 2: Are there any substantiated or validated evaluations to support the diagnosis of CFS/ME in adults and children?
  (Subquestion: In people presenting with early suspected CFS/ME (before 6 months) what are the risk factors/ prognostic flags that might be linked with progression to CFS/ME?)

- Question 3: Does the evidence show that any particular intervention or combination of interventions is effective in treatment, management or rehabilitation of adults and children with a diagnosis of CFS/ME?
  (Subquestion: In people presenting with early suspected CFS/ME what interventions might be effective in preventing progression to CFS/ME?)

- Question 4: What are the information needs of healthcare professionals, patients and carers?

- Question 5: What are the support needs of healthcare professionals, patients and carers?

2.5 Layout of chapters 4–7

For details of chapters and the layout, please see Structure of the guideline documentation.

2.6 Identifying the evidence

2.6.1 Literature search and evidence reviews

The aim of the literature search was to identify relevant, published evidence to answer the key clinical questions, in order to produce an evidence review using a systematic and transparent approach. One search was carried out to cover all five key clinical questions. The search was broad and aimed to pick up all studies of CFS/ME and related synonyms. Databases searched included Medline, EMBASE, Psych Info, CENTRAL, Social Science Citation Index, Science Citation Index, Index to Scientific and Technical Proceedings, PASCAL, Inside Conferences, AMED and HEED. Details of all literature searches are available in the systematic review (see Appendix 1). GDG members suggested further references. Evidence submitted by stakeholder organisations that was relevant to the key clinical questions and was of at least the same level of evidence as that identified by the literature searches was also included. Searches were conducted in May/June 2005, with update searches being carried out in August 2006. The extraction tables for the original search can be found at the end of Appendix 1 and for the update searches in Appendix 2.

Patient stakeholder organisations were invited to submit evidence on the 'patient experience' and the GDG reviewed and discussed the summaries of these (see Chapter 3 for details). This information was mainly from membership surveys. The use of patient surveys in guideline development is increasingly seen as important as such surveys allow a more complete picture to be established concerning the effectiveness of, and satisfaction with, given aspects of patient care (for example, a therapeutic intervention). However, information gathered through patient surveys is generally considered as relatively low-level evidence, for several reasons. The most important potential types of bias associated with patient surveys are the following:

selection bias: the systematic inclusion or exclusion of certain patients during selection to participate in a survey;

non-responder bias: systematic differences between participants who respond

and those who do not respond to a given survey;
social desirability bias: a tendency to answer questions in a way that a given community/society may regard as expected; and
confounder bias: when a relationship found between two variables in a given survey (for example, patient satisfaction with a therapeutic intervention) does not in fact reflect reality but rather is disturbed by the effect of one or more other variables (confounders, e.g. provider performance).[15]

In addition, there are other potential biases more intrinsic to a given survey itself (such as potential biases in a survey's 'usability', including its format, instructions and understandability; see [16]).

Randomised controlled trials (RCTs) are considered to be at the top of the hierarchy of evidence,[17] with patient surveys found further down the hierarchy. RCTs attempt to minimise many of the biases associated with patient surveys. For example, they may attempt to deal with the potential problem of non-responder bias (i.e. lost data from participants) through performing an intention-to-treat analysis on a dataset[18] or address the problem of confounder bias through attempting to equally distribute both known and unknown determinants of a given outcome (and therefore potential sources of bias) between groups through the randomisation of participants.[17] Thus, when evidence from an RCT is available to answer a given clinical question it is generally given priority over and above other types of evidence, including patient surveys.

The GDG found the information submitted by patient stakeholder organisations helpful in understanding the patient view. However, it also recognised that surveys from self-selected respondents are subject to bias and that this information was therefore not necessarily representative of the wider population of people with CFS/ME.

2.6.2 Response to criticisms of the evidence review

A large number of the criticisms of the evidence review appear to have been due to a misunderstanding about its nature and purpose. The evidence review was

commissioned as an update of the Centre for Reviews and Dissemination's (CRD's) original systematic review[13], and reviewed only RCTs and controlled trials of interventions for the treatment/management of CFS/ME. This review was then only one of the resources available to the GDG during the guideline development process (see the NICE Guidelines Manual 2006 for details as used in this guideline: www.nice.org.uk/guidelinesmanual). Other resources, including patient evidence and clinical expertise, were also considered by the GDG.

The aim of the review was to identify all relevant RCTs or controlled trials: it did not exclude any RCTs or controlled trials on the basis of their age, country of origin or validity. The validity of the trials was consistently highlighted throughout the review, with a discussion of the methodological flaws.

Much of the existing evidence is of poor quality, and the review was restricted to those study designs at the top of the evidence hierarchy, i.e. RCTs and controlled trials. Where RCTs or controlled trials are available, widening the inclusion criteria to include poorer study designs would not improve the quality of the evidence, but would introduce the problem of comparing and weighting data from different study designs, making the evidence even more difficult to interpret.

As noted above, RCT or controlled trial evidence is not the only information considered when developing clinical guidelines, which is why the GDG also considered the experiences of both patients and clinicians. Please see the detailed description of how the recommendations were developed later in Chapter 2.

The purpose of the review was not to determine, or report evidence relating to the possible underlying processes of CFS/ME; the review therefore summarised the evidence from the trials of interventions and did not comment on any association with possible underlying disease processes. Details of all the included trials, including reported adverse events, can be seen in Appendix 1.

2.6.3 Health economics

The Methods team health economist, liaising with other team members as appropriate, reviewed the literature to assess the economic evidence. As such evidence was limited, a broad evidence search was performed, designed to identify information about the costs or resources used in providing a service or intervention and/or the benefits that could be attributed to it. No criteria for study design were imposed a priori. In this way, any evidence that might be of use was more likely to be identified. Thus, papers were not restricted to RCTs or formal economic evaluations, but papers included were limited to those written in English and containing health economics information that could be generalised to England and Wales. Extraction was then undertaken on any formal economic evaluation identified, and the results were presented to the GDG. The extractions can be found in Appendix 2.

2.7 Reviewing and grading the evidence

The titles and abstracts of records retrieved by the searches, provided by the GDG or submitted by stakeholders were scanned for relevance to the key clinical questions. Those relevant were reviewed to identify the most appropriate evidence to help answer the key clinical questions and to ensure that the recommendations would be based on the best available evidence. This process involved selection of relevant studies; assessment of study quality; synthesis of the results; and grading of the evidence. The methods used are outlined below.

2.7.1 Review of the clinical evidence

Details of the review methods can be seen in the full review in Appendix 1. Studies were graded according to Chapter 7.2 of the NICE Guidelines Manual 2006 (available at www.nice.org.uk/guidelinesmanual).

2.7.2 Review of the health economics evidence

Health economics evidence was reviewed by the health economist in the Methods team. NICE methods were used (see the Guidelines Manual 2006 at

www.nice.org.uk/guidelinesmanual), and details of the reviews can be found in each of the relevant clinical chapters.

2.8 Developing evidence statements and recommendations using formal consensus methods

2.8.1 Background

Where there is a good evidence base of well-conducted experimental studies, this forms the basis for the development of clinical guideline recommendations. The evidence is synthesised into evidence statements which are clearly linked to the recommendations of the GDG.

As there is little good research evidence for some aspects of CFS/ME care at present, formal consensus methods were used to assist the GDG in making recommendations. The consensus methodology approach adopted was one of the methods reviewed in the 1998 Health Technology Assessment publication: *'Consensus development methods, and their use in clinical guideline development'*.[19]

2.8.2 RAND/UCLA Appropriateness Method (RAM)

A modified version of the RAND/UCLA Appropriateness Method (RAM) was used (http://www.rand.org/pubs/monograph_reports/MR1269/index.html). The Methods team adapted it for this guideline in consultation with Professor Rosalind Raine, who has researched this method in the UK and advised the Methods team and the GDG on its use. The RAM uses a highly structured list of clinical indications, and consideration is restricted to the basic measurement of appropriateness,[20] where the concept of appropriateness refers to the relative weight of thebenefits and harms of a medical or surgical intervention.

2.9 Use of the consensus methodology in guideline development

2.9.1 Overview of the use of consensus methods

The GDG used formal consensus methods at different stages in guidance development where required by the strength of the available evidence. At each stage, the GDG members:

1. rated the evidence statements privately and returned them to the Methods team for analysis and pooling

2. received the pooled results and, to aid discussions, their individual ratings and their position compared to other raters

3. discussed the statements on which there was not consensus. Wording was altered as necessary to improve clarity

4. re-rated statements.

This process was omitted for areas of the guideline where the GDG considered there was greater certainty on best practice and recommendations in these areas were developed through informal consensus methods according to the standard NICE methodology.

2.9.2 Ratings and measure of agreement

For the GDG consensus evaluation, agreement was rated using a 9-point Likert scale (see below). If the rater did not have an understanding of the statement (for example, the rater genuinely did not know whether antidepressants were appropriate), they were instructed to tick 'Don't know'.

1 2 3	4 5 6	7 8 9	'Don't know'
Disagree	Uncertain	Agree	

A researcher from Professor Raine's team analysed the results to determine strength of consensus (indicated by the median) and the level of agreement within the group (indicated by the mean absolute deviation from the median – the MADM).[21] The MADM measures variations about the median and does not give extra weight to extreme observations. This measure combines the group judgement for each item with the extent of agreement around each judgement. The operational definition of disagreement used was a new measure named the IPRAS (interpercentile range adjusted for symmetry).[20] This represents a new approach to measuring disagreement which has now been tested in a variety of datasets. It is a continuous measure that can be applied to any size of panel and can be used to create either stricter or more relaxed definitions of agreement and disagreement. Another advantage in comparison to the classic definition is that it smoothes the rigid frontier between 3–4 and 6–7 (that is, between 'disgree' and 'uncertain', and between 'uncertain' and 'agree'), and is a better measure of the degree of dispersion among ratings.

The overall group rating for a statement is categorised as AGREE (median rating > 6), DISAGREE (median rating < 4) or UNCERTAIN (median rating 4–6). A group rating UNCERTAIN* is used where the median rating indicates AGREE or DISAGREE but there is wide variation in the participants' individual ratings (see Figure 1 below).

The results were reported in terms of the numbers and identities of the statements attracting strong, moderate and weak support, and those for which there was disagreement. Results were pooled and presented as an aggregate. Each rater's results remained confidential at all times.

2.9.3 Stages of the process where formal consensus techniques were used

Evidence statements

The evidence statements were drafted and graded by the York team on the basis of the systematic review. The GDG members received the systematic review

and evidence statements before a GDG meeting, rated, discussed and edited, if necessary during the meeting, and then re-rated the evidence statements as described in sections 2.11.1 and 2.11.2. The evidence statements with a positive consensus agreement were included in the guideline. Evidence statements on which there was a consensus of disagreement or about which the GDG was 'uncertain' were discarded.

Clinical scenarios and cues

Over several meetings, the GDG used the method described in Murphy and colleagues[19] and Raine and colleagues[22] to develop and refine a series of statements known as clinical scenarios. Clinical scenarios are statements of options for the use of interventions. They were developed on the basis of the evidence, current practice, and the expertise of the GDG and the expert co-optee advisors.

The GDG took this step in addition to the usual NICE process to ensure transparency and fairness in decision-making in areas about which there was uncertainty and possible disagreement. Scenarios were developed related to diagnosis, investigations and management of CFS/ME on which, in the view of the GDG, there was uncertainty. Scenarios were not developed for the information and support sections.

Cues are factors that may influence clinical decision-making. Murphy and colleagues[19] describe them as 'dimensions or indications that group members are asked to take into account when making their decisions'. For this guideline, the cues were determined by the classifications of symptom severity[3] used in the CFS/ME Working Group report to the Chief Medical Officer[4], by information submitted by patient organisations, and by input from the GDG and expert co-optee advisors.

The GDG agreed that that the two crucial factors (i.e. cues) influencing clinical decision-making were the severity of CFS/ME symptoms and the age of the patient (adult or child).

Development of the questionnaire

The methodology used by Raine and colleagues rates appropriateness of treatment for each combination of clinical scenario and cue. In the example below, the CUES are in capitals and the *clinical scenarios* in italics:

- For a CHILD with MILD CFS/ME, *treatment A* is appropriate
- For a CHILD with MODERATE CFS/ME, *treatment A* is appropriate
- For a CHILD with SEVERE CFS/ME, *treatment A* is appropriate
- For an ADULT with MILD CFS/ME, *treatment A* is appropriate
- For an ADULT with MODERATE CFS/ME, *treatment A* is appropriate
- For an ADULT with SEVERE CFS/ME, *treatment A* is appropriate

A questionnaire was developed on this basis, which the GDG rated and discussed. The first version of the questionnaire was very lengthy; because each clinical scenario had six possibilities, there were over 700 statements to rate. The full questionnaire is in Appendix 3.

The GDG changed some ambiguous statements. They re-rated these and the statements that were rated as uncertain. Details of results and changes to statements are given by topic in Chapters 5 and 6.

Questionnaire to a wider group

The methodology recommended by Raine and colleagues advised the use of a one-round modified Delphi process (postal) involving a wider group (rather than the GDG alone) to inform the GDG.

This wider group questionnaire contained all the statements (clinical scenarios) that the GDG had rated as 'uncertain' on the second rating round. In addition, a 20% random sample of questions from each section on which the GDG had reached consensus (either agree or disagree) was also included in order to give

an indication of the range of the scenarios considered and the GDG's responses to date.

The Methods team contacted all stakeholder organisations registered with NICE in May 2005 and asked them to nominate 5 to 50 people with knowledge or experience of CFS/ME to complete the questionnaire. In order to ensure a representative sample of healthcare professionals with experience of the condition, nominees from the CFS/ME Clinical Centres were also solicited. People who had been nominated to join the GDG, but had not been selected were also invited to participate. Patients and carers were nominated by a stakeholder organisation, who was asked to obtain their agreement before the Methods team contacted them directly. Therefore ethical approval through an Ethics Committee was not sought. The standard letters sent to participants are in Appendix 4.

Wider group participants had to agree:

- to read the evidence review, including the evidence and evidence statements, and take part on this basis
- that the GDG would have final authority on the content of the guideline
- to complete the work and return the questionnaire with their ratings within the allotted deadlines.

Participants chose whether to receive the documents by post or email.

Participants were first sent the systematic review from York University (see Appendix 1) and the agreed evidence statements so that they understood the evidence base that the GDG had reviewed before completing the questionnaire.

Four weeks later, participants were sent the questionnaire (scenarios chosen for inclusion as above), and the GDG's combined consensus rating on these scenarios.

Participants were given a further 4 weeks to complete the questionnaire and return it to the NCC-PC. Postal questionnaire responses were input by professional data entry services.

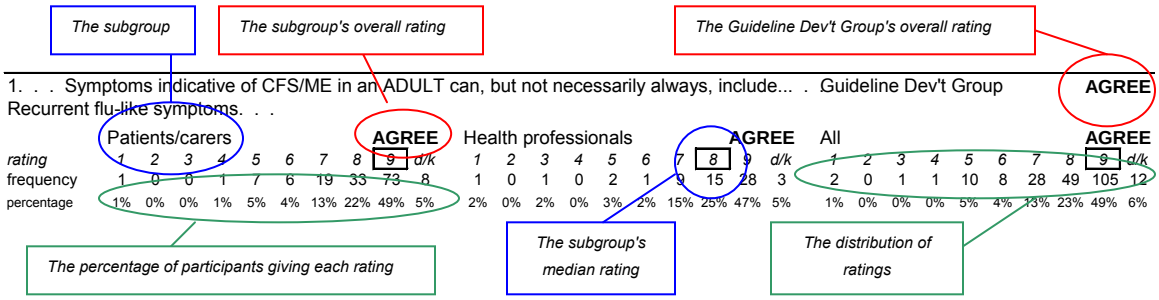
Questionnaires were sent to 399 participants. Of these, 219 completed the questionnaire (giving a response rate of 55%). The categories and numbers of respondents can be seen in the table below.

Patient	119
Carer	29
Healthcare professional (including professionals from the following groups - GPs, dietitians, immunologists, neurologists, nurses, occupational health physicians, occupational therapists, physiotherapists, psychiatrists, psychologists, infectious disease specialists)	63
Not given	8
TOTAL	219

The questionnaire was analysed as described in section 2.9.2.

The main output (see Figure 1) categorised participants as patients/carers or health professionals, and combined all participants in the 'All' category. The output shows the Guideline Development Group's overall rating. The distribution and percentage of ratings (including 'don't knows') are shown for each subgroup, along with the subgroup's overall rating. The median rating for a subgroup is indicated by a box around the value.

Figure 1 Explanation of results from wider survey questionnaire



In addition, the Methods team had median ratings broken down by separate healthcare profession categories if the GDG wanted a specialist rating on a particular question.

Examples follow of positive and negative comments received from wider survey participants. The first two are representative of many similar comments.

- ‘Good luck, I posted mine back to you yesterday!’
- ‘Many thanks for the ME/CFS material. I am doing my 'homework' and reading the attachments!’
- ‘I'm really sorry, but I've been unable to do this piece of work. I'm currently having a lengthy course of chemotherapy, and its effects have been more debilitating than I anticipated. I wish you well with the rest of the process and look forward to seeing the finished guideline.’
- ‘I truly believe that a lot of people without the condition would have a problem getting to grips with the information and questionnaire!!! I, for one will not be able to help you by returning the questionnaire.
  When I agreed to be sent the questionnaire I assumed it would be a simple task of answering questions, that would go some way to helping the medical profession reach a worthwhile conclusion. I did not think for one minute it would need over 450 pages of accompanying notes!!!’

- ‘How I, or anyone else with M.E. or even recovered could possibly read, digest and understand the NICE document enough to be able to answer the Questionnaire, is beyond my comprehension.
  I surely cannot be the only person who has had this problem, or am I the only honest one around?
  I would like this letter to go on record as I feel it is very important for Non-Sufferers to know how difficult a task this was for an M.E. Patient. Just writing this letter has been hard enough!’

- ‘I would like to say firstly how refreshing it is to receive such a rigorous, balanced and fair summary of existing research in the excellent (if bulky!) Evidence Review. The team at the University of York have done an extremely thoughtful and professional job and I would like them to know that their work is much appreciated. As I'm sure you're well aware, ME/CFS sufferers have the added misfortune of having contracted a "controversial" illness, so it's good to see an objective and thorough examination of existing research. Often in the past this research has been poorly analysed, with unreliable findings being "over-spun" in the National Press (for example research on NADH was described as a "cure" in several major newspapers in 1999 on the basis of one very small piece of not very well constructed research).
  The second point I would like to make is about the most severely affected ME/CFS sufferers. As a "moderate to severe" sufferer I found this questionnaire very challenging to complete in my current state (I should also say that I have some past experience of this kind of process as I worked in Market Research before becoming ill). I can understand why the wording has to be so complex, and why a Likert scale was used for example, but my concern is that once again within this process there is a very real danger that the voices of those most severely affected may not be heard loudly enough. This is particularly concerning, in my view, as much of the research evidence and most existing patient services already exclude those in greatest need by

default (attending major hospitals as outpatients is virtually impossible for severely affected patients). I also know from personal experience that it is in treating the most severely affected that the NHS in general and GPs in particular face the greatest challenges. I sincerely hope that this concern is in some way addressed within this process.'

The GDG met again to review the results of the survey and discuss areas of difference with the wider group to aid the drafting of recommendations.

Overall, there was good agreement between the GDG and the wider group in most areas. The GDG discussed all statements rated as 'uncertain', recognising that, as with other surveys, the results were subject to bias. The full results of the wider survey are given in Appendix 3 with the ratings presented by topic in each relevant chapter.

2.10 Developing recommendations

The Methods team drafted recommendations based on (i) the clinical scenarios on which the GDG had a consensus of agreement both among themselves and with the wider survey, (ii) analysis of the GDG discussion, and (iii) the evidence from the systematic review. The items on which the GDG had consensus of disagreement were reviewed individually by the GDG to decide whether they required a negative recommendation or no recommendation. These were presented by the Methods team to the GDG as per the normal NICE guideline development process.

The GDG received the drafted recommendations before a GDG meeting and were asked to rate their agreement with them on a numerical scale following discussion. They were then reviewed a second time and re-rated. The GDG added some additional general recommendations where they identified gaps in the specific recommendations. A final rating of recommendations was done after revisions made in response to the stakeholder comments.

Recommendations with a positive consensus rating were included in the guideline.

See Appendix 3 for details of the recommendation development and the ratings.

2.11 External review

The guidance has been developed in accordance with the NICE guideline development process, using additional consensus development. This included allowing registered stakeholders the opportunity to comment on the scope and the draft guidance. In addition, the final draft was reviewed by an independent Guideline Review Panel (GRP) established by NICE.

The comments made by stakeholders, peer reviewers and the GRP were collated and presented for consideration by the GDG. All comments were considered systematically by the GDG and the Methods team recorded the agreed responses. Responses can be seen on the NICE website www.nice.org.uk

3 The experience of people with CFS/ME

3.1 Introduction

This chapter describes the experiences of patients. Section 3.2 is a summary of submissions received from stakeholder organisations representing patients (please see Chapter 2 on the use of patient/membership surveys). This summary was reviewed by the GDG at their meeting in November 2005, at which time they were reviewing the evidence in Appendix 1. Section 3.3 contains the testimonies of the patient representatives on the Guideline Development Group. The testimonies present both positive and negative experiences of services and treatment and provide an important context to the guideline.

3.2 Summary of submissions by stakeholder organisations

3.2.1 Patient responses/experiences to management interventions for CFS/ME

*3.2.1.1 **Cognitive behavioural therapy (CBT)/modified CBT***

- '13% were made worse by CBT, 32% were not helped at all, 37% were helped a little and 18% were helped a lot.' *(Report on Survey of Members of Local ME Groups, Cooper 2000)*

- Mixed results for CBT depending on practitioner. Issues repeatedly cropped up about language and relationships indicating the problem may not be CBT but poorly practised CBT. *(Action for ME, Members Survey, 2003)*

- 7% found CBT helpful, 93% found CBT unhelpful. *(25% ME Group, Analysis Report, 2004)*

*3.2.1.2 **Graded exercise therapy (GET)***

- 'We need very, very gentle exercise/movement and yoga sessions (not graded exercise but exercise to keep muscles etc. going, but paced, not pushed at us).' *(Members Survey Report, 2004)*

- 'With regard to the comments … about CBT and Graded Exercises, many ME sufferers…have found that Pacing (i.e. learning how to pace oneself, how to live with and 'dole out to oneself' one's normally very low physical and cerebral energy levels, etc) is better.' *(Letter David Stuttard, 16 December 2004)*

- 'Graded exercise was felt to be the treatment that made more people worse than any other. 39% were made worse by this whereas, in contrast, only 2% were made worse by diet. Graded exercise was also considered to be the least helpful treatment or management schedule. Only 13% said that it helped a lot and 26% said that it helped a little.' *(Report on Survey of Members of Local ME Groups, Cooper 2000)*

- Only 16% of those surveyed had tried GET and half found it helpful and half stated that it harmed them. *(Action for ME, Members Survey, 2003)*

- 5% found GET helpful, 95% found GET unhelpful. *(25% ME Group, Analysis Report, 2004)*

*3.2.1.3 **Pharmacological treatment***

- '27% said they had been made worse by medication (not defined). Equally however 40% did say they had been helped a little by medication and 18% said they had been helped a lot*.' (Report on Survey of Members of Local ME Groups, Cooper 2000)*

- 55% found prescription medication (not defined) helpful. *(Action for ME, Members Survey, 2003)*

*3.2.1.4 **Complementary therapies***

- 'The reason that so many people with CFS had turned to complementary therapies was because they had found that their condition and sick role were accepted and that "many complementary practitioners had offered practical

advice on dealing with the illness on a day-to-day basis''.'[23;24] *(Featherstone 1998 & Hughes 2002)*

- Featherstone (1998) found that complementary therapy was often chosen as people felt '…recognized as the ultimate authority on their own body state.'

- '36% of respondents said that (alternative therapy) helped them a lot and 38% said that it helped a little. Thus a total of 74% of all respondents that had tried alternative therapy said that it had helped them in some way. *(Report on Survey of Members of Local ME Groups, Cooper 2000)*

- 44% agreed that complementary therapies had helped their symptoms. (*Action for ME, Members Survey, 2003)*

- 60% found alternative therapies helpful, 40% found alternative therapies unhelpful. *(25% ME Group, Analysis Report, 2004)*

*3.2.1.5 **Supplements***

- 51% said nutritional supplements had helped symptoms but 36% were uncertain of their benefit. *(Action for ME, Members Survey, 2003)*

*3.2.1.6 **Diet***

- 'A total of 73% of those who had indicated that they had tried some form of dietary therapy said that it had helped them and only 2 said that it had made them worse.' *(Report on Survey of Members of Local ME Groups, Cooper, 2000)*

- 59% found dietary changes helpful; 25% were uncertain and 16% reported feeling worse. *(Action for ME, Members Survey, 2003)*

*3.2.1.7 **Bed-rest***

- 'Complete bed-rest did make 10% of respondents worse. Yet 37% said they were helped a lot by doing this. Total bed-rest helped a total of 74% of

respondents who had done this.' *(Report on Survey of Members of Local ME Groups, Cooper 2000)*

- Rest, including bed-rest, helped 90%. *(Action for ME, Members Survey, 2003)*

*3.2.1.8 **Pacing***

- Pacing helped 90% of respondents. (Action for ME, Members Survey, 2003)
- 70% found pacing helpful, 30% found pacing unhelpful. *(25% ME Group, Analysis Report, 2004)*

3.2.2 General comments

- Management and treatment *(Action for ME, Membership survey, 2001)*,

	Helpful	No change	Made worse
Drug medication for pain	61%	28%	11%
Drug medication for sleep	67%	17%	16%
Pacing your activities	89%	9%	2%
Graded exercise	34%	16%	50%
Diet changes	65%	32%	3%
Nutritional supplements	62%	36%	3%
Rest, including bed-rest	91%	8%	1%
Cognitive behavioural therapy	7%	67%	26%
Other	75%	11%	14%

- 'These results show that many different kinds of treatments and regimes do help ME patients. Diet, alternative therapy and pacing seem to be the most successful, and yet there appears to be some room for medication, bed-rest and CBT. Even the least successful regime, graded exercise did help 39% of the respondents to some extent.' *(Report on Survey of Members of Local ME Groups, Cooper, 2000)*

3.2.3 Gaps in current treatment and care provision

- Symptom relief.
- Nutrition.
- Pain management.
- Multidisciplinary care that is holistic, enabling and focused on diagnosis, medical treatments, rehabilitation and adjustment to chronic illness.
- Self-management emphasis.
- Quality of life – health, social, economic and relationship factors.
- Telephone and one-to-one support. *(Members Survey Report, 2004)*

3.3 Personal testimonies from people with CFS/ME

3.3.1 Testimony 1 by GDG Patient Representative 1

Onset (sudden)

When holding my monthly departmental meeting after school where I was teaching, I suddenly felt weak, almost faint and then my vision went. My head felt as if someone was pressing on top of it at the same time as trying to fasten screws into the side of it. I could no longer hear what was going on around me, nor could I sit up and support my own weight. All this was accompanied by severe palpitations. My colleagues remarked upon the greyness of my face and

tried to get me to the medical room for a lie-down but my legs would not move even with their support. I remember thinking I know how to walk but was unable to transmit this to my legs.

Diagnosis (within 2 months in the private sector)

I was later taken home but decided it was better to consult my GP at once and find out what was the matter with me even though I felt quite 'normal' again by this time (about an hour later). I was lucky to be able to see my regular GP who has known me for some twenty years. He decided that I should see a cardiologist but feared that there were to be more investigations down the line. He gave me a sick-note which said PVFS (Post Viral Fatigue Syndrome) on it (the acronym meant absolutely nothing to me at the time) and I joked with him saying that if doctors don't know what they are dealing with, they invariably call it a virus of some sort. I was advised to rest as much as possible.

As I wanted to return to work in the shortest time possible and resume my life as I knew it (teaching, taking school trips abroad, walking the dogs daily, going swimming, cycling and enjoying a few ski trips per year), I decided to see the cardiologist privately. Two weeks later an electrocardiogram (ECG) plus a 24-hour heart monitor had shown no abnormalities. So back to the GP with a referral to an immunologist and because of the new, unexplained and strange headaches and hearing difficulties, he also thought it wise to make an appointment for a magnetic resonance imaging (MRI) scan.

The immunologist examined me thoroughly, took blood and urine samples and gave me a possible diagnosis of PVFS; Again this acronym! I asked him what this is and he informed me that once symptoms have persisted for six months it is called ME. I was amazed as I had heard of it in the context of Yuppie Flu and I was 52 at the time, so the 'Yuppie' label did not apply! Equally the MRI scan revealed no abnormalities and the diagnosis of PVFS/ME was confirmed but at no time did I get any other management advice apart from 'rest'.

Management advice

Although it was a great relief to put a name to these strange, seemingly unrelated symptoms, I now know that any one of the health professionals lacked the knowledge to give me management advice. I asked the consultant how this condition was treated and he just replied that there was no treatment. When I asked about complementary therapies, he was equally negative. My GP wrote a prescription for a tricyclic antidepressant and took great pains to explain that he did not think I was suffering from depression but that it was the only thing he knew about CFS/ME that helped people with the pain and it was a lower than normal dose. I refused to take the tablets but went back to the GP a year or so later asking for them as I had had enough of the pain, the sleeping problems and the stress and frustration by then.

Progression of illness

Although I had read many books by now about the condition, I still felt that the illness was for wimps, not active people like me! Naturally, without any proper management advice, I decided that I would cut back my activities and take rests in between them but I did not realise how much I had to cut back. I pushed myself through the pain and fatigue, the dizziness and balance problems, the muscle spasms and infections. And the result was inevitable: I became bed-bound, often too weak to eat, chew or lift the food to my mouth. I could no longer walk more than three or four steps, needed help with personal care and spent my time in a quiet and darkened bedroom.

Additional health problems arose

Firstly my hands became claw-like, especially the left one. My GP suspected Carpel Tunnel Syndrome – but investigations revealed that this was not the case but the reason was ‘unexplained’. I also lost a lot of weight which I put down to constant nausea; even water made me feel sick. The Infectious Diseases Department feared they had overlooked something in their original diagnosis and sent me for a colonoscopy, followed by a gastroscopy. Again this revealed no significant abnormalities apart from a few benign small polyps. I also had many

infections, especially problems with my teeth; constant abscesses resulted in four extractions. My reaction to the injections was so severe that my dentist had to do some research as to what to use to anaesthetise my gums. He cut back on the adrenaline but that stopped the effect of the injection; consequently I had to put up with the adverse after-effects rather have an extraction without numbing the area. I also suffered from a frozen shoulder which was extremely painful and took over one year to improve with the help of acupuncture. Suddenly all my joints had swollen up and were severely painful just like in arthritis. Three weeks later I was back to normal which confirmed my GP's suspicion that it was an attack of viral arthritis.

Problems with temperature control meant I could not get warm even with hot water bottles and extra layers on the bed but then at night I experienced extreme sweating which meant that bedclothes and bedding had to be changed, often more than once. I was also extremely sensitive to touch and could tolerate only loose material against my skin which made it very difficult to keep warm at times.

My cognitive dysfunction was extremely disabling, so much so that at times I did not recognise people, even my own family. It was OK if they entered the room and said who they were but if my son came to visit and I had forgotten that he was there, I would not know who was in the room.

I experienced pain to varying degrees in muscles, joints and nerves, sometimes burning at other times stabbing. Also tingling, pins and needles, and numb feelings in parts of my body were often quite pronounced and uncomfortable, especially when it affected my lips and tongue. Also periods of muscle spasms and cramps were experienced during the first few years. My worst experience was when I became suddenly paralysed. This was a symptom I had not read about and frightened me as well as convinced me that my diagnosis was wrong. But, again a referral to a specialist (a neurologist) who tested me for multiple sclerosis came back with negative results.

Friends, family, carers and benefits

My husband was in total denial when I was first diagnosed; perhaps he felt helpless and scared; he never talked about the condition with me but I left him suitable short articles 'randomly' lying around the house to ensure he could inform himself. Bit by bit I noticed that his understanding was improving and he found many ways of helping me and that included leaving me to it when needed. There was, however a time when he only went to work when he could safely leave me for some time. Then we decided that we must hire some help for housework, cooking and looking after me. It freed him up and made me feel less guilty and dependent.

Ironically it was the hired help who informed me about benefits which I did not know existed until then. So I applied for Incapacity Benefit after my teacher's pay run out – and was successful. I also contacted my teacher's union having been advised by Occupational Health, to help me get early retirement on ill health grounds. They were most hesitant, not to mention unhelpful; so I wrote a letter with the support of Occupational Health and was turned down. I decided to write a more forceful letter to Teachers' Pensions having gathered additional information from books and was successful this time.

My GP also advised me to apply for Disability Living Allowance (DLA) and get a parking badge as he was worried that I had not left the house in three years because of my walking difficulties. This turned out to be a real disaster as the visiting doctor did not believe that CFS/ME existed and stated that I had a mental health problem which stopped me from walking. I felt humiliated enough at feeling so useless and disabled and must admit that I had absolutely no self-confidence left. I never pursued the matter of DLA until my symptoms were a lot more stable and I felt stronger to research the matter thoroughly before re-applying – and this time successfully!

This was my worst period, learning to adjust to the illness as well as the loss of my job and my self-worth and having to fight for any money I was really entitled

to. There were also the comments of family, friends and colleagues who decided that I had a 'hidden agenda' or tried to get out of things. One person who I had worked with closely for some ten years even told me that I could stop pretending now I had my teacher's pension! All the odds seemed to be stacked against me and made me dreadfully ill.

Other treatments tried

Although I had acupuncture for my frozen shoulder, I found that the sessions had helped me relax and reduced the pains. I was lucky because my acupuncturist understood CFS/ME and I continued with the treatment until she had to return to China. I tried one or two other acupuncturists but did not get the same benefit. I also sought help from a homeopath (within the NHS). He managed to sort out my debilitating 'brainfog' to a great degree although the physical problems with walking, dizziness, fatigue, sleeping, headaches, infections, nausea and sickness persisted.

I went for reflexology, Reiki, even a healer in a desperate attempt to improve my health. It cost a lot of money, without any benefit to my quality of life. One thing I did find useful was cutting out dairy produce and wheat from my diet. It stopped the bloating after eating. After some months, I gradually re-introduced dairy foods and had no adverse effects. Wheat still presents a problem to me and I eat more or less wheat-free.

Turning point

In time I realised that there was no use in looking back and that I had to make the best of the situation. Help was at hand when a friend told me about a poetry competition. I spent days and sleepless nights composing and amending the poem – and it was published a few months later. I was amazed how dyslexic I had become; I transposed letters (and still do after ten years) and only realise what I have done when re-reading. Although I still spent most of the time in bed my poetry writing continued to keep me occupied and feeling positive. I progressed from there to short stories and enjoyed each success in being

published although I never wrote a bestseller. This had given me a new lease of life and with that came the most important turning point, and the acceptance of CFS/ME.

I threw away the books on CFS/ME and decided to be pragmatic and find out what worked for me; that happened after about three years. We, as a family, got gradually organised with a wheelchair, an electric scooter and a fully automatic car for me as well as my parking badge. Postural hypotension often caused collapses when going out. This set me back for a week or two but then I tried again going only to familiar places, asking for help or sitting down on the floor in a shop if needed, but I had to do away with inhibition and self-consciousness first. It took a lot of courage and ignoring what other people might think. I was determined to get back part of my life.

3.3.2 Testimony 2 by GDG Patient Representative 2

I was 38, extremely fit and had virtually never had a day off sick in 17 years of continuous work. That day I walked twenty minutes to the train station as usual; it was a normal day in every way. Halfway to Derby, where I had worked as a team manager for Social Services for several years, I suddenly began to feel extremely unwell in a way that I had never experienced before. I could not make sense of what was happening to me, and I never fully recovered from there. At the time I was neither stressed, nor depressed, nor someone who could be classed as a 'yuppie'.

There was the usual period of thinking that it was just a virus and that I would be over it soon, followed after some weeks by the realisation that it was a post viral condition and that it might take a few months. My mentality in such situations is to 'live for the day' and I could not believe that it would be long term.

Tests arranged by doctors revealed nothing wrong, apart from signs of having had a viral infection. Yet I had constant headaches (that were not stress headaches), and pain in my muscles that apart from the tiredness, meant that I was often virtually unable to walk. I could do little mentally; could not cope with

much stimuli such as light and loud noises. Even sitting as a passenger in a car was hard as everything moved too fast to cope with. 'Brain fog' is the best way to describe it, along with constantly feeling ill.

One GP examined my legs and told me there was nothing wrong with them, or me, and to go back to work, which was quite impossible. I would have made a formal complaint, but I was too tired and felt too vulnerable.

Another GP in the practice was sympathetic but could offer nothing but very low dose dosulepin for help with sleep. There was no other advice or help given to me. There was no specialist person or team to refer on to in my region. Since then I have had limited contact with the medical profession and no input from NHS therapists.

Within months it was clear that I might have CFS/ME, and I knew of other people who had experienced similar problems. There was no formal diagnosis made, just an acceptance by the GP and myself that it was ME. Support came from another person in a similar position and from the National ME organisations and their magazines. Obtaining information was not as easy in 1991 as it is now. The result was that there was much stress in having many of the strange symptoms that people with CFS/ME experience, but without knowing that these were commonly experienced due to the illness. For example, twitching muscles, muscle weakness, and pains that travelled around my head and body over the course of a few days, and many more.

After six months and having seen an occupational health specialist once, I returned to work. This was more from financial consideration than due to wellness. I had two years earlier begun a job share so that I could spend the other half of my working week training and working as a counsellor. I had to give the counselling up immediately when I became ill and was never able to return to it. Social Services arranged with me to work a bit of each day in an effort to work eighteen-and-a-half hours a week. There followed a nightmare twelve months of struggling to work, of struggling to do a few hours, struggling home, then

collapsing for the rest of the day. The next day would be the same, and so on: work – collapse, work – collapse. There was no other life, no social life, as nothing could be planned and there was no spare energy for me to use.

After 18 months life improved as I stopped feeling as if I had a constant dose of bad flu all the time. At the same time I was demoted at work and found a job where it was felt unimportant if I could not cope, even though this had never been a problem. The illness was mostly seen by my employer as simply an inability to cope with stress. I then had the double problem of proving myself to a new team who resented me being there as they felt I had been foisted on them. By luck however, rather than design, the new job meant I had much more control over my work. That was key for me to manage my condition. If I had a bad morning, I could work in the afternoon and I could do a certain amount from home. That meant I could use weekends and holidays to keep ahead of my work. The sense of control was key, and as a result I did not miss a day's work in the next eight years. Work was still a tremendous struggle however, and not just for weeks and months, but for years. I still had to use weekends and holidays to keep ahead of my work.

It is hard to know whether pushing myself as I did was good or bad in the long run. Certainly without work there would have been many days when I would have stayed at home and done nothing. It becomes the norm to work despite feeling a way that many people would probably go off sick if they felt the same.

Having always been extremely fit, I did my utmost to keep what fitness I could. Throughout this time I tried to walk if I could. Maybe only round the living room a few times a day, or round the garden. It was some months before I could walk around the block.

My life had to be much better planned. If I could only walk a bit each day, or do a bit of mental work each day, it was essential to prioritise what I did. Each walk upstairs needed to be planned to get the most out of it. Everything in life becomes totally unreliable. As I could only read five pages of a book in a day, I

had to prioritise what I read. And there were choices to make. When all I could do was to put out the washing in a day, but nothing else, then I would do that in order to at least contribute something to family life. When back at work, it was no good being 'last minute' in any way. 'Last minute' could be a bad day and then the work would not be done.

After a couple of years I was able to join a golf club, I would call in after work. On a good day I played three holes. Over months and years I gradually played more, less on bad days. But it did give objective data on how I was progressing. In the same way, I found keeping a diary was invaluable. Life was very much about learning to live without what I had enjoyed and done in the past, necessitating finding alternatives that I could still manage on limited energy. For example, I found creative outlets in painting and exercised through dancing.

Without any support from the health services, I have needed to work out for myself what seems to work for me and what does not. It is a bit like learning to drive a car, but without any instructor. It leads to lots of costly mistakes along the way, as well as the stress of just not knowing what it is best to do, or what might be affecting my health adversely.

The other things that have helped me have been a supportive wife and family that have accepted my illness. I was probably fortunate in that my children were 10 and 8 when I became ill; an age when they had become less physically demanding and could perhaps understand better. Nevertheless, such an illness has an immense impact on family life, physically and emotionally. For my children it meant that from being actively involved with them as I had been, there were many things I could no longer do with them. For my wife, it meant huge uncertainty over the present and the future. It meant having to adjust in our relationship. It meant huge uncertainty in knowing how best to deal with the situations that arose. It also meant having to take on many more physical tasks. In every way life became more demanding for her.

Living with CFS/ME is constantly about ups and downs, within each day, within each week, over months. For me there has been a very gradual improvement in a 'three steps forward and two steps back' way. After ten years I did have a major relapse that took some months to get over. I believe this was due to a combination of a viral infection and doing too much. I find that there is a ceiling to what I can do, and if I constantly try and break through that ceiling it leads to relapse. But there were positives in that it was a further opportunity to reassess my life. I decided that yoga and tai chi would be helpful, and learnt after ten years that I had probably never learnt to fully relax before, and that I could effectively improve my breathing.

I also found that for me personally the involvement of a nutritionist was helpful in looking at my diet and suggesting supplements. It was also someone who, unlike those I had had contact with in the NHS, gave my condition acceptance, time and understanding – but at a large financial cost to myself.

When there are few answers offered to you, you can become vulnerable to claims of countless people who state they have a cure. And what makes that even more difficult, is that the cures do appear to work for a few people, which drives you on in a search for a cure.

At the time of the relapse I was again offered low dose dosulepin for sleep problems. There was nothing else offered. I did suggest referral to the National ME Centre, but this was turned down. There was still nothing on offer in my region. As has been the way throughout, it has been a case of finding my own way, based on contact with other people with CFS/ME, as well as information from the national Associations and a few books as these became more available.

Whilst I would not wish CFS/ME on anyone, and it has caused immense suffering along the way, there are also many positives. Like many, it has meant that I have looked at life anew and reassessed what is of value and what is not. When time and energy is in short supply, I have taken chances and seized opportunities in a way that I would not before. I have become engaged in a

range of activities, both CFS/ME related and not. For example, due to my experiences, there have been the positives of setting up and being secretary for the local CFS/ME self-help group. I have been a tutor on the Expert Patient Programme for the last four years, and a non-executive director for my Primary Care Trust (PCT) for the last six years. With limited energy, I have needed to be ruthlessly efficient and effective in what I do.

Fifteen years on CFS/ME is still a daily part of my life. There is still the unpredictability of not knowing if tomorrow will be a bad or a good day. The bad days still bring their fair share of frustrations, days when I have limited concentration, can read virtually nothing, of constant headaches, or when my muscles may be weak and I can walk little. Thus I am still restricted in what I can do physically and mentally. It is that effect on both mind and body, which sets apart CFS/ME from many other long term conditions. At times it is difficult to know whether it is the effect on the brain or the body which is worse. Yet I still gently push at those barriers in the hope that I will continue to improve.

3.3.3 Testimony 3 by GDG Patient Representative 3

I was given a diagnosis of ME, and will therefore use that term in describing my condition, however I recognise that the guideline does not differentiate between ME and CFS.

It is impossible for me to get across to you just how debilitating and life-changing this illness is for me, my family and fellow sufferers, as the only way you could possibly understand it is to live it. Imagine you are in excruciating, unremitting and relentless pain throughout your body, you are completely exhausted but unable to sleep, when you do manage to get to sleep it is not a deep sleep, it is snatched, restless, often the sleep pattern is reversed, and you are constantly being woken up by the pain. Then you wake up feeling like you have had no sleep at all, that you have the worst flu you have ever had, feeling as if you have just run a marathon, you ache everywhere, your throat is sore and ulcerated, you are constantly nauseous and dizzy, unable to control your body temperature,

have hyperacuity and photophobia, your brain is in a fog, having a gentle shower is so painful it is like having your skin sandblasted, and even having a hug is painful – this is my life, not just on the odd day, but every hour of every day, year after year, and for me, decade after decade.

I am thirty-one and ME has taken, or rather stolen, two thirds of my life. I have been bedridden 80–100% of the time for more than half my life. My ill health started at the age of ten when I had suspected glandular fever, although the test was inconclusive, the blood picture was unusual, and around the same time I also suffered a gastro-intestinal infection. I am a Type-A personality, so I was not going to have a little thing like being ill keep me from my education and extra-curricular activities, which were numerous and varied, from the arts to sport and everything in between. So I insisted on returning to my normal life before I had fully recovered, but my body did not like this. I had constant recurring throat infections which the antibiotics weren't clearing (at one point I was on them continually for six months), and in the end I had my tonsils removed, but I reacted very badly to the anaesthetic, haemorrhaging. Although the tonsillectomy made things easier as it meant that I could swallow again (my tonsils were continually meeting in the middle of my throat) it didn't stop the throat infections, which I continued to have along with a severely ulcerated mouth. I developed asthma, for which I frequently required steroids. At aged 11 I had suspected meningitis, this is when the unrelenting head and neck pain and photophobia started, and have never left me. At this point I did stay off school, but despite being very ill school insisted that I attended, then, when they saw how ill I was, they panicked, called my GP, and sent me home. The GP did not understand what was happening to me and so I still did not heed my body and returned to school. Aged 12 the illness stepped up a gear and it started attacking my back and legs, leading to repeated spells using crutches, as it caused such pain to try and walk. I was gaining weight, despite becoming increasingly unable to tolerate food. Then the pain in my head and spine became so severe and debilitating, and the amount of time I was having to take off school became so frequent through constant infections/illnesses, that I was unable to leave my bed. My GP, finally,

referred me to my local hospital, when I was fifteen. It had been five years since I first became ill, with my GP constantly commenting that he, 'didn't like the look of this, but didn't know what was wrong or what to do about it', so he just left it. Despite my mother's efforts to get answers, she couldn't find any. I truly believe that if my illness had been identified when it first appeared, and appropriate advice been given, then I may not have gone on to become severely affected, which is what I feel happened to me by leaving me for five years.

When I reached the hospital I had become so desperately ill that I had reached collapsing point. I could barely stand, was in extreme excruciating pain throughout my body, had a multitude of seemingly random but debilitating symptoms, felt constantly as if I had a very bad bout of the flu and could hardly speak for the numerous large ulcers in my mouth. At the local hospital, I was put under the care of a rheumatologist who was brilliant. From the first time he saw me he told me that, 'I believe that you are very ill and I won't stop until I find out what is wrong'. After seeing me weekly in his clinic, which were a trial in themselves, as it meant leaving my bed to lay on the backseat of the car for the sheer agony of the journey, he could see that I was continuing to deteriorate and finally conceded that I was too ill to be at home and admitted me. By this point my illness, although undiagnosed, had already become multi-system/multi-organ. Within three days of being admitted I was seen by five specialists, as they feared for my life. Whilst in the hospital they thought I had suffered a mini stroke as I suffered from facial paralysis down one side, along with no responses in my arm and leg, and since that time I have had limited or no reflex responses. Eventually I was diagnosed with a terminal illness. I was put on a heavy treatment regime of about 16 drugs, including steroids, and hydrotherapy (what could be classed as graded exercise (GET) today). These turned out to be totally inappropriate for me, and led me to deteriorate further. Recognising this, the consultant stopped everything and differential diagnoses were looked at. Eventually a consultant haematologist, who had started taking an interest in cases like mine, was brought in and I was diagnosed with severe and chronic ME.

Over the past twenty years my symptoms have never left, only increased, for example, shortly after diagnosis I became unable to hold my head unaided, meaning that I was then, and am now, unable to stand, walk or hold my head unaided, my limbs tingle/pins and needles and regularly go into uncontrollable muscle spasms, I've developed palpitations and from the start my joints/muscles have been extremely painful, I could go on, but would probably need another page! My symptoms do go in cycles of severity, depending on what part of my body is particularly affected at the time, the core symptoms however have never gone away, or become easier, they are persistent and relentless. I cannot really do anything for myself, and must rely on my Mum for everything, from helping me to wash, to taking my body weight, to helping me to the toilet. I require 24/7 care. I am often too ill to even sit up or communicate; my Mum says that I am not really there, I have been swamped by the illness and I am neither coherent, nor very aware of what is happening around me. She says it is like watching me tread water, but when the illness consumes me, I have gone under and only the illness is left.

I have a consistently raised ESR (erythrocyte sedimentation rate) level, a high fibrinogen and platelet level (despite which I still fail to heal quickly, even a scratch can take a year), and low mean cell volume, other results fluctuate between normal and abnormal, for example my iron has just dropped again, last year it dropped to 2, this year to 4. The iron deficient anaemia would be easy to handle in other people but being an ME sufferer I have adverse reactions to medication and I cannot take iron tablets. The doctors feel that a blood transfusion is more likely to harm/kill me than help me, and this therefore leaves my health difficult to manage. My body also seems to have trouble absorbing vitamins and minerals and I find supplements difficult to tolerate, for example, when my B12 level had dropped, in case of side effects my consultant gave me an injection of $1/8^{th}$ of a normal dose of B12 and also had me in hospital, but my body interpreted the injection wrongly and reacted badly to it. I also had a bad reaction to oxygen, with the hypothesis of, and research showing, low oxygen in the blood, particularly to the brain, the suggestion was to try extra oxygen to see

if there was any improvement, so I was given 4% oxygen above the level we breathe, my body went into spasms, and the pain in my head became excruciating, this should not have happened, especially at that level, again showing the body's hypersensitivity. I have also developed co-morbid but associated conditions, and am under different consultants for these, all at a loss how to treat me due to the problems I have with tolerating treatments. My body has now become so compromised by the severe ME that I have been told by two consultants that they felt unable to operate on me as they feared that my hypersensitivity would prove fatal. Even trying to decide the safest local anaesthetic for urgent dental work, has prompted an eighteen month consultation with specialists. This is the reality for the severely affected, the simple becomes complex and life-threatening.

Aside from the relentless pain, one of the hardest things for me, being a natural academic, has been the impaired cognitive functions. Going from being an avid reader to having trouble following even a page in a book, not recognising the words (as if it is written in ancient Greek), not remembering the sentence, or paragraph, I have just read. I also went from being a straight 'A's student, to not being able to follow the simplest lesson, with my brain having difficulty processing the information, as if I am having to translate it. I also started having trouble communicating, forgetting my words mid sentence, going blank, and becoming muddled. These problems affected my education and I was treated abominably by my school, as they wrongly believed I was malingering, unfortunately this is not an unusual experience. This reaction was hard to accept because I loved school, and kept trying to return, even after hospitalisation. Eventually I had to accept that I had to leave school. I tried home-schooling for a while but this was woefully bad, and I was also unable to keep a schedule as I was so ill. For both myself, and my mother, the experience I had at high school, as a result of their disbelief in my illness, was both painful and traumatic. It was only later, when I wanted to try education again, and I reached my local college that I found the welcome, support and flexibility which is so vital, if I was only able to do an hour an odd week this was encouraged.

Everyday life is affected, my brother could not play music or have friends round because of my sensitivity to sound, and everyone lives in darkness, as I have photophobia. Everyone's diet changed as I became unable to tolerate different types of food, or even the smell of food being cooked. Even something as simple as sleeping causes difficulty for my family, as I have trouble sleeping due to the intense pain, and even when I am able to get to sleep, I have sleep reversal. This means that a normal daily routine goes out of the window, and nothing can be planned, as it depends on my sleep pattern at the time. This also impacts on my Mum, as she has an equally disrupted life and sleep/wake cycle as she has to care for my needs 24/7, so she is only ever able to get 2–3 hours unbroken sleep. Cleaning is also difficult as I am unable to tolerate the smells of the chemicals, for example, bleaching toilets or polishing. Holidays, seeing family and friends, and special occasions are foregone, even sitting at the table and having a family meal is virtually impossible. In short, ME is a drastic and life-changing experience, for all those who are affected by it, not just the sufferer.

Suffering from a severe illness causes great strain on your social interaction, and development. If you become ill as a child, as I did, friends soon stop coming. If you are lucky you have a couple of friends who stick around, but you are often too ill to see them. You miss out on everyday things, and rites of passage. The sufferer is not the only person to become isolated, the primary carer does also.

With ME, all aspects of family life are affected and financial problems are increased. For us personally, my mother, despite having a very understanding employer, eventually had to give up a very well paid job 15 years ago in order to care for me 24/7. There is very little help given to families, when a dependent disabled child becomes an adult, but is still a dependent. My Mum saw it as her place to care for me and not ask for monetary assistance, plus we hoped that it was a temporary situation, and it was not until a fellow professional pointed out that by not applying for benefits, she was denying me my rights, that we eventually applied. There are particular problems being allocated benefits – particularly Disability Living Allowance and Incapacity Benefit, especially given

the unpredictable nature of this illness. Applying for benefits is often a traumatic experience for ME sufferers as many, like myself, have been met with disbelieving doctors. The doctors who have visited me either didn't believe in the illness, and told me that, or were trying to rediagnose me as they didn't believe that ME could create such severity and debilitation, nor consist of so many severe neurological symptoms.

Despite being recognised/listed as a neurological condition by the World Health Organisation and the Department of Health, it has been my sad experience that help for people with this illness is few and far between. Patients like myself, and their carers, are still being met with disbelief and stigmatism by some of the medical profession, and in some cases treatment which is incredibly poor, inappropriate and inexcusable. There are some good doctors and these must be applauded. My consultant is a good doctor, but there is a real fear, and plausibility, that when he retires, my ME clinic, like many others in the country, will become diagnosis and therapy only. If this happens, the severely affected patients, such as myself, will be sent back to their GPs – many ill-equipped to deal with us, and/or do not believe in the illness – leaving us abandoned in the community with no medical support, or the necessary careful monitoring of our condition.

I have tried many therapies over the years, with many being detrimental to my health, for example graded exercise/activity programmes. I try to follow pacing/energy management, as this has been the most effective. But trying to stabilise my illness is extremely difficult as, against my consultant's advice (due to the detrimental effect on my health), I try to campaign for the rights of ME sufferers/people with disabilities.

Despite the severity of my illness I manage to keep a positive outlook, and follow the philosophy of 'Accept, Adapt, then Live'. I know that research has shown that my prognosis of remission, to any semblance of a normal life, is only 2%. This does not however stop me from being hopeful that I am in that 2%, or, that with appropriate research into the organic aetiology and pathogenesis of this illness,

that in the near future, hope of a cure, or treatment, to improve my quality of life will be renewed.

4 General principles of care

4.1 Introduction

The GDG reviewed and discussed the evidence for the key clinical questions on the support and information needs of people with CFS/ME. These topics are covered in sections 4.3 and 4.4 respectively. Guidance on support and information is inter-related and predicated on some general principles. Therefore, this chapter begins with some general recommendations covering both support and information which the GDG regarded as essential to the care of people with CFS/ME.

4.2 Recommendations

Note: numbers in square brackets are as in the NICE guidelines.

General principles of care [1.1]

Shared decision making [1.1.1]

Shared decision-making between the person with CFS/ME and healthcare professionals should take place during diagnosis and all phases of care. The healthcare professional should:

- Acknowledge the reality and impact of the condition and the symptoms.
- Provide information about the range of interventions and management strategies as detailed in this guideline (such as the benefits, risks and likely side effects).
- Provide information on the possible causes, nature and course of CFS/ME.
- Provide information on returning to work or education.
- Take account of the person's age (particularly for children younger than 12 years), the severity of their CFS/ME, their preferences and experiences, and the outcome of previous treatment(s).

- Offer information about local and national self-help groups and support groups for people with CFS/ME and their carers (see also the NHS Expert Patients Programme[†]). [1.1.1.1]

When providing care for children and young people, healthcare professionals should follow best practice as described in the national service frameworks for children for England or for Wales. [1.1.1.2]

Healthcare professionals should be aware that – like all people receiving care in the NHS – people with CFS/ME have the right to refuse or withdraw from any component of their care plan without this affecting other aspects of their care, or future choices about care. [1.1.1.3]

Healthcare professionals should recognise that the person with CFS/ME is in charge of the aims and goals of the overall management plan. The pace of progression throughout the course of any intervention should be mutually agreed. [1.1.1.4]

Healthcare professionals should provide diagnostic and therapeutic options to people with CFS/ME in ways that are suitable for the individual person. This may include providing domiciliary services (including specialist assessment) or using methods such as telephone or email. [1.1.1.5]

Support and information [1.1.2]

To facilitate effective management of the condition, healthcare professionals should aim to establish a supportive and collaborative relationship with the person with CFS/ME and their carers. Engagement with the family is particularly

[†] For more information see www.expertpatients.nhs.uk or www.eppwales.org

important for children and young people, and for people with severe CFS/ME. [1.1.2.1]

A named healthcare professional should be responsible for coordinating care for each person with CFS/ME. [1.1.2.2]

Healthcare professionals should provide accurate information to people at all stages of CFS/ME, starting from when a diagnosis is first being considered. This should be tailored to the person's circumstances, including the stage and duration of the condition, symptoms experienced and relevant personal and social factors. [1.1.2.3]

Information should be available in a variety of formats if appropriate (printed copy, electronic and audio), which people with CFS/ME and their carers can refer to at home and in the clinical setting. [1.1.2.4]

Provision of care [1.1.3]

Healthcare professionals responsible for caring for people with CFS/ME should have appropriate skills and expertise in the condition. [1.1.3.1]

Every person diagnosed with CFS/ME should be offered:

- information about the illness (see section 1.1.2)
- acceptance and understanding
- assistance negotiating the healthcare, benefits and social care systems
- assistance with occupational activities including work and education if appropriate (see section 1.4.5). [1.1.3.2]

An individualised management plan should be developed with the person with CFS/ME, and their carers if appropriate. The plan should be reviewed and changes documented at each contact. It should include:

- relevant symptoms and history

- plans for care and treatment, including managing setbacks/relapses
- information and support needs
- any education, training or employment support needs
- details of the healthcare professionals involved in care and their contact details. [1.1.3.3]

4.3 Information

This section outlines how good communication between healthcare professionals and patients is essential. People with CFS/ME have diverse information needs and they should be able to access accurate information suitable to their needs. The information patients are given should also be culturally appropriate and accessible to people who do not speak or read English. Carers and relatives should also be provided with the information they need.

4.3.1 Key clinical question 4

What are the information needs of healthcare professionals, patients and carers?

4.3.2 Evidence statements

[For details of the evidence gradings, please see Chapter 7 of the Guidelines Manual 2006, www.nice.org.uk/guidelinesmanual]

4.3.2.1	***Surveys of patient group members, carers, healthcare professionals (HCPs) and teachers report needs for more and better quality information and training regarding CFS/ME (Evidence level 3 and 4).***
4.3.2.2	***There is no evidence as to whether this need for information is specific to CFS/ME or on the content and appropriate mode of delivery of the information (Evidence level 3 and 4).***

4.3.3 Clinical evidence summary

Twelve research survey reports considered the information needs of adults with CFS/ME, their carers and healthcare professionals. Two guideline documents were also reviewed. All noted that there was a need for information, but opinions varied as to the source and type of required. There were no studies with a robust research design that evaluated the effectiveness of different types and sources of information.

In terms of children and adolescents, only two studies and one guideline document were identified. As for adults, the publications noted that there was a need for more information, but the source and type of information needed was less clear.

4.3.4 Health economics evidence summary

No studies were found that addressed the clinical question.

4.3.5 Clinical scenarios

The GDG decided that clinical scenarios would not contribute to decision-making in this area (see Chapter 2 for the details of how clinical scenarios are developed).

4.3.6 Recommendations

The recommendations relating to both information and support are merged in section 4.2 of this chapter.

4.3.7 Deriving recommendations

The GDG debated the need to provide information as soon as possible in the care pathway, but without alarming the patient and carers by giving a label of CFS/ME prematurely. The GDG reviewed the approach taken in the NICE clinical guideline on referral for suspected cancer (www.nice.org.uk/CG027).

The GDG discussed the media in which information should be given. Some people with CFS/ME will have cognitive difficulties, in particular difficulty reading, and they may therefore need a tape recording or a summary of the consultation in another format appropriate to their needs.

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

4.4 Support

People with CFS/ME should have the opportunity to make informed decisions about their care and treatment. For children and young people with CFS/ME, this will depend on their age and capacity to make decisions. It is good practice for healthcare professionals to involve the young person's parent(s) or guardian(s) in the decision-making process.

If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines – 'Reference guide to consent for examination or treatment' (2001) (available from www.dh.gov.uk). Since April 2007, it has been necessary for healthcare professionals to follow a code of

practice accompanying the Mental Capacity Act (summary available from www.dca.gov.uk/menincap/bill-summary.htm).

Loss of employment or education is generally detrimental to health and well-being[25]. Moreover, the longer that a person is off work due to illness or disability, the less likely they are to return to employment or education. Therefore, it is very important that work and education are addressed early in the care pathway for CFS/ME, and are reviewed regularly as part of the ongoing management programme.

In the case of adults, this would include working with the employer, education and social services to provide appropriate support, adaptations (for example, reduced or flexible working hours, flexible rest breaks, arrangements for home-working and reduced heavy physical work) and/or equipment (such as a wheelchair) so that the person can continue at, or return to, work or education. Occupational health services are best placed to facilitate rehabilitation back to work. However, in reality, the majority of employed people do not have access to specialist occupational health advice. Therefore, the healthcare professional who is leading care must be proactive in advising the person with CFS/ME and their employer about fitness for work and rehabilitation. A range of specialist advice and practical support for employment is available to adults with a disability, including Jobcentre Plus (www.jobcentreplus.gov.uk/JCP/Customers/Helpfordisabledpeople/index.html) and disability advisers within universities and colleges.

In the case of children and young people, there is a need to work with the family and the education provider (school, college, or university) to provide support. There needs to be close liaison between health, social care and education professionals so there is a common understanding of goals and objectives. Therefore, the view of the GDG was that a key worker responsible for coordinating care was needed. There may need to be a flexible approach involving home tuition and use of equipment that allows a gradual reintegration

into schools. It is important for the child or young person that their teachers and peers understand their situation and that they are being supported rather than stigmatised.

4.4.1 Key clinical question 5

What are the support needs of healthcare professionals, patients and carers?

4.4.2 Evidence statements

4.4.2.1	***Surveys of patients (largely but not exclusively from patient groups), carers, HCPs and others report mixed findings regarding the adequacy of support for CFS/ME patients (Evidence level 3 and 4).***
4.4.2.2	***Limited observational evidence was found regarding the perceived specific support needs of CFS/ME patients (Evidence level 3).***

4.4.3 Clinical evidence summary

Fourteen survey or interview studies provided evidence regarding the support needs of adults with CFS/ME, carers and healthcare professionals. Two guideline documents were also reviewed. One survey of healthcare professionals highlighted a need for support from medical colleagues and other relevant professionals such as social workers. All agreed that more support was needed. In addition, guidelines supported the need for collaborative working. Types of support for people with CFS/ME and carers varied and included support from health and social services.

Three survey or interview studies and one set of guidelines also provided evidence about the support needs of children and adolescents with CFS/ME, their carers and healthcare professionals. All agreed that more support was needed. The guidelines from The Royal College of Paediatrics and Child Health also supported closer liaison between paediatricians and schools.[1]

4.4.4 Health economics evidence summary

No studies were found that addressed the clinical question.

4.4.5 Clinical scenarios

The GDG decided that clinical scenarios would not contribute to decision-making in this area (see Chapter 2 for the details of how clinical scenarios are developed).

4.4.6 Recommendations

The recommendations relating to both information and support are merged in section 4.2 of this chapter.

4.4.7 Deriving recommendations

The view of the GDG was that support should be provided to assist the person with CFS/ME in maintaining as much of their normal life as possible. The emphasis should be on self-management with goals and objectives important to the individual.

The GDG discussed the issues for people with severe CFS/ME who were frequently isolated at home away from services and support. The view of the GDG was that all patients should have access to appropriate service and care regardless of their ability to attend hospitals or clinics. Sometimes, there could be follow-up contact by telephone or email. The point was made that small improvements in quality of life were very important.

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

5 Making a diagnosis of CFS/ME

5.1 Introduction

CFS/ME is a condition for which causation is uncertain and diagnostic criteria variable. Although a diagnosis of CFS/ME is straightforward in many cases, in others, reaching a diagnosis can be a particular problem, for a number of reasons.

- The onset may be relatively sudden or gradual, following a physical illness or stressful event, or apparently 'out of the blue'.
- The range of presenting symptoms is wide, and fatigue and pain may not always be the prominent disabling features at initial presentation.
- Patients may have been investigated extensively, but fruitlessly, for varied physical symptoms and may feel frustrated by the lack of help received from the medical profession by the time the diagnosis is made.
- Symptoms tend to vary in intensity and type over a period of weeks or months (and evolve into what is more clearly CFS/ME with time), leading to uncertainty for both the patient and clinician about the course and nature of the underlying problem.
- CFS/ME cannot be diagnosed by any test currently available.

However, clinicians can use pattern recognition to facilitate the diagnosis process. The diagnosis depends on recognition of a characteristic set of symptoms (see recommendations), appropriately classified according to type/range and by the affecting factors.

It is important to explore the nature of the fatigue (as with other symptoms), because the patient will then be able to clarify how different this experience is from everyday fatigue or fatigue associated with some other conditions.

A positive provisional diagnosis is most likely to be achieved by setting aside sufficient time to characterise the history upon which a diagnosis depends, and to recognise characteristic features, such as delayed symptoms (fatigue and malaise) after over-activity.

Consequently, diagnosis rests on the alertness of the clinician to the possibility of CFS/ME and a systematic approach to history-taking, examination and observation, assisted by the use of various investigations to rule out the possibility of other conditions.

Investigations have a particularly important role in ruling out the presence of alternative diseases. The patient is likely to be justifiably worried, and the clinician should investigate any symptoms that may indicate the presence of other serious conditions. 'Red flags'[‡] in the history and examination indicate the need for urgent specialised investigation.

Observation, over a limited period of time, in those patients with suggestive clinical features and negative investigations forms part of the process of diagnosis. This is needed to determine whether the condition meets diagnostic criteria for CFS/ME, or whether it is some self-limiting condition. Of course, should new symptoms develop, particularly 'red flags', the working diagnosis must be reviewed and further investigations instituted.

[‡] Defined as clinical features indicating an increased risk of other conditions that require urgent investigation.

5.1.1 Key clinical question 2

Are there any substantiated or validated evaluations to support the diagnosis of CFS/ME in adults and children?

5.1.2 Evidence statements

5.1.2.1 ***There is insufficient evidence to show that potential diagnostic tests for CFS/ME are useful diagnostically for adults and children. Specific diagnostic tests reviewed are:***

- the head-up tilt test (Evidence level II and III)
- five laboratory blood tests (fibrinogen, prothrombin fragment 1 + 2, thrombin–anti-thrombin complexes, soluble fibrin monomer (SFM) and platelet activation (CD62P, ADP)) (Evidence level III)
- auditory brainstem responses (Evidence level III)
- electrodermal conductivity (Evidence level III).

5.1.2.2 ***Evaluations of potential diagnostic tests for CFS/ME in children are of very limited validity (Evidence level III and IV).***

5.1.3 Key clinical subquestion 2

In people presenting with early suspected CFS/ME (before 6 months) what are the risk factors/prognostic flags that might be linked with progression to CFS/ME?

5.1.4 Evidence statements

5.1.4.1	***Clear risk factors for CFS/ME have not been identified (Evidence level 2–).***
5.1.4.2	***Clear risk factors for development of CFS/ME in children and young people have not been identified (Evidence level 2–).***

5.1.5 Clinical evidence summary

5.1.5.1 Summary of evidence presented in Appendix 1

The studies reviewed for question 2 assessed the utility of potential diagnostic tests. Of the 27 studies that met the inclusion criteria, only six were not of a low quality (level 3 or 4, where there was a higher risk of bias from various sources).

In the mainly case–control studies, the head-up tilt test, a panel of five laboratory tests (fibrinogen, prothrombin fragment 1 + 2, thrombin-anti-thrombin complexes, soluble fibrin monomer (SFM) and platelet activation (CD62P, ADP)), a test for auditory brainstem responses and electrodermal analysis were able to discriminate between people with CFS/ME and mainly healthy controls.

One case–control study involving 112 participants concluded that electrodermal analysis may be useful in the differential diagnosis of CFS/ME and depression.

When the evidence was reviewed for subquestion 2, there appeared to be an association between certain characteristics and CFS/ME; however, there were no definite prognostic flags for CFS/ME that would be useful to a clinician.

*5.1.5.2 **Additional clinical evidence***

No new evidence was found in the update searches.

However, a recent paper in the BMJ[26] concluded that 'prolonged fatigue states after infections are common and disabling' and that chronic fatigue syndrome (termed post-infective fatigue syndrome in the paper) was predicted 'largely by the severity of the acute illness, rather than by demographic, psychological, or microbiological factors'.

5.1.6 Health economics evidence summary

The investigations needed to rule out other significant disease before making a positive diagnosis of CFS/ME have a number of components which are of importance from an economic perspective.

Firstly, any aid towards either exclusion or diagnosis has a benefit in terms of clinical information to the clinician and to the individual. The value of this information is described in the systematic review, supplemented by the body of experience that exists within the wider healthcare community.

The second component, above and beyond the value of information gained through investigation before a definitive diagnosis has been made, is a possible negative effect on the patient of repetitive or extensive investigatory procedures. Therefore, if investigations can be undertaken simultaneously, this might improve the satisfaction of the individual for the same cost. The disbenefit of continued investigation must be weighed against the value of the clinical information the investigation is likely to elicit.

The third component is the cost attributable to these investigations. In the systematic evidence review, all investigations included some healthcare provider input, whether a consultation or the performance of a procedure. Any approach that produces the same outcome for less healthcare provider time will improve the cost effectiveness of the overall process.

After a positive diagnosis of CFS/ME has been made, the likelihood of the result of any investigation changing management should be considered, together with the potential improvement in quality of life, and these should be contrasted with the cost of the investigation and the disutility of the investigation to the individual.

5.1.7 Clinical scenario questionnaire to GDG and wider group

So that consistent principles were applied when rating the evidence statements, the GDG and the wider group assumed the following.

1. The person with CFS/ME and healthcare professionals involved in their care will make decisions in partnership. These are directed by the patient's personal preferences and build on the existing experience and skills of the professional.

2. All treatments are offered allowing the person with CFS/ME to refuse without compromising the further therapeutic relationship.

3. There is a good rapport in which the patient and their families/carers feel believed and validated.

4. Treatment is provided by the NHS in the context of availability of adequate numbers of competent, appropriately trained healthcare professionals.

5. Minimal waiting times for good-quality services are adhered to.

		GDG Round 1	GDG Round 2	Wider Group	Discussion
1(g)		The following investigations or examinations are appropriate in <u>establishing a</u> diagnosis of CFS/ME in an adult….			
	1. The head up tilt test	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. Neurological examination	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. Auditory brainstem responses	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. Electrodermal conductivity	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. Urinalysis for protein, blood, glucose	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. ECG if there are cardiological symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	7. **Endoscopy** if there are gastro-intestinal (gut) symptoms	Uncertain	Uncertain	Disagree	GDG was uncertain at round 2, progressed to wider survey

		GDG Round 1	GDG Round 2	Wider Group	Discussion
		Allergy test if there are gastro-intestinal (gut) symptoms	Coeliac antibodies if there are gastro-intestinal (gut) symptoms		The GDG found this question unclear and clarified for the second round
	8.	Uncertain	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	9.	Blood tests			
	a. Full Blood Count				Omitted from questionnaire and discussed in round 1 - Agreed
	b. Combined laboratory tests including fibrinogen, prothrombin fragment 1+2, thrombin-anti-thrombin complexes, soluble fibrin monomer (SFM) and platelet activation (CD62P, ADP)	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	c. Creatine Kinase	Agreed	…		Omitted from questionnaire and discussed in round 1
	d. Circulating red blood cell volume	Uncertain	Disagree		The GDG thought this referred to Full Blood Count which they regarded as uncontroversial. The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.

		GDG Round 1	GDG Round 2	Wider Group	Discussion
	e. Erythrocyte sedimentation rate	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	f. C-reactive protein	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	g. Electrophoresis	Uncertain	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	h. Ferritin	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	i. B12	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	j. Folate	Uncertain	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	k. Cholesterol	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1	GDG Round 2	Wider Group	Discussion
	l. Liver Function Tests	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	Lactate Dehydrogenase	Uncertain			In discussion this was clarified and the GDG decided that this was inappropriate as a diagnostic test.
	m. Thyroid Function Tests	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	n. Calcium	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
		General virus serology, including heterophile antibody tests for Infectious Mononucleosis	In the absence of any indicative history, general virus serology, including heterophile antibody tests for Infectious Mononucleosis are appropriate		This question was clarified to indicate in the absence of an indicative history.
		Uncertain	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
		Serology for chronic virus infections: HIV (Human Immunodeficiency Virus), hepatitis B & C	In the absence of any indicative history, serology for chronic virus infections: HIV, hepatitis B & C are appropriate		This question was clarified to indicate in the absence of an indicative history.

		GDG Round 1	GDG Round 2	Wider Group	Discussion
		Uncertain	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
		Serology for chronic bacterial infections e.g. borelliosis	In the absence of any indicative history, serology testing for chronic bacterial infections (e.g. borelliosis) is appropriate		This question was clarified to indicate in the absence of an indicative history.
		Uncertain	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
		Serology for latent infections: toxoplasma, EBV (Epstein Barr virus), CMV (cytomegalovirus)	In the absence of any indicative history, serology testing for latent infections: toxoplasma, EBV (Epstein Barr virus), CMV (cytomegalovirus) is appropriate		This question was clarified to indicate in the absence of an indicative history.
		Uncertain	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
1(h)		The following investigations or examinations are appropriate in establishing a diagnosis of CFS/ME in a child….			
	1. The head up tilt test	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1	GDG Round 2	Wider Group	Discussion
	2. Neurological examination	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. Auditory brainstem responses	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. Electrodermal conductivity	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. Urinalysis for protein, blood, glucose	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. ECG if there are cardiological symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	7. Endoscopy if there are gastro-intestinal (gut) symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
		Allergy test if there are gastro-intestinal (gut) symptoms	Coeliac antibodies if there are gastro-intestinal (gut) symptoms		The GDG found this question unclear and clarified for the second round

		GDG Round 1	GDG Round 2	Wider Group	Discussion
		Disagree	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
	9.	Blood tests			
	a. Full Blood Count				Omitted from questionnaire and discussed in round 1 - Agreed
	b. Combined laboratory tests including fibrinogen, prothrombin fragment 1+2, thrombin-anti-thrombin complexes, soluble fibrin monomer (SFM) and platelet activation (CD62P, ADP)	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	c. Creatine Kinase				Omitted from questionnaire and discussed in round 1 – Agreed at meeting
	d. Circulating red blood cell volume	Uncertain	Disagree	Uncertain	
	e. Erythrocyte sedimentation rate	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	f. C-reactive protein	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	g. Electrophoresis	Disagreed	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1	GDG Round 2	Wider Group	Discussion
	h. Ferritin	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	i. B12	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	j. Folate	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	k. Cholesterol	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	l. Liver Function Tests	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	Lactate dehydrogenase	Disagree			The GDG reached a consensus in the first round and the statement did not progress to Round 2
	m. Thyroid Function Tests	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1	GDG Round 2	Wider Group	Discussion
	n. Calcium	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
		Serology for chronic virus infections: HIV, hepatitis B & C	In the absence of any indicative history, general virus serology, including heterophile antibody tests for Infectious Mononucleosis are appropriate		This question was clarified to indicate in the absence of an indicative history.
		Uncertain	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	p. Serology for chronic virus infections: HIV, hepatitis B & C	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	q. Serology for chronic bacterial infections e.g. borelliosis	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
		Serology for latent infections: toxoplasma, EBV (Epstein Barr virus), CMV (cytomegalovirus)	In the absence of any indicative history, serology testing for latent infections: toxoplasma, EBV (Epstein Barr virus), CMV (cytomegalovirus) is appropriate		This question was clarified to indicate in the absence of an indicative history.
		Uncertain	Disagree	Agree	GDG was uncertain at round 2, progressed to wider survey

5.1.8 Recommendations

Note: numbers in square brackets are as in the NICE guidelines.

History, examinations and investigations [1.2.2]

A full history (including exacerbating and alleviating factors, sleep disturbance and intercurrent stressors) should be taken, and a physical examination and assessment of psychological wellbeing should be carried out. [1.2.2.1]

A child or young person who has symptoms suggestive of CFS/ME should be referred to a paediatrician for assessment to exclude other diagnoses within 6 weeks of presentation. [1.2.2.2]

The following tests should usually be done:

- urinalysis for protein, blood and glucose
- full blood count
- urea and electrolytes
- liver function
- thyroid function
- erythrocyte sedimentation rate or plasma viscosity
- C-reactive protein
- random blood glucose
- serum creatinine
- screening blood tests for gluten sensitivity
- serum calcium
- creatine kinase
- assessment of serum ferritin levels (children and young people only).

Clinical judgement should be used when deciding on additional investigations to exclude other diagnoses. [1.2.2.3]

Tests for serum ferritin in adults should not be carried out unless a full blood count and other haematological indices suggest iron deficiency. [1.2.2.4]

Tests for vitamin B_{12} deficiency and folate levels should not be carried out unless a full blood count and mean cell volume show a macrocytosis. [1.2.2.5]

The following tests should not be done routinely to aid diagnosis:

- the head-up tilt test
- auditory brainstem responses
- electrodermal conductivity. [1.2.2.6]

Serological testing should not be carried out unless the history is indicative of an infection. Depending on the history, tests for the following infections may be appropriate:

- chronic bacterial infections, such as borreliosis
- chronic viral infections, such as HIV or hepatitis B or C
- acute viral infections, such as infectious mononucleosis (use heterophile antibody tests)
- latent infections, such as toxoplasmosis, Epstein–Barr virus or cytomegalovirus. [1.2.2.7]

5.1.9 Deriving recommendations

The GDG decided that certain investigations (over and above routine screening tests such as those for anaemia, thyroid disease and coeliac disease) should be carried out to rule out other diseases and conditions, but it was not possible, or appropriate, to recommend a definitive, comprehensive list. The GDG discussed which investigations would help to rule out conditions with similar symptoms to those of CFS/ME.

The GDG decided that investigations should be carried out only where the history, signs or symptoms suggested an alternative diagnosis, and therefore many of the questions in the first round of the questionnaire were qualified to include this. Exceptions were tests for anaemia and thyroid function, and immunological tests for

coeliac disease, which the GDG decided should be undertaken in the absence of clinical indications.

Recommendation [1.2.2.7] above states that viral serology should not be carried out in the absence of a recent history suggesting viral infection. On reviewing the results from the wider survey, the GDG decided that it was difficult to establish a link between CFS/ME and serology indicating past viral infection, and that serological evidence of past infection would not alter the patient's management. Therefore the GDG could not recommend these tests routinely. The GDG also found that the evidence base was too weak to make a recommendation on EBV screening tests.

In the first round of the questionnaire many members of the GDG assumed that the clinical scenario regarding measurement of circulating red blood cell volume formed part of a full blood count, with which they agreed. After clarification, the GDG was uncertain whether a circulating red blood cell volume was in itself helpful in making a diagnosis. This went forward to the second round of the questionnaire where the GDG reached a consensus that it was not appropriate.

The GDG had mixed views about the value of measuring serum vitamin B12 levels, particularly as many laboratories will not carry out this investigation unless it is indicated by full blood count (FBC) and mean cell volume (MCV) results. As the GDG had a divergence of views, it was agreed that it should be included in the questionnaire for the wider group. The wider survey rated it as ‘uncertain’ but patients and carers ‘agreed’ that this test was appropriate. The GDG decided that this test should only be carried out if the results of the FBC and MCV suggest the presence of macrocytosis.

The view of the GDG was mixed regarding the testing of ferritin levels as part of diagnosis. One member reported that there was an RCT of women presenting with tiredness with normal haemoglobin but low ferritin. [Note: this was not in the evidence review as the subjects of the study did not have CFS/ME.] The GDG’s decision was that this was not a positive diagnostic tool. However, as for tests for

vitamin B12 levels, the GDG decided that ferritin levels should be tested if the results of the FBC and MCV suggested a microcytosis that may be due to iron deficiency.

In the wider survey, there was a trend to disagreement on the appropriateness of endoscopy as an investigation to aid diagnosis; a high proportion of respondents answered 'don't know'. The decision of the GDG was that a recommendation for routine endoscopy should not be made as this is a invasive investigation. Neither should a negative recommendation be made as endoscopy may be appropriate for certain individuals with particular symptoms and signs that would necessitate the exclusion of upper gastrointestinal pathology. In this context, endoscopy is an investigation not for CFS/ME, but for alternative or coexistent pathology.

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

5.2 Arriving at a diagnosis

5.2.1 Evidence statements

Key clinical question 1

Part 1 What are the existing case definitions for CFS/ME in adults and children?

Part 2 What evidence exists to substantiate or validate the existing case definitions for CFS/ME in adults and/or children?

Adults

5.2.1.1	***Evidence to substantiate existing case definitions of CFS or ME is limited. No studies have established the superiority of one case definition over another (Evidence level 2–).***
5.2.1.2	***Community-based studies have indicated that patients meeting CDC 1994 criteria form a more heterogeneous group than patients meeting CDC 1988 criteria (Evidence level 2–).***
5.2.1.3	***There is currently limited evidence that patients meeting Dowsett ME or the Canadian criteria are more likely to have more symptoms than those meeting CDC 1994 criteria (Evidence level 2–).***

Children

5.2.1.4	***Evidence to substantiate existing case definitions of CFS or ME in children and young people is very limited (Evidence level 2–).***
5.2.1.5	***One study has shown that adolescents who meet CDC 1994 criteria for CFS had more higher anxiety, depression, somatisation, school absence and illness attribution scores than those suffering with migraine or healthy controls.(Evidence level 2–).***

5.2.2 Clinical evidence summary

5.2.2.1 Summary of evidence presented in Appendix 1 Question 1 part 1 – diagnostic criteria

The current definitions of CFS/ME are characterised by descriptions of symptoms rather than by underlying causes. The systematic review conducted by the CRD at the University of York formed the primary evidence base for adult-onset CSF/ME in this guideline. Some of the criteria reviewed (presented in chronological order) are below; for the full list, see Appendix 1 Question 1: 'Criteria for case definitions of CFS and/ or ME' for a table of all criteria reviewed.

The Oxford Criteria of CFS/ME[§], developed in 1991 by a panel of clinicians and scientists, 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, and mood and sleep disturbance.[27]

[§] Note: the criteria are presented in chronological order, not in order of perceived utility.

In 1994, new criteria were drawn up by the US Centers for Disease Control (CDC), the 1994 CDC/Fukuda CFS Criteria.[28] The CDC definition included the requirement of the presence of new-onset fatigue lasting at least 6 months and the presence of at least four of eight other physical symptoms.

'A case of the chronic fatigue syndrome is defined by the presence of the following:

1) clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities; and

2) the concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue: self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities; sore throat; tender cervical or axillary lymph nodes; muscle pain; multijoint pain without joint swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and post-exertional malaise lasting more than 24 hours.'[28]

The 2003 Canadian definition[11] is more stringent and was developed by an international clinical CFS team. Fatigue in CFS/ME was characterized as '…post-exertional fatigue (with) a pathologically slow recovery period (it takes more than 24 hours to recover)'. The 2003 Canadian definition also states that cardinal symptoms are no longer optional and that patients must have neurological, immune and/or neuroendocrine manifestations.[11]

The Royal College of Paediatrics and Child Health in their 'Evidence based Guideline for the Management of CFS/ME' defined CFS/ME in children as '…generalized fatigue (fatigue causing disruption of daily life) persisting after routine tests and investigations have failed to identify an obvious underlying 'cause.''[1].

*5.2.2.2 **CFS/ME diagnostic criteria: adapted from comparative analysis by the New Zealand Guidelines Group 2003**[29]*

Diagnostic criteria in other guidelines

Australian 2002	UK 2002 (CMO Report)	US 2002	Canadian 2003
1. Fatigue • unexplained • persistent • > 6 months • new/definite onset • not resulting from exertion • not alleviated by rest • result in reduction in previous activity levels **AND** **2. Other symptoms** • concurrent with fatigue • persistent • >6 months • new/definite onset **Four or more of the following:** • impaired short-term memory/concentration • sore throat • tender cervical/ancillary lymph nodes • muscle pain • multijoint pain without arthritis • headaches (of new type/pattern/severity) • post-exertional malaise lasting > 24 hours **Idiopathic chronic fatigue:** Diagnose if formal criteria for CFS are not met and other conditions are excluded.	**1. Worsening of symptoms following physical or mental exertion** beyond the person's tolerance with a delayed impact and a prolonged recovery period. This is the prime feature of the condition. **PLUS some of other common symptoms:** **2. Tiredness or fatigue (physical and cognitive)** • excessive • persistent (> 6 weeks) **3. Cognitive impairment** • reduced attention span • impairment of short-term memory • word-finding difficulty • inability to plan/organise thoughts • spatial disorientation • loss of ability to concentrate **4. Post-exertional malaise** • may be flu-like symptoms **5. Pain** • persistent • poor response to standard analgesia May include • muscular pain • joint pain • neuropathic pain (with or without	**1. Unexplained fatigue** **AND** Any of the following: • impaired memory loss • sore throat, • tender neck (cervical) or armpit (axillary) lymph nodes, • muscle pain (myalgia), • headache, • unrefreshing sleep, • post-exertional malaise lasting more than 24 hours, and • multijoint pain (arthralgia) without swelling or redness **Symptom checklist:** • Prolonged (>24 hrs) generalised fatigue • Non-refreshing sleep • Sore throat • Painful cervical or axillary lymph nodes • Unexplained generalised muscle weakness • Generalised headaches	**1. Fatigue (physical and mental)** • unexplained • persistent • new/definite onset or • recurrent • results in substantial reduction in previous activity levels **AND** **2. Post-exertional malaise/fatigue** • inappropriate loss of physical and mental stamina • rapid muscular and cognitive fatigability • post exertional malaise and/or • pain and a tendency for other associated symptoms to worsen • recovery period of > 24 hours **AND** **3. Sleep dysfunction** • unrefreshing sleep and/or • sleep quantity or rhythm disturbances – a small number of people may not suffer sleep dysfunction but CFS/ME is the only diagnosis that fits **AND** **4. Pain** • a significant degree of myalgia. • may be experienced in muscles and/or

Australian 2002	UK 2002 (CMO Report)	US 2002	Canadian 2003
In routine clinical practice, a diagnosis of CFS may be appropriate even though the requirement of 4 out of 8 additional symptoms above is not formally met. Such patients can have comparable levels of disability, and may also benefit from the assessment and intervention strategies described in these guidelines.	paraesthesiae) • head pain and/or headache **6. Sleep disturbance** May include: • early morning wakening • insomnia • hypersomnia • unrefreshing sleep • disturbed sleep/wake cycle **7. Other symptoms** • Temperature disturbance • Dizziness, vertigo, postural hypotension • Increased sensitivity to sensory stimuli • Serious neurological symptoms − double vision, blackouts, atypical convulsions, loss of speech, and loss of swallowing necessitating nasogastric feeding in a minority of severely affected patients. • Recurrent sore throat +/- lymphadenopathy • Digestive disturbances − nausea, loss of appetite, indigestion, bloating, abdominal cramps, alternating diarrhoea and constipation. Symptoms are similar to irritable bowel syndrome (a differential diagnosis) • Intolerances − alcohol, foods, medication, or other substances	• Migratory painful joints without swelling or redness • Areas of lost or depressed vision • Visual intolerance of light • Forgetfulness • Excessive irritability • Confusion • Difficulty thinking • Inability to concentrate • Depression **Idiopathic chronic fatigue:** Diagnose if alternative causes for fatigue have been ruled out, but criteria for CFS are not met. Treat as CFS.	joints • may be migratory in nature • may be significant headaches of new type, pattern or severity - a small number of people may not suffer pain but CFS/ME is the only diagnosis that fits **AND** **5. Two or more of the following neurological/cognitive manifestations:** • confusion • impairment of concentration and short-term memory consolidation • disorientation • difficulty with information processing, categorising and word retrieval • perceptual and sensory disturbances e.g. spatial instability, disorientation and inability to focus vision Ataxia, muscle weakness and fasciculations are common. Overload phenomena may occur leading to 'crash' periods and/or anxiety – cognitive, emotional, and/or sensory e.g. photophobia, noise hypersensitivity. **AND** **6. At least 1 symptom from 2 of the following categories:** **A. Autonomic dysfunction** • Orthostatic intolerance – neurally mediated hypotension, postural orthostatic tachycardia syndrome, delayed postural hypotension

Australian 2002	UK 2002 (CMO Report)	US 2002	Canadian 2003
			• Light-headedness, extreme pallor • Nausea and irritable bowel syndrome • Urinary frequency and bladder dysfunction • Palpitations with or without cardiac arrhythmias • Exertional dyspnoea. **B. Neuroendocrine manifestations** • Heat/cold intolerance • Marked weight change – anorexia or abnormal appetite • Loss of adaptability and worsening of symptoms with stress. **C. Immune manifestations** • Tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms • General malaise • New sensitivities to food, medications and/or chemicals. **AND** **7. Chronic duration** Symptoms persisting for at least 6 months. Preliminary diagnosis may be possible earlier. Three months is appropriate for children. It usually has a distinct onset (although it may be gradual). **AND** **8. Exclusion of active disease processes that explain most of the symptoms.** **Idiopathic chronic fatigue:** If the patient

Australian 2002	UK 2002 (CMO Report)	US 2002	Canadian 2003
			has unexplained prolonged fatigue (6 months or more), but has insufficient symptoms to meet the criteria for ME/CFS, it should be classified as idiopathic chronic fatigue.

AGREE appraisals of included guidelines

For information, reviewers in the NCC-PC applied the AGREE Appraisal tool to the guidelines included in the New Zealand Guidelines Group (NZGG) comparative review. Results were as follows.

	Overall assessment NCC-PC (number of reviewers in agreement)	**Comments from NCC-PC**	**Comments on rigour from NZGG**
Australian 2002	Recommend (with provisos or alterations) (2/2)	• Seems to be a very well produced, methodologically sound guideline. • The formation of the GDG group includes all relevant professionals, as well as a patient presence. • Key recommendations are easily found, and are specific. • Guideline has been piloted previously on target users.	• Search strategies not detailed, but statement that NHMRC guidelines for guidelines followed (implies systematology) • No discussion of outcomes • Not enough attention to harms and risks • Outdated evidence base
Canadian 2003	Would not recommend (3/3)	• This guideline reads like a description of the results, but without the description of the methodology. There is not enough detail of the process the group went through when assessing the evidence and formulating their recommendations. • No key clinical questions were described, and the patient population was not specifically taken into account. • Poor methodology in my opinion. • However, as there is such a lack of evidence, the discussion around the non-systematically evidence reviews is interesting and the recommendations are very detailed. • But, methodologically poor guidelines overall. • Little documentation and accountability.	• Follows evidence-based and consensus protocols • No search strategies detailed, but research base is comprehensive and current • Excellent consideration of risks/harms as well as benefits
CMO 2002	Recommend (with provisos or alterations) (2/2)	• These guidelines are explicit and unambiguous in their recommendations. • Methodologically, some key aspects are left out (incl. cost analysis for implementation, procedure for updating), but more	• Good sources of information: research, consumer submissions, clinical experience) • No systematic searching

		importantly the authors fail to specifically describe the clinical questions used. • GDG includes the majority of relevant professionals, however does not include some of the specified target users (physiotherapists, occupational therapists, etc).	• Limited scope of literature reviewed (overlooks much non-UK literature). • Limited appraisal of evidence. • No levels of evidence or grading of recommendations. • No links between evidence and body of report – more information in annexes than report. • Glossing over of some potential harms – e.g. of medications. • Makes some recommendations which may be harmful (e.g. GET). • Couldn't be effectively peer-reviewed due to poor referencing.
US New Jersey 2002	Would not recommend (2/2)	• This document is more of a theoretical text book/ manual than a clinical guideline. • Recommendations are hidden in the narrative, and key messages are not identifiable. • There is no description of the guideline methodology. • No patient perspective is taken into account.	• No systematic literature search, but comprehensive, up-to-date literature base supporting guideline, with no obvious gaps.

Domain and overall scores were as follows.

	Australia		Canada		CMO		US New Jersey	
	NCC-PC	NZ	NCC-PC	NZ	NCC-PC	NZ	NCC-PC	NZ
Scope and purpose	61%	63%	26%	83%	61%	92%	28%	86%
Stakeholder involvement	79%	70%	14%	70%	54%	77%	17%	71%
Rigour of development	45%	58%	13%	73%	45%	63%	12%	78%
Clarity and presentation	67%	57%	33%	80%	75%	77%	21%	73%
Applicability	17%	33%	9%	51%	33%	60%	0%	44%
Editorial independence	33%	47%	6%	48%	42%	50%	8%	67%
Overall	**52%**	**57%**	**16%**	**70%**	**52%**	**70%**	**15%**	**72%**

Common features as noted by the New Zealand Guidelines Group[29]

1. Fatigue (physical and mental)

• unexplained

• persistent

AND some of

2. Post-exertional malaise/fatigue: inappropriate loss of physical and mental stamina with long recovery period

3. Sleep disturbance

May include

• early morning wakening

• insomnia

• hypersomnia

• unrefreshing sleep

• disturbed sleep/wake cycle

4. Pain

May include

• muscles and/or joint pain

• significant headaches of new type, pattern or severity

• painful lymph nodes

• sore throat

5. 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: diagnose if alternative causes for fatigue have been ruled out, but criteria for CFS

are not met. Treat as CFS.

5.2.2.3 Summary of evidence presented in Appendix 1 Question 1 part 2 – case definitions

The evidence base for existing case definitions of CFS/ME is not robust. Although 36 studies were reviewed by the CRD, study designs were primarily case–control, with small sample sizes and different comparative groups ranging from healthy individuals to severely ill people[5]. Diagnostic criteria for CFS/ME varied among studies. Outcomes of fatigue, impaired sleep, cognition, concentration, quality of life and social functioning generally appeared to be significant among CFS/ME patients. However, measurement of these outcomes was essentially subjective and therefore potentially biased. Tests of cognitive function and assessment of functional ability were more robust, and these generally appeared to be impaired in CFS/ME patients. Higher depression scores were noted among CFS/ME patients in some studies but it was unclear whether depression occurred before or after CFS/ME symptoms began. In an earlier review by Mulrow, Ramirez, Cornell and Allsup[30] the authors concluded that there were no studies that provided the basis of a definitive case definition. It would appear that this is still the case.

Fatigue is a cardinal feature of patients with a diagnosis of CFS/ME. The expected consequences of fatigue follow, including effects on cognitive ability and concentration, and general functional capabilities. However support for specific physical and psychological features of the syndrome was weak and inconsistent in the studies reviewed for this guideline.

*5.2.2.4 **Update searches***

One case–control study[31] (n = 227) was identified that implemented the recommendations of the International CFS Study Group[28] for the diagnosis of CFS. The international recommendations were compared to the 'usual algorithm' based on patients' subjective responses to direct questions about fatigue, reduction in daily activities and presence of at least 4 case defining symptoms. Only 13% of patients who met 1994 surveillance criteria for CFS met those same criteria in this study, indicating fluctuation in illness levels over time. Forty per cent of patients fulfilled the CFS criteria of the International CFS Study Group using a clinically empirical definition, based on functional impairment, fatigue and accompanying symptoms. Thus, the clinically empirical case definition may be less affected by illness fluctuations and more truly reflect the underlying chronic illness process.

5.2.3 Health economics evidence summary

The literature review identified no published cost-effectiveness studies of a suitable structure and quality. Therefore, the GDG were presented with an outline of the key cost-effectiveness considerations in the diagnosis, investigation and referral of individuals with suspected CFS/ME.

When an individual first enters primary care, most likely with an uncertain diagnosis, the healthcare professional has available a range of exclusory procedures and approaches, each either suggesting an alternative diagnosis to CFS/ME or adding evidence to corroborate a CFS/ME diagnosis. The choice of the point at which diagnosis is made (i.e. when we define the evidence as 'weighty enough') has economic considerations, in that we have to accept a number of either false negatives, false positives, or most likely, both. This idea is illustrated in the use of receiver operating characteristic (ROC) curves. Such curves were not identified in the diagnosis of CFS/ME.

While such curves were not identified, the trade-off between false negatives and false positives illustrated by this approach is crucial when discussing diagnosis. Assuming all other factors are held constant, if a false negative becomes relatively more problematic (however that is defined) than a false positive, it would be logical to diagnose when the evidence supporting a diagnosis is smaller. However, if the opposite is true, we should be more willing to delay the diagnosis.

The costs attached to false diagnoses

False positives		**False negatives**	
Individual	**Structural**	**Individual**	**Structural**
Stress associated with a diagnosis	Cost of initial CFS/ME treatment/management	Condition has deteriorated over time	Cost of treating/managing incorrect condition
Delayed treatment/management of true condition	Increased cost of treating true condition if this has become more severe	–	Increased cost of treating CFS/ME if this has become more severe

While there is evidence on these elements of the decision-making process, evidence of the magnitude of each of these relative to the others is largely inconclusive and the likelihood of being able to contrast the negative aspects of a false negative with the negative aspects of a false positive is small.

5.2.4 Clinical scenario questionnaire to GDG and wider group

So that consistent principles were applied in rating the evidence statements, the GDG and the wider group assumed the following.

1. The person with CFS/ME and healthcare professionals involved in their care will make decisions in partnership. These are directed by the patient's personal preferences and build on the existing experience and skills of the professional.

2. All treatments are offered allowing the person with CFS/ME to refuse without compromising the further therapeutic relationship.

3. There is a good rapport in which the patient and their families/carers feel believed and validated.

4. Treatment is provided by the NHS in the context of availability of adequate numbers of competent, appropriately trained healthcare professionals.

5. Minimal waiting times for good-quality services are adhered to.

The symptoms listed in the clinical scenarios were derived from the common features in the Australian, Canadian, US and UK guidance. [1;6;11;28]

		GDG Round 1	GDG Round2	Wider Group	Discussion
1(a)	Fatigue indicative of CFS/ME in an adult…..				
	1. is persistent and/or recurrent	Agree			The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. is unexplained by mental or physical conditions	Agree			The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. results in substantial reduction in previous activity levels	Agree			The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. characterised by post-exertion malaise and/or fatigue (often delayed with slow recovery)	Agree			The GDG reached a consensus in the first round and the statement did not progress to Round 2
1(b)	Other symptoms indicative of CFS/ME in an adult can, but not necessarily always, include….				
	1. Difficulty with sleeping (e.g. early morning waking, insomnia, hypersomnia, unrefreshing sleep, disturbed sleep/wake cycle)	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. Muscles and/or joint pain	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. Significant headaches of new type, pattern or severity	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1	GDG Round2	Wider Group	Discussion
	4. Painful lymph nodes	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. Sore throat	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. Cognitive impairment for example confusion, difficulty thinking, inability to concentrate, impairment of short-term memory, word-finding difficulty, inability to plan/organise thoughts, spatial disorientation, difficulty with information processing	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	7. Physical or mental exertion making symptoms worse	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	8. Recurrent flu-like symptoms	Agree	Agree	Agree	Random selection for wider survey
	9.	9 Neuroendocrine symptoms e.g. orthostatic intolerance, nausea and palpitations	9. Orthostatic intolerance (problems standing upright), nausea and palpitations	Orthostatic intolerance (problems standing upright), nausea and palpitations	GDG did not consider the symptoms as neuroendocrine and reworded and re-rated
		Agree	Agree	Agree	
	10	Autonomic symptoms e.g. loss of thermostatic stability and marked weight change	Significant weight change(s)		The GDG decided that the grouping of the symptoms was confusing. The symptoms were separated and re-rated.

		GDG Round 1	GDG Round2	Wider Group	Discussion
		Uncertain	Uncertain		GDG decided that weight loss was a concern of other conditions but not a symptom of CFS/ME and that weight gain was not a significant symptom but the consequence of inactivity.
	11		Loss of thermostatic stability (difficulty controlling temperature)		
		Not included	Agree		
1(c)	After ruling out other possible likely causes of the symptoms, a diagnosis of CFS/ME should be made in an Adult				
	1. After symptoms have persisted for at least 6 weeks	Uncertain	Disagree	Uncertain	Random selection for wider survey
	2. After symptoms have persisted for at least 4 months	Agree	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	3. After symptoms have persisted for at least 6 months	Agree	Agree	Agree	Random selection for wider survey
1(d)	Fatigue indicative of CFS/ME in a child is….				
	1. persistent and/or recurrent	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1	GDG Round2	Wider Group	Discussion
	2. unexplained by mental or physical conditions	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. results in substantial reduction in previous activity levels	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. characterised by post-exertion malaise and/or fatigue (often delayed with slow recovery)	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
1(e)	Other symptoms indicative of CFS/ME in a child can, but not necessarily always, include…..				
	1. Difficulty with sleeping (e.g. early morning wakening, insomnia, hypersomnia, unrefreshing sleep, disturbed sleep/wake cycle)	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. Muscles and/or joint pain	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. Significant headaches of new type, pattern or severity	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. Painful lymph nodes	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. Sore throat	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1	GDG Round2	Wider Group	Discussion
	6. Cognitive impairment for example confusion, difficulty thinking, inability to concentrate, impairment of short-term memory, word-finding difficulty, inability to plan/organise thoughts, spatial disorientation, difficulty with information processing	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	7. Physical or mental exertion making symptoms worse	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	8. Recurrent flu-like symptoms	Agree	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
		9. Neuroendocrine symptoms e.g. orthostatic intolerance and palpitations	8. Orthostatic intolerance (problems standing upright), nausea and palpitations	Orthostatic intolerance (problems standing upright), nausea and palpitations	The GDG decided that the grouping of the symptoms was confusing. The symptoms were separated and re-rated.
		Uncertain	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
		10. Autonomic symptoms e.g. loss of thermostatic stability and marked weight change	9. Significant weight change(s)	Significant weight change(s)	The GDG decided that the grouping of the symptoms was confusing. The symptoms were separated and re-rated.
		Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey

		GDG Round 1	GDG Round2	Wider Group	Discussion
			10. Loss of thermostatic stability (difficulty controlling temperature)		Discussed and not included in wider survey
			Uncertain	…….	
1(f)	After ruling out other possible likely causes of the symptoms, a diagnosis of CFS/ME should be made in a child….				
	1. After symptoms have persisted for 6 weeks	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	2. After symptoms have persisted for 4 months	Agree	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	3. After symptoms have persisted for 6 months	Agree	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.

5.2.5 Recommendations

Note: numbers in square brackets are as in the NICE guidelines.

Presentation [1.2]

Presenting symptoms suspicious of CFS/ME [1.2.1]

CFS/ME is recognised on clinical grounds alone. Primary healthcare professionals should be familiar with and be able to identify the characteristic features of CFS/ME. [1.2.1.1]

Healthcare professionals should consider the possibility of CFS/ME if a person has:

- fatigue with all of the following features:
  - new or had a specific onset (that is, it is not lifelong)
  - persistent and/or recurrent
  - unexplained by other conditions
  - has resulted in a substantial reduction in **activity** level
  - characterised by post-exertional malaise and/or fatigue (typically delayed, for example by at least 24 hours, with slow recovery over several days)

  and

- one or more of the following symptoms:
  - difficulty with sleeping, such as insomnia, hypersomnia, unrefreshing sleep, a disturbed sleep–wake cycle

- muscle and/or joint pain that is multi-site and without evidence of inflammation
- headaches
- painful lymph nodes without pathological enlargement
- sore throat
- cognitive dysfunction, such as difficulty thinking, inability to concentrate, impairment of short-term memory, and difficulties with word-finding, planning/organising thoughts and information processing
- physical or mental exertion makes symptoms worse
- general malaise or 'flu-like' symptoms
- dizziness and/or nausea
- palpitations in the absence of identified cardiac pathology. [1.2.1.2]

Healthcare professionals should be aware that the symptoms of CFS/ME fluctuate in severity and may change in nature over time. [1.2.1.3]

Signs and symptoms that can be caused by other serious conditions ('red flags') should not be attributed to CFS/ME without consideration of alternative diagnoses or comorbidities. In particular, the following features should be investigated[**]:

[**] Follow 'Referral guidelines for suspected cancer' (NICE clinical guideline 27) or other NICE guidelines as the symptoms indicate. See www.nice.org.uk for details.

- localising/focal neurological signs
- signs and symptoms of inflammatory arthritis or connective tissue disease
- signs and symptoms of cardiorespiratory disease
- significant weight loss
- sleep apnoea
- clinically significant lymphadenopathy. [1.2.1.4]

Re-assessment before diagnosis [1.2.4]

If symptoms do not resolve as expected in a person initially suspected of having a self-limiting condition, primary healthcare professionals should listen carefully to the person's and their family and/or carers' concerns and be prepared to reassess their initial opinion. [1.2.4.1]

If considering the possibility of CFS/ME or another serious alternative condition, primary healthcare professionals should consider discussion with a specialist if there is uncertainty about the interpretation of signs and symptoms and whether a referral is needed. This may also enable the primary healthcare professional to communicate their concerns and a sense of urgency to secondary healthcare professionals if symptoms are unusual. [1.2.4.2]

Diagnosis [1.3]

Making a diagnosis [1.3.1]

A diagnosis should be made after other possible diagnoses have been excluded and the symptoms have persisted for:

- 4 months in an adult
- 3 months in a child or young person; the diagnosis should be made or confirmed by a paediatrician. [1.3.1.1]

When a diagnosis of CFS/ME is made, healthcare professionals should provide honest, realistic information about CFS/ME and encourage cautious optimism.

- Most people with CFS/ME will improve over time and some people will recover and be able to resume work and normal activities.
- However, others will continue to experience symptoms or relapse and some people with severe CFS/ME may remain housebound.
- The prognosis in children and young people is more optimistic. [1.3.1.2]

The diagnosis of CFS/ME should be reconsidered if none of the following key features are present:

- post-exertional fatigue or malaise
- cognitive difficulties
- sleep disturbance
- chronic pain. [1.3.1.3]

5.2.6 Deriving recommendations

Diagnostic criteria

The GDG reviewed the existing diagnostic criteria, but did not consider them particularly helpful in clinical practice when making a definitive diagnosis or managing the condition.

The Gibson Inquiry[2] recently reviewed diagnostic criteria and concluded that the Canadian criteria[11] were a useful contribution to defining the clinical condition of CFS/ME. They are more detailed than the Oxford criteria[27], for example. However, since the cause or causes of CFS/ME are unknown, we cannot be sure that the proposed criteria do accurately identify people who have CFS/ME. It is possible that diagnostic criteria that delineate a particular set of symptoms wrongly exclude patients with early disease or with minor disability, when such patients might benefit from early intervention and avoid progression to severe or prolonged disability. As the Gibson Inquiry made clear, research is required into the biological basis of CFS/ME, but until that research has been completed the clinician and the patient need practical guidance.

The GDG recognised that if broader criteria were used, some people might be falsely diagnosed with CFS/ME when in fact they have other conditions that would respond to appropriate treatment. Therefore, the GDG viewed the diagnosis of CFS/ME as a process rather than a discrete, isolated event (see next section – The diagnostic process).

The case definition or diagnostic criteria were proposed by Carruthers et al.[11] and are followed in the Canadian guidelines.

Table 1 Clinical working case definition of CFS/ME from the Canadian guidelines[11]

A patient with ME/CFS will meet the criteria for fatigue, post-exertional malaise and/or fatigue, sleep dysfunction, and pain; have two or more neurological/cognitive manifestations and one or more symptoms from two of the categories of autonomic, neuroendocrine and immune manifestations; and

adhere to item 7.

Fatigue: The patient must have a significant degree of new onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level.

Post-exertional malaise and/or fatigue: There is an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post-exertional malaise and/or fatigue and/or pain and a tendency for associated symptoms within the patient's cluster of symptoms to worsen. There is a pathologically slow recovery period – usually 24 hours or longer.

Sleep dysfunction: There is unrefreshed sleep or sleep quantity or rhythm disturbances such as reversed or chaotic diurnal sleep rhythms.

Pain: There is a significant degree of myalgia. Pain can be experienced in the muscles and/or joints, and is often widespread and migratory in nature. Often there are significant headaches of new type, pattern or severity.

Neurological/cognitive manifestations: *Two or more* of the following difficulties should be present: confusion, impairment of concentration and short-term memory consolidation, disorientation, difficulty with information processing, categorizing and word retrieval, and perceptual and sensory disturbances – e.g. spatial instability and disorientation and inability to focus vision. Ataxia, muscle weakness and fasciculations are common. There may be overload phenomena: cognitive, sensory – e.g. photophobia and hypersensitivity to noise – and/or

emotional overload, which may lead to 'crash' periods and/or anxiety.

At least one symptom from two of the following categories:

Autonomic manifestations: orthostatic intolerance – neurally mediated hypotension (NMH), postural orthostatic tachycardia syndromes (POTS), delayed postural hypotension; light-headedness; extreme pallor; nausea and irritable bowel syndrome; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmias; exertional dyspnoea.

Neuroendocrine manifestations: loss of thermostatic stability – subnormal body temperature and marked diurnal fluctuation, sweating episodes, recurrent feelings of feverishness and cold extremities; intolerance of extremes of heat and cold; marked weight change – anorexia or abnormal appetite; loss of adaptability and worsening of symptoms with stress.

Immune manifestations: tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms, general malaise, new sensitivities to food, medications and/or chemicals.

The illness persists for at least 6 months. It usually has a distinct onset, although it may be gradual. Preliminary diagnosis may be possible earlier: 3 months is appropriate for children.

To be included, the symptoms must have begun or have been significantly altered after the onset of this illness. It is unlikely that a patient will suffer from all symptoms in criteria 5 and 6. The disturbances tend to form symptom clusters

that may fluctuate and change over time. Children often have numerous prominent symptoms but their order of severity tends to vary from day to day. There is a small number of patients who have no pain or sleep dysfunction, but no other diagnosis fits except ME/CFS. A diagnosis of ME/CFS can be entertained when this group has an infectious illness type onset. Some patients have been unhealthy for other reasons prior to the onset of ME/CFS and lack detectable triggers at onset and/or have more gradual or insidious onset.

Exclusions: Exclude active disease processes that explain most of the major symptoms of fatigue, sleep disturbance, pain, and cognitive dysfunction. It is essential to exclude certain diseases, which would be tragic to miss: Addison's disease, Cushing's syndrome, hypothyroidism, hyperthyroidism, iron deficiency, other treatable forms of anaemia, iron overload syndrome, diabetes mellitus, and cancer. It is also essential to exclude treatable sleep disorders such as upper airway resistance syndrome and obstructive or central sleep apnoea; rheumatological disorders such as rheumatoid arthritis, lupus, polymyositis and polymyalgia rheumatica; immune disorders such as AIDS; neurological disorders such as multiple sclerosis (MS), Parkinsonism, myasthenia gravis and B12 deficiency; infectious diseases such as tuberculosis, chronic hepatitis, Lyme disease, etc.; primary psychiatric disorders and substance abuse. Exclusion of other diagnoses, which cannot be reasonably excluded by the patient's history and physical examination, is achieved by laboratory testing and imaging. If a potentially confounding medical condition is under control, then the diagnosis of ME/CFS can be entertained if patients meet the criteria otherwise.

Co-morbid entities: fibromyalgia syndrome (FMS), myofascial pain syndrome (MPS), temporomandibular joint syndrome (TMJ), irritable bowel syndrome (IBS), interstitial cystitis, irritable bladder syndrome, Raynaud's phenomenon, prolapsed mitral valve, depression, migraine, allergies, multiple chemical sensitivities (MCS), Hashimoto's thyroiditis, Sicca syndrome etc. Such co-morbid entities may occur in the setting of ME/CFS. Others such as irritable bowel syndrome may precede the development of ME/CFS by many years, but then become associated with it. The same holds true for migraines and depression. Their association is thus looser than between the symptoms within the syndrome. ME/CFS and FMS often closely connect and should be considered to be 'overlap syndromes'.

Idiopathic chronic fatigue: if the patient has unexplained prolonged fatigue (6 months or more) but has insufficient symptoms to meet the criteria for ME/CFS, this should be classified as idiopathic chronic fatigue.

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

The diagnostic process

The GDG considered whether making a confirmed diagnosis of CFS/ME was necessary, as once this is done healthcare professionals may not continue to consider

other possibilities and risk overlooking another potentially serious condition. 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.

In the first stage of the process, CFS/ME is suspected. This requires the clinician to have knowledge of the presenting features of CFS/ME.

The second stage involves systematic assessment to determine the likelihood of CFS/ME and to rule out other conditions. The assessment includes clinical examination, appropriate investigations and, depending on the duration of symptoms, a period of observation, subject to the findings of the investigations.

In the third stage, the diagnosis is reached, other conditions having being ruled out. At this stage, standard diagnostic criteria may be used if found helpful by the clinician and patient in assessing the extent of symptoms. However, the criteria should not be used to restrict interventions to only a limited group of patients.

In the fourth stage, the patient is reviewed at regular intervals and the diagnosis reconsidered if new symptoms or signs arise or if the patient's condition deteriorates or fails to improve.

The timing of diagnosis was discussed by the GDG. There was no evidence on when a diagnosis should be made, although some of the diagnostic criteria (see Appendix 1 Q.1) required that symptoms persisted for 6 months. There was concern about leaving a diagnosis this late and this perhaps resulting in a delay in access to services and support. On the other hand, there was also concern about making a diagnosis including

the word ‘chronic’ at an early stage in the illness. There was general consensus that, depending on individual circumstances, a diagnosis in a child should generally be made at about 3 months following the onset of symptoms. This is in accordance with the Royal College of Paediatrics & Child Health (RCPCH) guideline.[1] The GDG considered that 4 months was an appropriate timeframe for adults.

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

Signs and symptoms

There was strong agreement that persistent, debilitating, post-exertional fatigue characterised CFS/ME. Such fatigue may be accompanied by a wide spectrum of other symptoms. Healthcare professionals should be therefore be aware of other symptoms that frequently present with fatigue, in order to raise awareness of the possibility of CFS/ME, and promote appropriate, early intervention.

The GDG discussed ‘red flag’ symptoms – those that might indicate another serious illness. These included the following.

Weight loss: while weight gain might be an indication of CFS/ME, unexplained weight loss is not generally characteristic of CFS/ME and could signify a more acute disease such as cancer. It was noted that people with CFS/ME may have explained weight loss due to difficulty eating. This would need to be managed but was not a symptom defining CFS/ME.

Spatial disorientation is not generally characteristic of CFS/ME, and is usually indicative of brain damage. Concentration and memory difficulties ('brain fog') are, however, typical.

Sleep apnoea: if a patient has sleeping problems, the healthcare professional should ask specifically about symptoms that suggest a diagnosis of sleep apnoea as suspected sleep apnoea requires prompt referral and investigation.

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

History and examination

The GDG decided that, as for investigations, the examination, based on the history, should be targeted to 'rule out' other conditions. The GDG's view was that the individual doing the examination should have competencies in the recognition of CFS/ME.

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

5.3 Referral to specialist CFS/ME care

5.3.1 Evidence statements

No evidence was found regarding referral to specialist CFS/ME care.

5.3.2 Clinical evidence summary

There is currently no robust evidence concerning timescales for referring to a specialist or to specialist CFS/ME centres people in whom a diagnosis of CFS/ME is suspected or has already been made.

As is reflected in the recommendations, the GDG decided that referral to specialists or specialist CFS/ME centres is dependent on the following factors: local service provisions; and the severity of the individual's condition. Any decisions on the types of investigations or therapies to be accessed should be made between the lead healthcare professional and patient.

5.3.3 Health economics evidence summary

No evidence on referral was identified.

5.3.4 Clinical scenario questionnaire to GDG and wider group

So that consistent principles were applied in rating the evidence statements, the GDG and the wider group assumed the following.

1. The person with CFS/ME and healthcare professionals involved in their care will make decisions in partnership. These are directed by the patient's personal preferences and build on the existing experience and skills of the professional.

2. All treatments are offered allowing the person with CFS/ME to refuse without compromising the further therapeutic relationship.

3. There is a good rapport in which the patient and their families/carers feel believed and validated.

4. Treatment is provided by the NHS in the context of availability of adequate numbers of competent, appropriately trained healthcare professionals.

5. Minimal waiting times for good-quality services are adhered to.

		GDG Round 1	GDG Round 2	Wider Group	Discussion
1(i)		For an adult with mild CFS/ME symptoms a referral for specialised care is appropriate….			
	1. as soon as symptoms occur	Disagree	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	2. only after symptoms have persisted for about 4-6 weeks following treatment in primary care	Disagree	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	3. only after symptoms have persisted for about 3-4 months following treatment in primary care	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	4. only after symptoms have persisted for at least 6 months following treatment in primary care	Uncertain	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	5. never or only very exceptionally	Agree	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
1(j)		For an adult with moderate CFS/ME symptoms a referral for specialised care is appropriate….			
	1. as soon as symptoms occur	Disagree	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	2. only after symptoms have persisted for about 4-6 weeks following treatment in primary care	Disagree	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey

		GDG Round 1	GDG Round 2	Wider Group	Discussion
	3. only after symptoms have persisted for about 3-4 months following treatment in primary care	Uncertain	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	4. only after symptoms have persisted for at least 6 months following treatment in primary care	Agree	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	5. never or only very exceptionally	Agree	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
1(k)		For an adult with severe CFS/ME symptoms a referral for specialised care is appropriate….			
	1. as soon as symptoms occur	Uncertain	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
	2. only after symptoms have persisted for about 4-6 weeks following treatment in primary care	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	3. only after symptoms have persisted for about 3-4 months following treatment in primary care	Uncertain	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	4. only after symptoms have persisted for at least 6 months following treatment in primary care	Agree	Agree		
	5. never or only very exceptionally	Agree	Disagree		The interpretation of this statement was discussed at the GDG meeting and subsequently re-rated. The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.

		GDG Round 1	GDG Round 2	Wider Group	Discussion
1(l)		For a child with mild CFS/ME symptoms a referral for specialised care is appropriate….			
	1. as soon as symptoms occur	Disagree	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	2. only after symptoms have persisted for about 4-6 weeks following treatment in primary care	Disagree	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	3. only after symptoms have persisted for about 3-4 months following treatment in primary care	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	4. only after symptoms have persisted for at least 6 months following treatment in primary care	Uncertain	Uncertain	Disagree	GDG was uncertain at round 2, progressed to wider survey
	5. never or only very exceptionally	Agree	Disagree		The interpretation of this statement was discussed at the GDG meeting and subsequently re-rated. The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
1(m)		For a child with moderate CFS/ME symptoms a referral for specialised care is appropriate….			
	1. as soon as symptoms occur	Uncertain	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	2. only after symptoms have persisted for about 4-6 weeks following treatment in primary care	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey

		GDG Round 1	GDG Round 2	Wider Group	Discussion
	3. only after symptoms have persisted for about 3-4 months following treatment in primary care	Uncertain	Agree	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	4. only after symptoms have persisted for at least 6 months following treatment in primary care	Agree	Agree	Disagree	GDG was uncertain at round 2, progressed to wider survey
	5. never or only very exceptionally	Agree	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
1(n)		For a child with severe CFS/ME symptoms a referral for specialised care is appropriate….			
	1. as soon as symptoms occur	Uncertain	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
	2. only after symptoms have persisted for about 4-6 weeks following treatment in primary care	Uncertain	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	3. only after symptoms have persisted for about 3-4 months following treatment in primary care	Agree	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	4. only after symptoms have persisted for at least 6 months following treatment in primary care	Agree	Agree	Disagree	GDG was uncertain at round 2, progressed to wider survey
	5. never or only very exceptionally	Agree	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.

5.3.5 Recommendations

Note: numbers in square brackets are as in the NICE guidelines.

Referral to specialist CFS/ME care [1.5]

Any decision to refer a person to specialist CFS/ME care should be based on their needs, the type, duration, complexity and severity of their symptoms, and the presence of comorbidities. The decision should be made jointly by the person with CFS/ME and the healthcare professional. [1.5.1.1]

Referral to specialist CFS/ME care should be offered:

- within 6 months of presentation to people with mild CFS/ME
- within 3–4 months of presentation to people with moderate CFS/ME symptoms
- immediately to people with severe CFS/ME symptoms. [1.5.1.2]

5.3.6 Deriving recommendations

The GDG found no research evidence on the criteria for or the timing of referral to specialist CFS/ME care. The GDG recognised that the need to intervene early in the course of the illness must be balanced against the effects of a referral for possibly self-limiting symptoms, which raises anxiety and unnecessarily labels the patient. As there was no certainty on the most appropriate time to refer the GDG decided to include these questions in the wider survey. These results were also uncertain.

Referral for specialist advice

The GDG, with advice from the children's expert co-optee,advisors, decided that children should be cared for by a general paediatrician and thus an early referral to general paediatric services was required. This recommendation is in line with the National Service Framework for Children[32] (see http://www.dh.gov.uk). The paediatrician can exclude other illnesses and manage symptoms. Adults may be

cared for by their general practitioner in the first instance unless there is a need for specialist advice on the most appropriate management of symptoms.

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

Transitional care

Transitional care is recognised as a key component of adolescent healthcare as young people move from paediatric to adult services. Most young people make this transition successfully but some adolescents find it more difficult for a number of reasons and this may include young people with chronic illnesses/disabilities.[33]

It is clearly important that there are positive outcomes in the transfer of care yet, whilst there is evidence from young people and parents that transition processes need to be improved, many healthcare professionals are not sure what changes should be implemented in practice.[33]

The literature review by Janet E McDonagh of the evidence base for transition from paediatric to adult services 'Growing Up Ready for Emerging Adulthood'[33] provides examples of transitional models and details the key components of transition. Other useful resources can be found on the Department of Health's website, such as the 'Good Practice Guide Transition: getting it right for young people', 'National Service Framework database of emerging practice', 'Transition - Getting it Right' DVD and additional resources to support service development for transition for young people with long-term health conditions. Please see http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/ChildrenServices/Transitions/fs/en

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

Referral to a multidisciplinary team specialising in CFS/ME

The GDG decided that a referral should be made following a diagnosis. However, this may be a provisional rather than a definitive diagnosis. The view of the GDG was that 3–6 weeks following the onset of symptoms was generally too short a time but that 6 months was 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 multidisciplinary team specialising in CFS/ME. However, the timing needed to be based on individual circumstances, as people with severe symptoms needed to be referred immediately.

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

5.4 A conceptual framework for patients, carers and healthcare professionals when making a diagnosis of CFS/ME

Different people hold different beliefs about the underlying causes of CFS/ME based on the available evidence and their personal experience of living with or caring for this condition. It is unclear whether CFS/ME is one condition or part of a spectrum of similar conditions that have overlapping features. The current debate about the causes and definition of CFS/ME has generated a need for further well-designed research, focusing on key areas; for example, how do the symptoms of CFS/ME originate and develop? What are the best ways of subgrouping patients to aid in diagnosis and management? What are the predisposing, precipitating and perpetuating factors in CFS/ME?

As the Gibson Inquiry report made clear, the available evidence is very limited: 'although there are many theories as to its cause or causes, none have been proven beyond reasonable doubt', and 'research has been undertaken which offered tantalizing glimpses of abnormalities in sufferers but thus far no specific causal factor has been established'.[2]

The range of views held by different people about the causes of CFS/ME were reflected in the views held by members of the GDG. Consideration of the causes of CFS/ME was outside the scope of the guideline, and the aim of the GDG was to reach consensus on practical clinical management in order to improve the care of people with CFS/ME. In working towards this aim, the GDG adopted the following approach, which may also be helpful to healthcare professionals caring for people with CFS/ME.

- Recognition of the limitations of available evidence about the underlying cause(s) of CFS/ME.
- Avoidance of dogmatic belief in a particular view.

- Encouragement of further appropriate research to identify causative factors and hence further effective treatments and therapeutic approaches.

- Adoption of a patient-centred approach that fosters a mutual respect between patients/carers and healthcare professionals as people. Respect is given to others' views in a patient-centred approach where shared decision-making about treatment plans can occur, and personal views or beliefs are not allowed to impede any individual's access to care and support.

6 Management

6.1 Introduction

The GDG was clear that there must be an integrated approach to the management of care for the individual with CFS/ME. There needs to be good communication and regular contact between the healthcare professional and the individual. The healthcare professional should use their clinical judgement to tailor the investigations and interventions required to individual need.

As there are many different symptoms that may concern the patient or the healthcare professional, the healthcare professional needs to have an appropriate level of training in CFS/ME, to avoid over- or underinvestigation of these symptoms.

Complex cases of CFS/ME are common and many patients will be seen by a large number of healthcare professionals. This can lead to unnecessary duplication of investigations and fragmentation of ongoing care. To avoid this, one named clinician should have responsibility for coordinating care for a person with CFS/ME.

There was one key clinical question for this chapter and the evidence and resulting recommendations are presented in four sections: CBT, GET, activity management and other therapeutic interventions (section 6.3); pharmacological interventions (section 6.4); dietary interventions and supplements (section 6.5); and complementary therapies (section 6.6).

6.2 Key clinical question 3 and subquestion 3

Does the evidence show that any particular intervention or combination of interventions is effective in treatment, management or rehabilitation of people with a diagnosis of CFS/ME?

(Subquestion: In people presenting with early suspected CFS/ME what interventions might be effective in preventing progression to CFS/ME?)

6.3 CBT, GET, activity management and other therapeutic interventions

6.3.1 Introduction

It is recognised that patients would access the expertise of the appropriate healthcare professional for advice and support, but the GDG considered that patients should take the lead on any intervention(s) to manage their CFS/ME. The objectives of any programme must be agreed with the patient. They should understand the aims and objectives, and be willing to take part. The suitability, preference, ordering and timing of interventions should be discussed and this may be an iterative process. It was noted that individuals are likely to need staged interventions, where increases in either the severity or complexity of symptoms trigger the use of different interventions or different intensities of intervention (either a reduction – see the section on setbacks/relapses, or an increase – for example the pharmacological treatment of symptoms), as appropriate.

In this guideline, the GDG has used specific definitions of the different therapeutic interventions, and these have been included in the recommendations. Because of the complex nature of these therapies, the GDG considered that some additional information and descriptions would also help the healthcare professionals responsible for delivering these interventions or involved in the care of people accessing them. Such descriptions have been included in the following sections; for a more complete list, please refer to the Glossary.

6.3.1.1 Cognitive behavioural therapy (CBT)

CBT is a specific psychological therapy, based on underlying theoretical principles, with a broad evidence base across a variety of conditions. CBT as recommended for use with people with CFS/ME is described in detail in the recommendations.

CBT is an evidence-based therapy for CFS/ME. It is a collaborative approach that aims to reduce the levels of symptoms, disability and distress associated with CFS/ME. CBT or psychological approaches to CFS/ME do not imply that symptoms are psychological, 'made up' or in the patient's head. CBT is used as part of the overall management for many conditions, including cardiac rehabilitation, diabetes and chronic pain.

6.3.1.2 Graded exercise therapy (GET)

GET is an evidence-based professionally mediated approach to CFS/ME involving appropriate physical assessment, mutually negotiated and meaningful goal-setting and education. An achievable baseline of physical activity is agreed, followed by individually tailored and planned increases in the duration of exercise. This is followed in turn by an increase in intensity when the patient is able, taking into account their preferences and objectives, current activity patterns, sleep, setbacks/relapses and other factors, with the objective of improving symptoms and functioning.

Assessment before beginning a GET programme

An appropriate assessment will include the patient's history, activity patterns, symptom patterns, functional capacity, sleep patterns, medication and current physical capacity, and other factors as appropriate.

Physical capacity can be determined by a simple, global measure such as a walking test or sit-to-stand test, alongside measures of heart rate and perceived exertion. To avoid triggering post-exertional symptoms, a detailed, strenuous or lengthy physical assessment of range of movement, aerobic fitness or strength should be avoided.

Goals of a GET programme

In clinical trials the ultimate goal of GET that showed benefit was to achieve and maintain 30 minutes of moderate aerobic exercise 5 days out of 7 (for example, a brisk walk). In clinical practice, patient-centred goals should be developed

(which may be less or more than those used in the clinical trials). Through discussion, it should be agreed how this could be achieved in everyday life, according to the patient's individual circumstances and physical ability: for example, a 2 x 15 minutes daily brisk walk to the shop, or a return to some previous active hobby, such as cycling or gardening.

It is important to note that while this is the ultimate (long-term) goal of the GET programme, the patient will not start their programme at this level. The first short-term goal may be gentle stretching or a small, slow walk which (for those that are able) is gradually increased to 30 minutes.

Person centredness

Some patients with CFS/ME report that exercise programmes have been applied inflexibly at times, without consideration of individual circumstances and goals, sometimes with significant adverse responses. Inevitably, patients can feel at a great disadvantage if they are not in control of the programme, their goals and their rate of progression. It is essential that agreement and negotiation are at the very centre of a GET programme, forming a cornerstone at every stage, so that patients feel in control of the activity and their rates of progression.

Healthcare professionals delivering a GET programme should do so with a degree of caution, recognising that for many patients with CFS/ME, GET can cause an increase in symptoms which can be distressing.

Important differences between GET and a general exercise programme

GET is a structured, mutually developed and monitored programme that plans gradual increments of exercise or physical activity, using a specific method shown to be successful for patients with CFS/ME in published research. This is in contrast to a general exercise programme involving simply 'going to the gym' or 'just getting walking a bit more', or perhaps 'swimming a few lengths every day'.

What makes GET different from a general exercise programme is the delivery by and liaison with a trained professional (such as a physiotherapist), activity analysis before starting the programme, and mutually agreed starting points and progression.

A GET programme is delivered in partnership with the patient, and after a thorough assessment of current daily activity. It would not be appropriate, for example, for a patient to undertake a GET programme involving swimming if they cannot get up and get dressed every day. The start to their programme is likely to involve a physical functional task involving personal care, for example, or gentle stretches. A ***GET*** programme, as described in the guideline recommendations [1.6.2.11-21], is evidence based for ambulant people with mild or moderate symptoms of CFS/ME and has been shown to be of benefit; a ***general exercise programme*** is not evidence based for this patient population and can do patients more harm than good.

Unsuccessful general exercise programmes, perhaps undertaken independently by the patient, or under brief advice from professionals not adequately trained in the use of GET, are often begun at a high, unachievable level, with an inappropriately rapid rate of progression, or without adequate professional supervision or support. An unstructured and poorly monitored or progressed exercise programme can cause significant symptom exacerbation, and can arguably make CFS/ME worse.

GET for people with severe CFS/ME

The research trials of GET reviewed in this guideline recruited mainly ambulant participants, with few, if any, people with severe CFS/ME. However, in clinical practice, elements of GET are commonly used successfully in this patient group, such as a gradual increase in gentle walking, or gentle stretches. However, some patients report that they have significant reservations about exercise (aerobic exercise in particular) and that exercise can significantly adversely affect their symptoms and function. It is unlikely that patients with severe CFS/ME will

be undertaking aerobic exercise, although they may be able to start the non-aerobic component of the GET programme (such as gentle stretches). If they reach the stage at which aerobic exercise is added to a programme, it is likely that they will now be classified as having moderate or mild CFS/ME.

Activity management strategies (as described in the recommendations) may be an appropriate initial choice of management for people who have severe CFS/ME, or those who do not wish to participate in a GET programme. However, it should be noted that activity management also is not supported by research evidence for people who have severe CFS/ME, but is recommended by expert clinicians. GET may be an appropriate addition to activity management if and when a patient wishes to, or feels ready and able to, further develop their physical capacity and functioning.

*6.3.1.3 **Activity management***

Activity management is a person-centred, collaborative approach to managing symptoms. It is goal directed and promotes the skills of activity grading and analysis to enable patients to improve and/or maintain their function and sense of well-being in self-care, work and leisure roles.

Activity management is the approach that many therapists adopt for those with severe or moderate CFS/ME, and indeed it teaches skills for life to those moving towards a return to work and higher levels of productivity. Patients should have ongoing access to and contact with therapists who use this (and any of the other approaches), such as community rehabilitation teams, occupational therapists, physiotherapists and rehabilitation care assistants. Ideally, patients should be able to refer themselves for 'top-up' sessions should life demands make it necessary.

*6.3.1.4 **Pacing***

Pacing is a self-management approach, drawing on some concepts used in activity management, which many patients have reported helpful. However, there is currently no research evidence to support its use, or to determine

whether it is beneficial overall. There are several definitions of pacing and the definition as used in this guideline can be found in the Glossary.

*6.3.1.5 **Sleep management***

This includes techniques such as sleep hygiene, which uses behavioural approaches, and changes in environmental conditions which can be introduced to improve the quality of sleep.

*6.3.1.6 **Relaxation***

Relaxation is described as a state characterised by a reduction in physical and mental arousal, leading to feelings of peace, and release from tension and anxiety. Achieving it often requires practice but it can be a helpful strategy for people with CFS/ME.

Relaxation training and memory aids such as organisers and written resource manuals may also be helpful for addressing cognitive problems.

*6.3.1.7 **Management of setbacks/relapses***

People with CFS/ME have variations in the severity of their symptoms and will experience setbacks/relapses or transient increases in fatigue and other symptoms. These setbacks/relapses can vary significantly in their duration and severity, being anything from a slight reduction in function through to severe symptoms resulting in significant disability.

Setbacks/relapses are to be expected as part of the normal course of CFS/ME. With effective management, the frequency, severity and duration of setbacks/relapses should reduce.

Setbacks/relapses appear to be caused by different things; triggers can include, for example, sleep disturbance, overactivity, stress or an active infection (such as a common cold). However, it may not always be possible to identify a cause.

Advice on managing setbacks/relapses may vary according to the cause. For example, it may be advisable to maintain an exercise programme, in agreement

with the patient, if stress has been a causative factor, but not if there is an active infection. Difficulty may arise in distinguishing symptoms caused by CFS/ME from those of an active infection, as such symptoms are often similar (for example, increased fatigue, myalgia, headache, sore throat). In this situation, measurable evidence can be helpful (such as taking temperature with a thermometer, evidence of sputum). If an active infection is present, a different approach would then be used.

*6.3.1.8 **Use of equipment and adaptations***

Although many patients with CFS/ME require equipment or adaptations at times for a limited period, others may need to use them in the longer term. Ongoing assessment is needed to ensure that any risks associated with prolonged, inappropriate use of equipment or adaptations are reduced.

6.3.2 Evidence statements

Clinical effectiveness evidence statements

6.3.2.1 ***Cognitive behavioural therapy is effective in adults and has been shown to reduce symptoms, improve function and improve quality of life (Evidence level 1+)***

6.3.2.2 ***Such evidence that is available in children indicates cognitive behavioural therapy is effective in improving physical function, fatigue, school attendance and symptoms (Evidence level 1+)***

6.3.2.3 ***Five trials investigating incremental physical exercise programmes showed improvements in adults in various health outcomes including mental and physical fatigue, global improvement, disability, sleep, mood and cognition (Evidence level 1+)***

6.3.2.4 ***Two trials investigating incremental activity programmes showed improvements in adults in various health outcomes including all of the outcomes listed. (Evidence level 2)***

6.3.2.5 ***Trials used different approaches to incremental physical activity including graded exercise, graded activity and pacing, individually and in combination. It is unclear whether one has a greater beneficial effect than another. (Evidence level 2)***

Cost effectiveness evidence statements

6.3.2.6 ***The only estimate of cost effectiveness suggests the cost per quality-adjusted life year (QALY) of CBT for people with CFS/ME relative to no-protocol medicine to be £16,036. This estimate includes costs from a NHS perspective.***

6.3.2.7 ***Evidence suggests that treatment effects of interventions for CFS/ME are incurred over a longer period of time than the follow-up of 14 months, as evaluated in one trial. Although it was decided to not extrapolate on methodological grounds, it can be assumed that if some benefit was maintained to a time horizon of 5 years, the cost per QALY will fall.***

6.3.2.8 ***There is insufficient evidence to suggest that group CBT is cost effective relative to individual CBT.***

6.3.2.9 ***No studies were identified dealing with the cost effectiveness of long courses of CBT relative to short courses.***

6.3.2.10 ***Computerised cognitive behavioural therapy is cost effective in other areas of medicine. There is no evidence regarding the generalisability of this result to CFS/ME.***

6.3.3 Clinical evidence summary

6.3.3.1 ***Summary of evidence presented in Appendix 1***

Adults

Ten RCTs met the inclusion criteria for assessment of CBT or modified CBT in people diagnosed with CFS according to one of the recognised case definitions; one also included people with postviral fatigue syndrome. Validity scores (see

Appendix 1) for these studies ranged from 1 to 18, with four studies scoring > 13. Comparators differed among studies: CBT was compared to routine medical care in four studies, to relaxation in two studies, to guided support in one study and to leukocyte injections and controls in another study. One study had a sample size of n = 270, the others had sample sizes of < 60.

Eight of the studies reported beneficial effects of CBT on physical functioning, fatigue and global improvement. Two studies with low validity scores (1 and 3 respectively) showed no significant difference.

Six studies of other regimes with either mixed methods or behavioural interventions were reviewed. Only one was a high-quality RCT and this study of multiple symptom-based interventions (including supplements) found significant improvements in favour of the treatment group in symptom scores. However, in such studies it is difficult to determine which interventions are responsible for the observed effects.

Graded exercise therapy

Five RCTs were reviewed which assessed the effects of GET in patients with CFS. Sample sizes ranged from 49 to 148. Validity scores ranged from 9 (two studies) to 17 (three studies). Significant improvements in measures of fatigue and physical function were found in all five RCTs. When exercise was combined with fluoxetine there was no additional effect.

Children

One controlled trial of rehabilitation/CBT in children reported significant improvements in the treatment group in measures of global well-being.

6.3.3.2 Additional clinical evidence

Expert Patient Programme

The Expert Patient Programme (EPP) was introduced into the NHS in 2001. It provides an opportunity for patients with chronic long-term conditions to develop

new skills to manage their condition on a day-to-day basis through participation in generic lay-led group workshops. Information is available at http://www.expertpatients.nhs.uk/index.aspx

The CFS/ME Service Investment Programme 2004–2006 received mixed feedback regarding the suitability of the EPP for CFS/ME patients.[34] The results of the feedback identified important considerations in using EPP in a CFS/ME context and also noted significant disadvantages of the programme in a CFS/ME setting.{1171] There was general support within the GDG for the use of such programmes, when delivered appropriately, to help people with mild or moderate CFS/ME to manage their symptoms. However, there was less support for the use of peer support programmes for people with severe CFS/ME.

Update of evidence following the systematic review

An update search of evidence on treatments for CFS/ME published following the original review produced five new studies that met the inclusion criteria. A systematic review of interventions for CFS/ME{215}, which searched only PsychInfo and Medline and failed to describe the quality assessment criteria, concluded that CBT generally appeared to be effective. RCTs evaluating GET were also found to have an overall beneficial effect on fatigue and functional work capacity.

Group CBT was compared to education and support and standard medical care in one RCT (n = 153). The authors concluded that 'group CBT did not achieve the expected change in the primary outcomes (SF-36 physical and mental health) but significant improvements were seen in fatigue, mood, and physical fitness'.[35]

A small RCT[36] (n = 47) evaluated the impact of a community-based programme consisting of an illness management group and one-to-one peer counselling. Significant gains were observed for programme participants across all categories – interpersonal, energy, material, work, well-being and mastery resources. The

sample size and subjectivity of the assessment tools limit the generalisability of this study.

6.3.4 Health economics evidence summary

6.3.4.1 Introduction

The clinical benefits of interventions for CFS/ME have been shown in a number of papers (please find detailed descriptions in Appendix 1). The precise nature of the trial design used to evaluate these interventions is of importance but there is little doubt that there are interventions that can improve quality of life. These interventions can be costly, often involving input from more than one member of a multidisciplinary team. A full literature search was undertaken to appraise the volume and quality of the available cost-effectiveness studies.

6.3.4.2 Initial search results

The cost-effectiveness literature search yielded 60 unique records. The abstracts were reviewed, three papers were ordered and their results were extracted. All were cost-effectiveness studies, cost–utility studies or cost–consequence studies, written in English and dealing with interventions regularly used for CFS/ME. Two of the papers primarily considered patients with chronic fatigue rather than CFS/ME. Using the CDC 1994 criteria[28], the proportion of the chronic fatigue population with CFS/ME in these studies was 28% and 29%. The extent to which these studies can be extended to a CFS/ME population is discussed at a later point. All three papers were based on published clinical trials. Some information about the interventions is provided in this section and these details should be considered as a summary of the more detailed analysis in the systematic review.

A Dutch study (Severens et al.[37]) looked at the cost effectiveness of CBT for CFS/ME patients. The analysis was based on a trial where patients were randomly assigned to CBT, guided support groups (SGs) or a no protocol-based intervention in primary care.[38] The authors collected cost and quality of life (QoL)

data at baseline, after the 8-month treatment period and at follow-up, 6 months after discontinuation of treatment. QoL was measured using a EuroQol questionnaire. It should be noted, however, that there was a difference in the groups at baseline (0.486 for the CBT group and 0.526 for the control, no p value stated). Please refer to Table 2 for details. There does not appear to have been any attempt to correct for this difference between comparison groups, and this may have led to bias in the analysis. Sensitivity analysis was carried out to test the robustness of the result when the incremental health gain is reduced. Please refer to Section 6.3.5.4 for details.

In the paper, the costs collected were associated with the following: GP care, medical specialist CFS/ME care, physiotherapy, psychology and alternative care provision. The authors noted immediately that the QoL of patients in the SGs was lower than in the no protocol-based intervention group (no p value stated). Since the costs in the former exceeded those in the latter, it was dominated and hence excluded from the rest of the economic evaluation.

Table 2 The results from the Severens study[37] (costs in 1998 Euros)

Intervention	QoL (Intake)	QoL (8 mths)	Costs (0–8 mths)	QoL (14 mths)	Costs (0–14 mths)
CBT	0.4859	0.5817	€2076	0.6014	€2534
No protocol	0.5257	0.5779	€839	0.5999	€1504
Difference (CBT – no protocol)	–0.0398	0.0038	€1648	0.0015	€1030

Using these data, the authors estimated that the cost per QALY relating to a perspective comprising: (1) a protocol-based treatment costs; (2) treatment costs, other medical costs and patients costs; and (3) these costs plus productivity costs were €60,108, €51,642 and €21,375 respectively. It should be noted that there was a high degree of uncertainty around the ICER (incremental cost-effectiveness ratio) in non-parametric bootstrapping analysis for varying willingness-to-pay thresholds.

Conventional NICE methodology suggests interventions should be viewed from the perspective of the NHS and personal social services. For the reported resource use, NHS specific items were identified and priced to meet the NICE methodology standard. Using the reported QALY differences at 14 months, the baseline result amounts to £16,036 per QALY. The costing of the study to meet NICE standard will be described in detail in Section 6.3.5.

The second paper was a UK study that looked at the cost effectiveness of CBT, graded exercise and usual care for patients with fatigue in primary care.[39] Again, this paper was based on a published clinical trial.[40] However, the study population was patients with chronic fatigue, of which only a proportion (29%) fulfilled the CDC criteria and thus were CFS/ME patients. It has to be borne in mind that results from this paper are not readily generalisable from chronic fatigue patients to CFS/ME patients, and data on the CFS subgroup were underpowered.[40]

The paper reported that:

'consenting patients were randomized to six sessions of CBT or GET. Sessions each lasted 45 min. CBT was delivered by trained cognitive behavioural therapists and included an initial assessment, activity planning, homework and establishing a sleep routine. The aim of the CBT was to enable patients to address negative beliefs regarding symptoms, self-expectations and self-esteem. GET was tailored to each patient's physical capacity and aimed for a gradual increase in aerobic activities, especially walking, and was delivered by physiotherapists.'

The employed effectiveness data from the clinical trial[40] demonstrated a reduction in fatigue in 41 (79%) patients receiving CBT, compared to 35 (71%) patients in the GET arm. For fatigue patients, the cost-effectiveness study estimated that the incremental cost of CBT relative to GET was £519 at baseline (90% CI –£814 to £1904, p = 0.522). However, at follow-up, CBT resulted in a net saving of –£193 (90% CI –£946 to £458, p = 0.62). The authors note that

costs and outcomes of CBT and GET were similar, although if values were placed on outcomes, CBT showed improved cost effectiveness.

On the basis of cost-effectiveness acceptability curve analysis, CBT appeared to be more cost effective. For cost-effectiveness studies, the uncertainty reflected in clinical effectiveness papers by statistical significance is replaced with cost-effectiveness acceptability curves. To allow inter-procedural comparison, it is preferable for a cost-effectiveness study to use a generic measurement of outcome with some suggested valuation of an incremental outcome such as a QALY). However, this paper illustrates the probability of the intervention being cost effective based on the valuation of an incremental improvement in the Chalder fatigue scale. For example, the authors estimated that a societal valuation of a four-point improvement of £5000 would mean that there is a 76.6% probability of CBT being cost effective relative to GET for patients with chronic fatigue.

As mentioned above, a CFS/ME subgroup analysis of the trial on which this cost-effectiveness analysis was based could not be carried out due to lack of power, and conclusions from fatigue patients could not be transferred to the CFS/ME population. Despite this, the trial paper reported consistency with other evidence, showing a trend for 'CBT to have a slight advantage, particularly in the group with CFS'.

Lastly, the literature search identified a UK cost–consequence study which looked at the effect of CBT and counselling in primary care[41] and was based on the results of a clinical trial.[42] Again, the study population was a chronic fatigue population, of which only a proportion were CFS/ME patients (28%). The clinical paper did not provide adequate subgroup analysis for those in the trial meeting 1994 CDC criteria.[28]

Therefore, if costs of CBT or counselling in a CFS/ME population are not generalisable from chronic fatigue patients, cost-effectiveness conclusions for CFS/ME patients cannot be reached.

For the general fatigue population, the paper found that a comparison of change scores between baseline and 6-month assessment revealed no statistically significant differences between the groups receiving CBT and counselling in terms of aggregate healthcare costs, patient and family costs or incremental cost effectiveness (cost per unit of improvement on the fatigue score).

6.3.5 Further work after the presentation of results

The GDG considered that the papers dealing primarily with people with chronic fatigue rather than CFS/ME were only of use as background material and results could not be generalised to CFS/ME patients. The group also considered that the timescale employed by the authors in the Dutch paper (Severens et al.[37]) was insufficient to show the full benefits and extending the timescale was considered.

*6.3.5.1 **Extending the timescale of the Dutch study***

The Dutch economic evaluation[37] looked at the costs and benefits of CBT and guided support groups relative to the natural course over 8 months of treatment and 6 months of follow-up. There is evidence suggesting that for some patients, the benefit of CBT can extend beyond that, and up to 5 years. Deale and colleagues reported that 68% of patients receiving CBT rated themselves as 'much improved' or 'very much improved' at a 5-year follow-up relative to 36% who received relaxation therapy.[43]

The implicit assumption in Severens and colleagues'[37] selection of a 14-month timescale is that the costs and benefits beyond this period return to baseline. The GDG considered that, while both benefits and costs of treatment would be skewed towards the earlier periods, costs would be more so. Assuming that people receiving CBT gain an improvement in utility compared to exercise therapy, and assuming that this can be generalised to the relaxation comparator used by Deale and colleagues,[43] maintaining some of the utility gain for a longer period will improve the cost effectiveness of CBT. However, the potential bias posed by the differences in comparison groups for the utility outcome variable at baseline led to the decision that an extrapolations over longer time periods was

not sufficiently supported. This is in agreement with Severens and colleagues, who state in their paper that extrapolation over time "was invalid due to [a] lack of understanding between CFS and health state valuation".[37]

*6.3.5.2 **Costing of the Dutch study to meet NICE methodology standards***

As stated earlier, the Dutch study[37] reported incremental costs per QALY from a treatment protocol, treatment plus patient cost and societal perspective (please see Section 6.3.4.2). In order to meet NICE methodology standards, it was decided to use 2006 NHS prices to match the reported resource use from the trial. This helped to subsequently anticipate the cost effectiveness of CBT in a UK setting.

The paper subdivides costs over the 14 months to those occurring in the treatment period and those occurring during the follow-up period. The costs, together with the effectiveness results of this study, are shown in Table 2. From the original costs presented in this table can be seen that during the intervention period of the first 8 months, there were higher costs in the treatment group than in the 'no protocol' comparison group. Meanwhile, the reported resource use in the follow up period in months 8-14 showed that people who had received CBT had lower service use uptake and referrals than the no protocol group. Thus, some of the treatment costs can be expected to be offset by lower follow-up care costs.

For the cost adjustment to a UK NHS perspective, we used 2006 reference costs for Health and Social Care [44], in accordance with NICE methodology. The results of the costing is presented in Table 3.

Table 3 Costing results using resource uses reported that reflect the NHS perspective

	CBT 0-8 mths	CBT 0-14 mths	NP 0-8 mths	NP 0-14 mths
CBT therapy	£832.00	£832.00	n/a	n/a
GP	£31.20	£55.20	£52.80	£86.40
Medical specialist	£49.20	£73.80	£86.10	£159.90
Physiotherapist	£49.00	£115.50	£129.50	£231.00
Psychologist	£33.00	£33.00	£85.80	£184.80
Total (0-8 months)	£994.40		£354.20	
Total (0-14 months)		£1,109.50		£662.10
Difference (∆ 0-14mths)				*£447.40*

Table 3 shows the health services used by CFS patients during the treatment period (0-8 months) and during the treatment period and follow up (0-14) in 2006 Pound Sterling from an NHS perspective. The results shown in Table 3 reflect the study finding of cost savings during follow up for CBT patients offsetting some of the initial CBT treatment costs. The cost difference in the treatment period (£640.20) is higher than the cost difference, that is, the increment, over the entire study period (£447.40).

The NHS perspective excluded some of the trial protocol costs, and although unlikely, may not include cost items that would be included in this perspective. Deterministic sensitivity analysis has been carried out to anticipate the level of uncertainty surrounding the incremental cost figure used. Please see Section 6.3.5.3 for details.

With the costs adjusted to a UK perspective, costs were combined with the Dutch study's effectiveness results to present an ICER. Table 4 summarises the results of the costing and effectiveness data, while Table 5 presents the incremental cost effectiveness ratio based on these figures.

Table 4: Combining UK costing results with Severens paper[37] utility scores

	CBT Costing results	CBT Reported utility gain	NP Costing results	NP Reported Utility gain
Total study period (0-14 months)	£1,109.50	0.0737	£662.10	0.0458

The estimate of the incremental cost effectiveness ratio of £16,036 per QALY comparing CBT with no protocol presented in Table 5 lies below the £20-30,000 per QALY willingness to pay threshold and would therefore be considered cost effective.

Table 5: Incremental analysis using UK costing results and utility scores Severens paper[37]

	Cost	Utility	ICERs
NHS cost increment CBT-NC	£447.40		
Severens utility increment		0.02790	£16,035.84

As stated in section 6.3.4.2, there are some serious concerns regarding the difference at baseline utility, and additional sensitivity analysis was carried out. Please see section 6.3.5.4 for details and results.

6.3.5.3 Sensitivity of the ICER estimate to changes in incremental costs

Table 6: Sensitivity analysis for varying incremental cost for CBT compared with no protocol

	Incremental cost	Incremental effectiveness	ICERs
Varied costs CBT-NC	£20.00		
Severens utility increment		0.02790	£716.85
Varied costs CBT-NC	£200.00		
Severens utility increment		0.02790	£7,168.46
Varied costs CBT-NC	£400.00		
Severens utility increment		0.02790	£14,336.92
Varied costs CBT-NC	£600.00		
Severens utility increment		0.02790	£21,505.38
Varied costs CBT-NC	£800.00		
Severens utility increment		0.02790	£28,673.84
Varied costs CBT-NC	£1,000.00		
Severens utility increment		0.02790	£35,842.29

One-way sensitivity analysis shows that the ICER is not highly sensitive to changes in costs for a care programme containing CBT. If the incremental costs for CBT were increased to almost double (to £800), while keeping all other parameters constant, the cost effectiveness estimate then is £28,674 per QALY.

6.3.5.4 Sensitivity of the result to changes in utility gain

As stated in previous sections, there is a significant difference in baseline QoL between the groups, with the CBT group reporting a lower value than the no-protocol group. This uncontrolled source of bias can result in false treatment effects through regression to the mean effect.

In order to anticipate the magnitude of uncertainty, we conducted some basic sensitivity analysis. It should be noted that although there are methods to adjust for differences in baseline utilities, that is, regression based techniques[45], such adjustment was not undertaken in this analysis.

Table 7 presents the results for the sensitivity analysis carried out to anticipate uncertainty surrounding the ICER for CBT compared to no protocol by means of utility gain value changes. It has not been possible to carry out regression based sensitivity analysis using covariates as we did not have access to the trial data. Therefore we resorted to other methods for a deterministic, one way sensitivity analysis.

Table 7: Results from sensitivity analyses (SA) A and B for changes in utility gain

SA-A	Cost	Utility	ICERs
Increm. costs (NHS persp.)	£447.40		
Changes in utility gain:			
75% utility gain		0.020925	£21,381.12
50% utility gain		0.01395	£32,071.68
25% utility gain		0.006975	£64,143.37
SA-B			
£CBT-£NC	£447.40		
Util(CBT)-Util(NC)		0.012950	£34,548.26
After averaging difference in baseline		0.001579	£283,420.81

As it has not been possible to correct for a potential bias, for univariate sensitivity analysis A (SA-A), the reported utility gain was reduced to 75%, 50% and 25% of its original value. For sensitivity analysis B (SA-B) the areas under the curve were calculated using the reported baseline values, as well as an averaged baseline. The area under the curve calculation may not be a valid attempt to correct, however, it resulted in very small differences in QALY gains and therefore shows how sensitive the result to variations in utility gain is. Moreover, graphs illustrated how the difference at baseline affects the areas under the curves, particularly since they become almost identical at 8 and 14 months follow up.

Sensitivity analyses A and B yielded new sets of utility values, which are displayed in Table 7 and were, together with the NHS perspective costs (Section 6.3.5.3) used to calculate new ICERs. In sensitivity analysis A, the ICER is below £25,000 at the lower utility value. If the sensivity analysis is changed to a reduction of utility gain by 50%, CBT is at £32,071 per QALY less likely to be still cost effective. If the increment in utility is reduced to 25% of its present value, CBT does not appear cost effective (£64,143 per QALY).

Sensitivity analysis B shows that the area under the curve calculation leads to CBT being unlikely to be cost effective with £34,548 per QALY. When the baseline difference is equalised, the ICER shoots up to £283,421. This emphasises the importance of correcting for differences at baseline for future guideline updates as regression to mean effect could have a significant impact on the cost effectiveness result.

As stated previously, there is some indication that if any effect of treatment endures in a subset of the population for up to 5 years, the estimates of cost effectiveness in Severens[37] are possibly too low, however, it is not possible to quantify these.

6.3.5.5 Is group CBT cost effective relative to education and support and standard medical care?

The GDG felt it would be worthwhile exploring the issue of group CBT. A 12-month follow-up study with 153 participants looked at this area.[35] The study was based in the health psychology department of a general hospital and compared group CBT, education and support (EAS), and standard medical care (SMC). The CBT programme was designed to *'attempt to modify thoughts, beliefs and behavioural responses to symptoms and illness with a view to increasing adaptive coping strategies'.* The authors give four key areas of therapy.

The key elements of group CBT highlighted by the authors were,

- 'Elucidation of core beliefs about their illness and its management

- Monitoring of activity levels and introduction of appropriate aerobic, strength and stretching exercises designed to increase fitness, balance and confidence in exercise

- Behavioural modification of sleep patterns and mood management advice

- Goal setting'[35]

The EAS group was included to allow for the effect of receiving a therapy per se and for the cost of the time of the therapist. Both group CBT and EAS were delivered by the same therapists, to cohorts of between 8 and 12 individuals in a series of 8 fortnightly meetings, each lasting 2 hours.

The group CBT intervention branch had statistically significantly higher SF36 scores ($p = 0.019$) and lower fatigue scores ($p = 0.027$), and were able to walk faster as measured by shuttle walking ($p = 0.0013$) relative to the SMC group. Relative to the EAS group, the group CBT patients walked faster and were less fatigued ($p = 0.047$ and $p = 0.011$ respectively). The lack of a statistically significant difference in SF36 scores between EAS and group CBT could be due to the effect of CBT being somewhat diluted by the use of larger groups.

There were severe limitations, and reported data relating to cost effectiveness are based on poor quality. Incremental cost-effectiveness ratios (ICERs) were not reported because there was no difference in utility. In addition, the study was underpowered to detect significant differences in costs for performing a cost minimisation analysis. The alternative to cost minimisation analysis would be to use the bootstrapping technique to obtain a cost-effectiveness acceptability curve (CEAC). However, the authors of the study deemed this approach unsuitable since 'the data quality does not justify the application of sophisticated statistical techniques'.

Therefore conclusions regarding recommendations on group CBT in relation to EAS and SMC cannot be drawn, and conclusive comparisons between group CBT and individual CBT require further research.

6.3.5.6 Cost effectiveness of differing quantities of CBT contact time

As suggested by the GDG, CBT is usually performed over around 12 sessions. However, two trials look at the effect of CBT performed over only 6 sessions.[40;46] As described previously, Ridsdale[40] did find considerably poorer outcomes from 6 sessions of CBT in people with CFS/ME than in those with general chronic fatigue. However, in people with CFS/ME, fatigue scores still fell by 26% on Chalder's fatigue scale. The cost-effectiveness issue is whether the additional benefit gained by extending CBT from 6 to 12 or more sessions is a good use of resources.

No papers were identified comparing different lengths of CBT courses. Therefore, comparison between studies was necessary. To compare shorter and longer courses of CBT, studies containing the same outcome measures are needed. If there is a common outcome measure between a paper looking at a short course, and one looking at a relatively long course, incremental cost-effectiveness analysis can be undertaken. However, the measurement of outcomes in CFS/ME is variable and there was no outcome measure common to papers covering short and long regimes. As with any clinical decision, it is important to constantly appraise progress and expectations of the programme. Thus, if clinician and patient feel that a short course has proven adequate, and further CBT is likely to be of little extra value, the cost of extending therapy should be taken into account.

6.3.5.7 Cost effectiveness of computerised cognitive behavioural therapy in CFS/ME

There were no identified papers looking at the cost effectiveness of this approach in CFS/ME. Previous NICE technology appraisal guidance deals with the use of computerised cognitive behavioural therapy (CCBT) for depression and anxiety (see www.nice.org.uk/TA097).[47]

It should be noted that this appraisal deals with a very different issue. However, in the absence of evidence in a CFS/ME population, the GDG considered the costing and efficacy data from the assessment report as background information.

The Assessment Group for the appraisal developed a decision-analytic model, looking at three specific CCBT products for depression. Since the interventions are not designed for a condition comparable to CFS/ME, the differences between the interventions are not relevant. What is potentially noteworthy is the range of costs of adopting these strategies. The Assessment Group identified costs in the following areas: licence fees, computer hardware, screening of patients for suitability, clinical support, capital overheads and training of staff. The incremental cost of supplying CCBT was £40 (£397 compared to £357 for 'treatment as usual'). It should be noted that the cost of 1 hour of healthcare provider time is significant. If there is a benefit in providing these computerised services, it might be viable to replace a small section of CBT time with ongoing CCBT support.

The QALY gains through CCBT reported in this appraisal are not of significant interest for this CFS/ME discussion since they refer to a wholly different patient group. However, for information, the assessment report suggests a gain of 0.032 QALYs per individual. If the incremental cost is assumed to generalise to a CFS/ME patient group, and a societal willingness to pay of £20 000 is assumed, the QALY gain required is 40/20,000 = 0.002.

Thus, in so far as the costs and outcomes are generalisable, the evidence suggests that CCBT is cost effective relative to no CCBT.

6.3.6 Clinical scenario questionnaire to GDG and wider group

So that consistent principles were applied in rating the evidence statements, the GDG and the wider survey group assumed the following.

1. The person with CFS/ME and healthcare professionals involved in their care will make decisions in partnership. These are directed by the patient's

personal preferences and build on the existing experience and skills of the professional.

2. All treatments are offered allowing the person with CFS/ME to refuse without compromising the further therapeutic relationship.

3. There is a good rapport in which the patient and their families/carers feel believed and validated.

4. Treatment is provided by the NHS in the context of availability of adequate numbers of competent, appropriately trained healthcare professionals.

5. Minimal waiting times for good-quality services are adhered to.

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
3(a)		**A programme consisting of a planned increases of aerobic exercise is appropriate….**	**A programme consisting of increases of aerobic exercise (i.e. exercise which increases the pulse rate) is appropriate….**		Question changed and re-rated
	1. for **adults** with CFS/ME with **mild** symptoms	Agree	Agree		The GDG reached a consensus in round 2 and the statement did not progress to wider survey
	2. for **adults** with CFS/ME with **moderate** symptoms	Uncertain	Agree	Disagree	Random selection for wider survey
	3. for **adults** with CFS/ME with **severe** symptoms	Uncertain	Disagree		The GDG reached a consensus in round 2 and the statement did not progress to wider survey
	4. for **children** with CFS/ME with **mild** symptoms	Uncertain	Agree		The GDG reached a consensus in round 2 and the statement did not progress to wider survey
	5. for **children** with CFS/ME	Uncertain	Agree		The GDG reached a consensus in round 2 and the statement did not

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	with **moderate** symptoms				progress to wider survey
	6. for **children** with CFS/ME with **severe** symptoms	Uncertain	Uncertain	Disagree	GDG was uncertain at round 2, progressed to wider survey
3(b)		**A programme which allows the person to find a baseline, followed by gradual and sustainable increases in activity/exercise (physical, emotional, cognitive) is appropriate….**	**A programme which allows the person to find a baseline, followed by gradual and sustainable increases in activity/exercise (physical, emotional, cognitive) is appropriate….**		
	1. for **adults** with CFS/ME with **mild** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for **adults** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for **adults** with CFS/ME with **severe** symptoms	Agree	Agree		The GDG discussed the severely affected following round 1 and due to their uncertainty decided to progress this to Round 2 to be consistent with children.

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	4. for **children** with CFS/ME with **mild** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for **children** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for **children** with CFS/ME with **severe** symptoms	Uncertain	Uncertain	Disagree	GDG was uncertain at round 2, progressed to wider survey
		A programme based upon planned increases in duration of physical activity/exercise followed by increases in intensity leading to aerobic exercise is appropriate….	**A programme based upon planned increases in duration of physical activity/exercise followed by increases in intensity leading to aerobic exercise (i.e. exercise which increases the pulse rate) is appropriate….**		
3(c)	1. for **adults** with CFS/ME with **mild** symptoms	Agree			The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for **adults** with CFS/ME with **moderate**	Agree			The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	symptoms				
	3. for **adults** with CFS/ME with **severe** symptoms	Uncertain	Disagree		The GDG reached a consensus in round 2 and the statement did not progress to wider survey
	4. for **children** with CFS/ME with **mild** symptoms	Agree			The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for **children** with CFS/ME with **moderate** symptoms	Agree			The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for **children** with CFS/ME with **severe** symptoms	Uncertain	Uncertain	Disagree	GDG was uncertain at round 2, progressed to wider survey
3(d)		**A programme that encourages self management and builds on the skills of the individual is appropriate**			
	1. for **adults** with CFS/ME with **mild**	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	symptoms				
	2. for **adults** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for **adults** with CFS/ME with **severe** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. for **children** with CFS/ME with **mild** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for **children** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for **children** with CFS/ME with **severe** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
3(e)		**A programme involving assessment and management of the emotional impact of CFS/ME is**			

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
		appropriate….			
	1. for **adults** with CFS/ME with **mild** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for **adults** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for **adults** with CFS/ME with **severe** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. for **children** with CFS/ME with **mild** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for **children** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for **children** with CFS/ME with **severe**	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	symptoms				
3(f)		**Techniques that improve the quality of relaxation and restorative rest are appropriate….**	…		
	1. for **adults** with CFS/ME with **mild** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for **adults** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for **adults** with CFS/ME with **severe** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. for **children** with CFS/ME with **mild** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for **children** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	6. for **children** with CFS/ME with **severe** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
3(g)		**Setting an individually tailored self management strategy (with patient-centred goals) is appropriate….**			
	1. for **adults** with CFS/ME with **mild** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for **adults** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for **adults** with CFS/ME with **severe** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. for **children** with CFS/ME with **mild** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	5. for **children** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for **children** with CFS/ME with **severe** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
3(h)		**A strategy that always maintains activity levels at substantially less than full capacity in order to have reserve energy for the body to heal itself (can be known as the envelope theory) is appropriate….**			
	1. for **adults** with CFS/ME with **mild** symptoms	Uncertain	Disagree		The GDG reached a consensus in round 2 and the statement did not progress to wider survey
	2. for **adults** with CFS/ME with **moderate** symptoms	Uncertain	Disagree	Agree	Random selection for wider survey
	3. for **adults** with CFS/ME with **severe** symptoms	Uncertain	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
	4. for **children** with CFS/ME	Uncertain	Disagree		The GDG reached a consensus in round 2 and the statement did not

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	with **mild** symptoms				progress to wider survey
	5. for **children** with CFS/ME with **moderate** symptoms	Uncertain	Disagree		The GDG reached a consensus in round 2 and the statement did not progress to wider survey
	6. for **children** with CFS/ME with **severe** symptoms	Uncertain	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
3(i)		**A strategy which involves monitoring thoughts and discusses alternative cognitive or behavioural strategies is appropriate….**			
	1. for **adults** with CFS/ME with **mild** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for **adults** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for **adults** with CFS/ME	Agree	…		The GDG reached a consensus in the first round and the statement did not

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	with **severe** symptoms				progress to Round 2
	4. for **children** with CFS/ME with **mild** symptoms	Uncertain			The GDG decided that this was not consistent with other responses to this statement and could not see any reason why children with mild symptoms should be different from children with moderate or severe and therefore this did not progress.
	5. for **children** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for **children** with CFS/ME with **severe** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
3(j)		**A programme that encourages patients to extend their activity capacity is appropriate….**			
	1. for **adults** with CFS/ME with **mild** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	2. for **adults** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for **adults** with CFS/ME with **severe** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. for **children** with CFS/ME with **mild** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for **children** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for **children** with CFS/ME with **severe** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
3(k)		**Strategies to normalise sleep patterns are appropriate….**			
	1. for **adults** with CFS/ME with **mild**	Agree	…		The GDG reached a consensus in the first round and the statement did not

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	symptoms				progress to Round 2
	2. for **adults** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for **adults** with CFS/ME with **severe** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. for **children** with CFS/ME with **mild** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for **children** with CFS/ME with **moderate** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for **children** with CFS/ME with **severe** symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
3(l)		**Complete rest (cognitive, physical and emotional) during significant increases in symptoms (a 'set-back') is appropriate….**			

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	1. for **adults** with CFS/ME with **mild** symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for **adults** with CFS/ME with **moderate** symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for **adults** with CFS/ME with **severe** symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. for **children** with CFS/ME with **mild** symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for **children** with CFS/ME with **moderate** symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for **children** with CFS/ME with **severe** symptoms	Uncertain	Disagree		The GDG reached a consensus in round 2 and the statement did not progress to wider survey

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
3(m)		**Equipment and adaptations (e.g. a wheelchair) that aims to allow patients to improve independence and quality of life should be provided as part of a management plan….**			
	1. for **adults** with CFS/ME with **mild** symptoms	Uncertain	Disagree		The GDG reached a consensus in round 2 and the statement did not progress to wider survey
	2. for **adults** with CFS/ME with **moderate** symptoms	Uncertain	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
3(n)	3. for **adults** with CFS/ME with **severe** symptoms	Agree	…		
	4. for **children** with CFS/ME with **mild** symptoms	Uncertain	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
	5. for **children** with CFS/ME with **moderate** symptoms	Agree			The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for **children** with CFS/ME	Agree			The GDG reached a consensus in the first round and the statement did not

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	with **severe** symptoms				progress to Round 2
3(p)		**See Below**	**Individual Cognitive Behaviour Therapy (CBT) is appropriate….**		Reworded substantially see table below for original wording
	1. for **adults** with CFS/ME		Agree	Uncertain	Random selection for wider survey
	2. for **children** with CFS/ME		Agree		The GDG reached a consensus in round 2 and the statement did not progress to wider survey
			Group Cognitive Behaviour Therapy (CBT) is appropriate….		
	1. for **adults** with CFS/ME		Agree	Uncertain	Random selection for wider survey
	2. for **children** with CFS/ME		Agree		The GDG reached a consensus in round 2 and the statement did not progress to wider survey
		See Below	**Cognitive Behaviour Therapy (CBT) combined with an activity programme is appropriate….**		
	1. for **adults** with CFS/ME		Agree		The GDG reached a consensus in round 2 and the statement did not progress to wider survey

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	2. for **children** with CFS/ME		Agree		The GDG reached a consensus in round 2 and the statement did not progress to wider survey

The statements below were included in the first round only. When discussed the GDG decided that they were not required in the second round as they were either unclear, duplicated or too detailed.			
1. 3(n)	**Graded Exercise Therapy (GET) is appropriate….**		Described in the statements above, GDG decided this was unnecessary.
	1. for adults with CFS/ME with mild symptoms	Agree	
	2. for adults with CFS/ME with moderate symptoms	Uncertain	
	3. for adults with CFS/ME with severe symptoms	Uncertain	
	4. for children with CFS/ME with mild symptoms	Uncertain	
	5. for children with CFS/ME with moderate symptoms	Uncertain	
	6. for children with CFS/ME with severe symptoms	Uncertain	
2. 3(o)	**Graded Activity Therapy (GAT) is appropriate….**		Described in the statements above, GDG decided this was unnecessary.
	1. for adults with CFS/ME with mild symptoms	Agree	
	2. for adults with CFS/ME with moderate symptoms	Agree	
	3. for adults with CFS/ME with severe symptoms	Agree	
	4. for children with CFS/ME with mild symptoms	Agree	
	5. for children with CFS/ME with moderate symptoms	Agree	
	6. for children with CFS/ME with severe symptoms	Agree	
3. 3(p)	**Pacing is appropriate….**		Term is not clearly defined, therefore no useful information would be gained by including this statement.
	1. for adults with CFS/ME with mild symptoms	Uncertain	
	2. for adults with CFS/ME with moderate symptoms	Uncertain	
	3. for adults with CFS/ME with severe symptoms	Agree	
	4. for children with CFS/ME with mild symptoms	Uncertain	
	5. for children with CFS/ME with moderate symptoms	Uncertain	
	6. for children with CFS/ME with severe symptoms	Agree	
4. 3(q)	**Individual (one on one) GET is appropriate….**		There were too many factors contributing to the answer to

			make this statement useful
	1. for adults with CFS/ME with mild symptoms	Uncertain	
	2. for adults with CFS/ME with moderate symptoms	Uncertain	
	3. for adults with CFS/ME with severe symptoms	Agree	
	4. for children with CFS/ME with mild symptoms	Uncertain	
	5. for children with CFS/ME with moderate symptoms	Uncertain	
	6. for children with CFS/ME with severe symptoms	Agree	
5. 3(r)	**Individual (one on one) GAT is appropriate….**		There were too many factors contributing to the answer to make this statement useful
	1. for adults with CFS/ME with mild symptoms	Uncertain	
	2. for adults with CFS/ME with moderate symptoms		
	3. for adults with CFS/ME with severe symptoms	Agree	
	4. for children with CFS/ME with mild symptoms	Uncertain	
	5. for children with CFS/ME with moderate symptoms	Uncertain	
	6. for children with CFS/ME with severe symptoms	Agree	
6. 3(s)	**Individual (one on one) pacing is appropriate….**		There were too many factors contributing to the answer to make this statement useful
	1. for adults with CFS/ME with mild symptoms	Agree	
	2. for adults with CFS/ME with moderate symptoms	Agree	
	3. for adults with CFS/ME with severe symptoms	Agree	
	4. for children with CFS/ME with mild symptoms	Uncertain	
	5. for children with CFS/ME with moderate symptoms	Uncertain	
	6. for children with CFS/ME with severe symptoms	Agree	
7. 3(t)	**About 6 sessions of group GET is appropriate….**		There were too many factors contributing to the answer to make this statement useful
	1. for adults with CFS/ME with mild symptoms	Uncertain	
	2. for adults with CFS/ME with moderate symptoms	Uncertain	
	3. for adults with CFS/ME with severe symptoms	Uncertain	
	4. for children with CFS/ME	Uncertain	

	with mild symptoms		
	5. for children with CFS/ME with moderate symptoms	Uncertain	
	6. for children with CFS/ME with severe symptoms	Uncertain	
8. 3(u)	**About 6 sessions of group GAT is appropriate….**		There were too many factors contributing to the answer to make this statement useful
	1. for adults with CFS/ME with mild symptoms	Uncertain	
	2. for adults with CFS/ME with moderate symptoms	Uncertain	
	3. for adults with CFS/ME with severe symptoms	Uncertain	
	4. for children with CFS/ME with mild symptoms	Uncertain	
	5. for children with CFS/ME with moderate symptoms	Uncertain	
	6. for children with CFS/ME with severe symptoms	Uncertain	
9. 3(v)	**About 6 sessions of group pacing is appropriate….**		There were too many factors contributing to the answer to make this statement useful
	1. for adults with CFS/ME with mild symptoms	Uncertain	
	2. for adults with CFS/ME with moderate symptoms	Uncertain	
	3. for adults with CFS/ME with severe symptoms	Disagree	
	4. for children with CFS/ME with mild symptoms	Uncertain	
	5. for children with CFS/ME with moderate symptoms	Uncertain	
	6. for children with CFS/ME with severe symptoms		
10. 3(w)	**About 12 sessions of activity management therapy (e.g. GET, GAT or pacing) is appropriate….**		There were too many factors contributing to the answer to make this statement useful
	1. for adults with CFS/ME with mild symptoms	Uncertain	
	2. for adults with CFS/ME with moderate symptoms	Uncertain	
	3. for adults with CFS/ME with severe symptoms	Uncertain	
	4. for children with CFS/ME with mild symptoms	Uncertain	
	5. for children with CFS/ME with moderate symptoms	Uncertain	
	6. for children with CFS/ME with severe symptoms	Uncertain	
11. 3(x)	**The addition of Cognitive Behaviour Therapy (CBT) techniques to other self-management and/or activity**		There were too many factors contributing to the answer to make this statement useful

	management strategies is appropriate….		
	1. for adults with CFS/ME with mild symptoms	Agree	
	2. for adults with CFS/ME with moderate symptoms	Agree	
	3. for adults with CFS/ME with severe symptoms	Agree	
	4. for children with CFS/ME with mild symptoms	Uncertain	
	5. for children with CFS/ME with moderate symptoms	Agree	
	6. for children with CFS/ME with severe symptoms	Agree	
12. 3(y)	**Individual Cognitive Behaviour Therapy (CBT) is appropriate….**		This statement was abridged to adults and children only as above. Severity was not regarded as a factor in whether INDIVIDUAL Group Cognitive Behaviour Therapy was appropriate.
	1. for adults with CFS/ME with mild symptoms	Uncertain	
	2. for adults with CFS/ME with moderate symptoms	Agree	
	3. for adults with CFS/ME with severe symptoms	Agree	
	4. for children with CFS/ME with mild symptoms	Uncertain	
	5. for children with CFS/ME with moderate symptoms	Uncertain	
	6. for children with CFS/ME with severe symptoms	Agree	
13. 3(z)	**Group Cognitive Behaviour Therapy (CBT) is appropriate….**		This statement was abridged to adults and children only above as severity was not regarded as a factor in whether Group Cognitive Behaviour Therapy was appropriate.
	1. for adults with CFS/ME with mild symptoms	Uncertain	
	2. for adults with CFS/ME with moderate symptoms	Uncertain	
	3. for adults with CFS/ME with severe symptoms	Uncertain	
	4. for children with CFS/ME with mild symptoms	Uncertain	
	5. for children with CFS/ME with moderate symptoms	Uncertain	
	6. for children with CFS/ME with severe symptoms	Uncertain	
14. 3(aa)	**Cognitive Behaviour Therapy (CBT) combined with an activity programme is appropriate….**		This statement was abridged to adults and children only above as severity was not regarded as a factor.

	1. for adults with CFS/ME with mild symptoms	Agree	
	2. for adults with CFS/ME with moderate symptoms	Agree	
	3. for adults with CFS/ME with severe symptoms	Agree	
	4. for children with CFS/ME with mild symptoms	Uncertain	
	5. for children with CFS/ME with moderate symptoms	Uncertain	
	6. for children with CFS/ME with severe symptoms	Uncertain	
15. 3(ab)	**About 6 sessions of Cognitive Behaviour Therapy (CBT) is appropriate….**		Including this statement was not a priority and was discarded for brevity
	1. for adults with CFS/ME with mild symptoms	Uncertain	
	2. for adults with CFS/ME with moderate symptoms	Uncertain	
	3. for adults with CFS/ME with severe symptoms	Disagree	
	4. for children with CFS/ME with mild symptoms	Uncertain	
	5. for children with CFS/ME with moderate symptoms	Uncertain	
	6. for children with CFS/ME with severe symptoms	Uncertain	
16. 3(ac)	**About 12 sessions of Cognitive Behaviour Therapy (CBT) is appropriate….**		Including this statement was not a priority and was discarded for brevity
	1. for adults with CFS/ME with mild symptoms	Uncertain	
	2. for adults with CFS/ME with moderate symptoms	Agree	
	3. for adults with CFS/ME with severe symptoms	Agree	
	4. for children with CFS/ME with mild symptoms	Uncertain	
	5. for children with CFS/ME with moderate symptoms	Uncertain	

6.3.7 Recommendations

Note: numbers in square brackets are as in the NICE guidelines.

Advice on symptom management before diagnosis [1.2.3]

Advice on symptom management should not be delayed until a diagnosis is established. This advice should be tailored to the specific symptoms the person has, and be aimed at minimising their impact on daily life and activities. [1.2.3.1]

Function and quality-of-life management [1.4.2]

Sleep management

Healthcare professionals should provide tailored sleep management advice that includes:

- Explaining the role and effect of disordered sleep or sleep dysfunction in CFS/ME.
- Identifying the common changes in sleep patterns seen in CFS/ME that may exacerbate fatigue symptoms (such as insomnia, hypersomnia, sleep reversal, altered sleep–wake cycle and non-refreshing sleep).
- Providing general advice on good sleep hygiene[††].
- Introducing changes to sleep patterns gradually.
- Regular review. [1.4.2.1]

If sleep management strategies do not improve the person's sleep and rest, the possibility of an underlying sleep disorder or dysfunction should be considered, and interventions provided if needed. [1.4.2.2]

[††] For general advice on sleep hygiene, see the NHS Direct website (www.nhsdirect.nhs.uk).

Sleep management strategies should not include encouraging daytime sleeping and naps. People with CFS/ME should be advised that excessive sleep does not generally improve physical or mental functioning, and excessive periods of daytime sleep or frequent napping may further disrupt the sleep–wake cycle. [1.4.2.3]

Rest periods

Rest periods are a component of all management strategies for CFS/ME. Healthcare professionals should advise people with CFS/ME on the role of rest, how to introduce rest periods into their daily routine, and the frequency and length appropriate for each person. This may include:

- Limiting the length of rest periods to 30 minutes at a time.
- Introducing 'low level' physical and cognitive activities (depending on the severity of symptoms).
- Using relaxation techniques (see recommendation 1.4.2.6). [1.4.2.4]

Healthcare professionals should review the use of rest periods regularly as part of the patient's management plan. [1.4.2.5]

Relaxation

Relaxation techniques appropriate to the person with CFS/ME should be offered for the management of pain, sleep problems and comorbid stress or anxiety. There are a number of different relaxation techniques (such as guided visualisation or breathing techniques) that can be incorporated into rest periods. [1.4.2.6]

Pacing

People with CFS/ME have reported **pacing** to be helpful in self-managing CFS/ME. However, healthcare professionals should advise people with CFS/ME that, at present, there is insufficient research evidence on the benefits or harm of pacing. [1.4.2.7]

Diet [1.4.3]

See also recommendations on managing nausea (1.4.1.4) and bowel symptoms (1.4.1.5), and use of supplements (1.4.7.2–4).

Healthcare professionals should emphasise the importance of a well-balanced diet in line with 'The balance of good health'[‡‡]. They should work with the person with CFS/ME to develop strategies to minimise complications that may be caused by nausea, swallowing problems, sore throat or difficulties with buying, preparing and eating food. [1.4.3.1]

Healthcare professionals should emphasise the importance of eating regularly, and including slow-release starchy foods in meals and snacks. The physiological consequences of not doing so should be explained to the person with CFS/ME. [1.4.3.2]

Equipment to maintain independence [1.4.4]

For people with moderate or severe CFS/ME, providing or recommending equipment and adaptations (such as a wheelchair, blue badge or stairlift) should be considered as part of an overall management plan, taking into account the risks and benefits for the individual patient. This may help them to maintain their independence and improve their quality of life. [1.4.4.1]

[‡‡]Food Standards Agency (2006) 'The balance of good health'. London: Foods Standards Agency. Available from www.food.gov.uk/multimedia/pdfs/bghbooklet.pdf

Education and employment [1.4.5]

Having to stop their work or education is generally detrimental to people's health and well-being. Therefore, the ability of a person with CFS/ME to continue in education or work should be addressed early and reviewed regularly. [1.4.5.1]

Healthcare professionals should proactively advise about fitness for work and education, and recommend flexible adjustments or adaptations to work or studies to help people with CFS/ME to return to them when they are ready and fit enough. This may include, with the informed consent of the person with CFS/ME, liaising with employers, education providers and support services, such as:

- occupational health services
- disability services through Jobcentre Plus
- schools, home education services and local education authorities
- disability advisers in universities and colleges. [1.4.5.2]

For people with CFS/ME who are able to continue in or return to education or employment, healthcare professionals should ensure, with the person's informed consent, that employers, occupational health or education institutions have information on the condition and the agreed management plan. [1.4.5.3]

Education

Healthcare professionals should follow the guidance from the Department for Children, Schools and Families[§§] on education for children and young people with medical needs, or equivalent statutory guidance. [1.4.5.4]

[§§] See www.dcsf.gov.uk

Healthcare professionals should work closely with social care and education services to ensure a common understanding of the goals of the person with CFS/ME. The use of a flexible approach should be discussed, including home tuition and use of equipment that allows a gradual reintegration into education. [1.4.5.5]

Time in education should not be used as a sole marker of progress of CFS/ME, and education should not be the only activity a person undertakes. There should be a balance between time spent attending school or college and doing homework, and time spent on home and social activities. [1.4.5.6]

Employment

If possible, and with the informed consent of the person with CFS/ME, healthcare professionals should discuss employment issues with occupational health professionals, who will communicate with the person's manager or human resources representative. If there is no access to occupational health services, the responsible clinician should liaise with the employer directly[***]. [1.4.5.7]

Strategies that should not be used for CFS/ME [1.4.6]

The following strategies should not be offered to people with CFS/ME:

- Advice to undertake unsupervised, or unstructured, vigorous exercise (such as simply 'go to the gym' or 'exercise more') because this may worsen symptoms.

[***] NHS Plus has produced guidance on the occupational aspects of the management of CFS/ME, available from www.nhsplus.nhs.uk (search for 'chronic fatigue syndrome').

NICE is developing guidance on the management of long-term sickness and incapacity; publication is expected in December 2008 (details available from www.nice.org.uk).

- Specialist management programmes (see section 1.6) delivered by practitioners with no experience in the condition. [1.4.6.2]

Although there is considerable support from patients (particularly people with severe CFS/ME) for the following strategies, healthcare professionals should be aware that there is no controlled trial evidence of benefit:

- Encouraging maintenance of activity levels at substantially less than full capacity to reserve energy for the body to heal itself (sometimes known as the envelope theory).
- Encouraging complete rest (cognitive, physical and emotional) during a setback/relapse. [1.4.6.3]

Strategies for managing CFS/ME should not include:

- Prolonged or complete rest or extended periods of daytime rest in response to a slight increase in symptoms.
- An imposed rigid schedule of activity and rest. [1.4.6.4]

Specialist CFS/ME care [1.6]

After a patient is referred to specialist care, an initial assessment should be done to confirm the diagnosis. [1.6.1.1]

If general management strategies (see section 1.4) are helpful for a person with CFS/ME, these should be continued after referral to specialist CFS/ME care. [1.6.1.2]

Cognitive behavioural therapy, graded exercise therapy and activity management programmes [1.6.2]

Choosing and planning treatment

An individualised, person-centred programme should be offered to people with CFS/ME. The objectives of the programme should be to:

- sustain or gradually extend, if possible, the person's physical, emotional and cognitive capacity
- manage the physical and emotional impact of their symptoms. [1.6.2.1]

The rationale and content of the different programmes, including their potential benefits and risks, should be fully explained to the person with CFS/ME. Healthcare professionals should explain that no single strategy will be successful for all patients, or during all stages of the condition. [1.6.2.2]

Healthcare professionals should recognise that the person with CFS/ME is in charge of the aims of the programme. The choice of the programme, its components, and progression throughout the programme should be mutually agreed and based on:

- the person's age, preferences and needs
- the person's skills and abilities in managing their condition, and their goals (such as improvement or treatment of deterioration of symptoms, prevention of relapse or maintenance)
- the severity and complexity of symptoms
- physical and cognitive functioning. [1.6.2.3]

Cognitive behavioural therapy (CBT) and/or graded exercise therapy (GET) should be offered to people with mild or moderate CFS/ME and provided to those who choose these approaches, because currently these are the interventions for which there is the clearest research evidence of benefit. [1.6.2.4

If a full CBT or GET programme is inappropriate or not available, components of CBT or GET should be offered, either individually or more effectively in combination with:

- activity management strategies (see 1.6.2.22)
- sleep management (see 1.4.2.1–3)

- relaxation techniques (see 1.4.2.6). [1.6.2.5]

The choice of programme, its components and progression through it should be reviewed regularly, taking into account the goals and abilities of the person with CFS/ME, and other approaches agreed as necessary. [1.6.2.6]

Healthcare professionals should advise people with CFS/ME to contact them if they experience an increase in symptoms that lasts for longer than a few days after starting the specialist programme, or if symptoms are severe or distressing. [1.6.2.7]

Cognitive behavioural therapy (CBT)

A course of CBT should be delivered only by a healthcare professional with appropriate training in CBT and experience in CFS/ME, under clinical supervision. The therapist should adhere closely to empirically grounded therapy protocols. [1.6.2.8]

CBT should be offered on a one-to-one basis if possible. [1.6.2.9]

CBT for a person with CFS/ME should be planned according to the usual principles of CBT, and should include:

- Acknowledging and validating the person's symptoms and condition.
- Explaining the CBT approach in CFS/ME, such as the relationship between thoughts, feelings, behaviours and symptoms, and the distinction between causal and perpetuating factors.
- Discussing the person's attitudes and expectations.
- Developing a supportive and collaborative therapeutic relationship.
- Developing a shared formulation and understanding of factors that affect CFS/ME symptoms.
- Agreeing therapeutic goals.
- Tailoring treatment to the person's needs and level of functioning.

- Recording and analysing patterns of activity and rest, and thoughts, feelings and behaviours (self-monitoring).
- Establishing a stable and maintainable activity level (baseline) followed by a gradual and mutually agreed increase in activity.
- Challenging thoughts and expectations that may affect symptom improvement and outcomes.
- Addressing complex adjustment to diagnosis and acceptance of current functional limitations.
- Developing awareness of thoughts, expectations or beliefs and defining fatigue-related cognitions and behaviour.
- Identifying perpetuating factors that may maintain or exacerbate CFS/ME symptoms to increase the person's self-efficacy (sense of control over symptoms).
- Addressing any over-vigilance to symptoms and related checking or reassurance-seeking behaviours by providing physiological explanations of symptoms and using refocusing/distraction techniques.
- Problem solving using activity management and homework tasks to test out alternative thoughts or beliefs, such as undertaking pleasure and mastery tasks (tasks that are enjoyable and give a sense of accomplishment).
- Building on existing assertion and communication skills to set appropriate limits on activity.
- Managing sleep problems, for example by addressing any unhelpful beliefs about sleep, behavioural approaches to sleep disturbance, stress management, and/or relaxation training (see recommendations 1.4.2.1–6).
- Treating any associated or comorbid anxiety, depression or mood disorder according to NICE clinical guidelines on these conditions (see section 6).

- Offering information on managing setbacks/relapses (see section 1.7). [1.6.2.10]

Graded exercise therapy (GET)

GET should be delivered only by a suitably trained GET therapist with experience in CFS/ME, under appropriate clinical supervision. [1.6.2.11]

GET should be offered on a one-to-one basis if possible. [1.6.2.12]

People with mild or moderate CFS/ME should be offered GET that includes planned increases in the duration of physical activity. The intensity should then be increased when appropriate, leading to aerobic exercise (that is, exercise that increases the pulse rate). [1.6.2.13]

GET should be based on the person's current level of activities (such as physical activity, daily routines, sleep patterns and frequency of setbacks/relapses) and emotional factors, vocational or educational factors and individual goals (details of these may be obtained from an activity diary). The programme should also include sleep and relaxation strategies (see recommendations 1.4.2.1–6). [1.6.2.14]

When planning GET, the healthcare professional should:

- Undertake an activity analysis to ensure that the person with CFS/ME is not in a 'boom and bust' cycle before they increase the time spent in exercise.
- Discuss with the person the ultimate goals that are important and relevant to them. This might be, for example, a twice-daily short walk to the shops, a return to a previous active hobby such as cycling or gardening, or, for people with severe CFS/ME, sitting up in bed to eat a meal.

- Recognise that it can take weeks, months or even years to achieve goals, and ensure that this is taken into account in the therapy structure (for example, by setting short- and medium-term goals).
- Explain symptoms and the benefits of exercise in a physiological context. [1.6.2.15]

When starting GET, the healthcare professional should:

- Assess the person's current daily activities to determine their baseline.
- Agree with them a level of additional low-intensity exercise that is sustainable, independent of daily fluctuations in symptoms, and does not lead to 'boom and bust' cycles. This may be sitting up in bed or brushing hair, for example, for people with severe CFS/ME, or gentle stretches or a slow walk.
- Encourage them to undertake this exercise for at least 5 days out of 7, or build up to this level if and when possible.
- Advise them that this level of exercise may mildly increase symptoms for a few days (for example, a mild to moderate increase in stiffness and fatigue), explain why this may occur and discuss strategies to mitigate it.
- Offer information on the management of setbacks/relapses (see section 1.7). [1.6.2.16]

Progressing with GET

When the low-intensity exercise can be sustained for 5 days out of 7 (usually accompanied by a reduction in perceived exertion), the duration should be reviewed and increased, if appropriate, by up to 20%. For example, a 5-minute walk becomes 6 minutes, or a person with severe CFS/ME sits up in bed for a longer period, or walks to another room more often. The aim is to reach 30 minutes of low-intensity exercise. [1.6.2.17]

When the duration of low-intensity exercise has reached 30 minutes, the intensity of the exercise may be increased gradually up to an aerobic heart rate zone, as assessed individually by a healthcare professional. A rate of 50–70% maximum heart rate is recommended. [1.6.2.18]

Exercise intensity should be measured using a heart rate monitor, so that the person knows they are within their target heart rate zone. [1.6.2.19]

If agreed GET goals are met, exercise duration and intensity may be increased further if appropriate, if other daily activities can also be sustained, and in agreement with the person with CFS/ME. [1.6.2.20]

Maintaining exercise

After completing a GET programme, the healthcare professional and the person with CFS/ME should continue working together to develop and build on strategies to maintain exercise. Support should be available, if needed, to enable the person to reinforce the learning and lifestyle changes made and continue GET beyond discharge. [1.6.2.21]

Activity management

Activity management is a goal-oriented and person-centred approach tailored to the needs of the person with CFS/ME. It should include:

- Understanding that activities have physical, emotional and cognitive components, and identifying these components.
- Keeping a diary that records cognitive and physical activity, daytime rest and sleep. This will help to set baseline levels of activity (a stable and sustainable range of functioning), identify patterns of over- and underactivity, and develop an activity/exercise strategy.
- Establishing a baseline; specific activities may need to be increased or decreased while this is happening.
- Gradually increasing activity above the baseline in agreement with the person.

- Planning daily activities to allow for a balance and variety of different types of activity, rest and sleep. This may include making a weekly activity schedule.
- Spreading out difficult or demanding tasks over the day or week.
- Splitting activities into small achievable tasks according to the person's level of ability/functioning, followed by gradual increases in the complexity of the tasks.
- Monitoring, regulating and planning activities to avoid a 'boom and bust' cycle.
- Goal setting, planning and prioritising activities.
- Explaining the role of rest in CFS/ME and helping the person work out how to build in rest periods and achieve a productive day (see recommendations 1.4.2.1–6).
- Regularly reviewing activity levels and goals.
- Offering information on the management of setbacks/relapses (see section 1.7). [1.6.2.22]

Management of setbacks/relapses [1.7]

Preparing for a setback/relapse [1.7.1]

People with CFS/ME should be advised that setbacks/relapses are to be expected as part of CFS/ME. [1.7.1.1]

Healthcare professionals and people with CFS/ME should develop a plan for managing setbacks/relapses, so that skills, strategies, resources and support are readily available and accessible when needed. This plan may be shared with the person's carers, if they agree. [1.7.1.2]

During a setback/relapse [1.7.2]

Setbacks/relapses may be triggered by factors such as unexpected/unplanned activities, poor sleep, infection or stress. Healthcare professionals, in discussion with the person with CFS/ME, should try to identify the cause(s) of a

setback/relapse, but it should be recognised that this may not always be possible. [1.7.2.1]

When managing a setback/relapse, the management plan should be reviewed. Healthcare professionals should discuss and agree an appropriate course of action with the person with CFS/ME, taking into account:

- the person's experience
- possible causes of the setback/relapse, if known
- the nature of the symptoms
- the severity and duration of the setback/relapse
- the current management plan. [1.7.2.2]

When managing setbacks, healthcare professionals should put strategies into place that:

- Include relaxation and breathing techniques.
- Maintain activity and exercise levels if possible, by alternating activities with breaks and pacing activities, as appropriate.
- Involve talking to families and carers, if appropriate.
- Recognise distressing thoughts about setbacks/relapses such as 'this means I'll never get better', but encourage optimism.
- Involve reconsidering and revising the levels and types of symptom control. [1.7.2.3]

In some setbacks/relapses, it may be necessary to reduce, or even stop, some activities and increase the frequency and/or duration of rest periods to stabilise symptoms and re-establish a baseline activity level. This should be discussed and agreed with the person with CFS/ME. [1.7.2.4]

People with CFS/ME should be advised to minimise daytime sleep periods. However, healthcare professionals should recognise that this is not always

possible, depending on the severity of a person's symptoms and the setback. [1.7.2.5]

After a setback/relapse [1.7.3]

After a setback/relapse, healthcare professionals should review the person's activity levels to re-establish a baseline and review the management plan. A gradual return, when possible, to previous exercise and functional routines should be encouraged. Activity should be increased gradually. [1.7.3.1]

Healthcare professionals should advise on:

- Slowly decreasing the frequency and duration of rest periods.
- Continuing the use of relaxation techniques, even when the person with CFS/ME is beginning to feel better. [1.7.3.2]

After a setback, healthcare professionals and people with CFS/ME should review the experience to determine, if possible, whether triggers can be managed in the future, and put strategies in place to do this. [1.7.3.3]

6.3.8 Deriving recommendations

Discussion of the evidence

In reviewing the evidence, the GDG were aware that there was a lack of consistency in terminology and an absence of trial protocols, particularly with respect to graded exercise, graded activity and pacing. This made it difficult to compare like with like across studies.

The GDG regarded the evidence of benefit strongest for CBT, which was clearly defined in the studies. There was a discussion about the construction of a CBT programme. With regard to the number of sessions of CBT, one trial of good methodological quality looked at CBT delivered over 13–16 sessions. The greatest benefit was shown where there was a 6–12-month follow-up. The authors also looked at a 5-year follow-up and these benefits were maintained. The delivery of CBT was also important; it was clear that it needed to be

delivered by someone with defined competencies but not necessarily a psychiatrist.

The GDG was clear that CBT was not about unhelpful advice or dictation of illness beliefs, but about changes in lifestyle and learning to achieve improvement within the patient's abilities. In addition, the objectives of the programme must be agreed with the patient, and they must clearly be willing to take part. The GDG did not regard CBT or other behavioural therapies as curative or directed at the underlying disease process, which remains unknown. Rather, such interventions can help some patients cope with the condition and experience improved functioning, and consequently a improved quality of life.

As CBT is a labour-intensive intervention, it is an expensive option and the GDG considered whether less expensive interventions could be used in certain circumstances (e.g. CCBT). The GDG considered that there was no evidence available for CCBT in this population group and they would be unwilling to recommend it. However, the possibilities of using CCBT as an adjunct for follow-up or relapse prevention were hypothesised.

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

Areas where little evidence was found

Little or no evidence was found for the effectiveness of sleep management, rest, relaxation or pacing for people with CFS/ME. The GDG's view was that advice on these self-help techniques would be helpful as patients generally find them useful.

The GDG found it difficult to find a precise definition for activity management and therefore to find evidence for its effectiveness. As it is based on similar principles

and goals to graded exercise therapy the GDG made consensus recommendations regarding activity management.

No evidence was found on the management of setbacks and therefore the GDG devised consensus recommendations. Stakeholders commented that the term 'relapse' was preferred by patients. However, the view of the GDG was that relapse was defined differently clinically and to use the term in isolation would cause confusion.

Questionnaire

The GDG agreed that evidence-based CBT as discussed above was appropriate, but was uncertain about the benefits of individual versus group CBT. In the wider survey healthcare professionals agreed that both were appropriate, whereas patients were uncertain about, and disagreed with, individual and group CBT respectively. Because of the high-quality evidence showing the benefits of CBT, the GDG recommended it as best practice, but did not make a recommendation regarding individual versus group CBT as there was neither evidence nor consensus. The GDG noted that it was always the patient's choice whether or not to participate. They acknowledged that CBT has not always been applied appropriately or consistently. Therefore they have made detailed recommendations on how it should be delivered.

With regard to GET, because of the confusion of terminology and protocols in the studies, the GDG developed clinical scenario statements that detailed the approach rather than naming the intervention.

Both the evidence and the GDG consensus support gradual increases in aerobic exercise in people with mild to moderate CFS/ME. The patients in the wider survey did not support this view, as indicated by the response to 3a2 (see section 6.3.6). Healthcare professionals rated this as 'uncertain' but did not disagree with the statement. The view of the GDG was that all interventions have the potential to cause harm as well as provide benefit. GET is no different, but the overall research evidence is that the benefits outweigh any harmful effects.

Some patient surveys have described poor experiences with exercise therapies, though these experiences were usually from unstructured or inflexible exercise programmes, often delivered by untrained personnel. Such poor experiences should be avoidable by using a programme based on patient participation and in which the patient retains control over goal-setting and the pace of progress. This is a core feature of GET. The GDG has therefore developed detailed recommendations describing the intervention as well as recommendations about what is appropriate.

There was both a lack of evidence and no consensus about whether GET is appropriate for people, in particular children, with severe CFS/ME. Therefore the GDG did not recommend GET for people with severe CFS/ME but elements of it may be appropriate.

There is no evidence to support the 'envelope theory' of maintaining levels at substantially less than capacity in order to have a reserve. The results from the wider group indicated that patients generally support this approach while healthcare professionals do not. The GDG supported the view that people with CFS/ME need to learn to 'listen to' body energy levels in order to manage their daily life and that sudden large increases in activity were not advisable. There was however, concern that consistently maintaining activity levels at lower than capacity would not lead to an improvement in symptoms and/or level of functioning.

6.4 Pharmacological interventions

6.4.1 Evidence statements

6.4.1.1 ***At present, there is equivocal and limited evidence on the overall benefits of pharmacological treatments for CFS/ME. (Evidence level 1+)***

6.4.1.2 ***The evidence shows that immunoglobulin therapy in adults with CFS/ME is not of benefit (Evidence level 1+)***

6.4.1.3 ***Little evidence exists on interventions for those severely affected with CFS/ME.***

6.4.1.4 ***The evidence shows that immunoglobulin therapy in children with CFS/ME is not of overall benefit (Evidence level 1+)***

6.4.1.5 ***There is insufficient evidence of benefit of other immunological therapies. (Evidence level 1-)***

6.4.2 Clinical evidence summary

6.4.2.1 ***Summary of evidence presented in Appendix 1***

The view of the GDG was that symptomatic treatment should be provided on the basis of general principles of symptom management, except where it was inappropriate for people with CFS/ME. As discussed in the introduction (section 1.5), the GDG did not address the general management of individual symptoms as each symptom would have needed a guideline in itself. The evidence review presented was based on searches of the evidence for the management of CFS/ME (see key clinical questions above), not for the management of individual symptoms. (For example, a trial looking at the management of neuropathic pain in patients with CFS/ME would have been identified.)

The pharmacological studies reviewed included treatment with anticholinergic agents, antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs)), NADH (nicotinamide adenine dinucleotide), dexamphetamine, antihypertensive agents and steroids. Study quality was variable, with validity scores ranging from 2 to 19. Sample sizes were generally small with half of the 21 studies retrieved having fewer than 50 participants. Very few of the RCTs evaluating pharmacological interventions suggested a beneficial effect.

No benefit was found in patients with CFS/ME from treatment with anticholinergic agents, antidepressants, antihypertensives or growth hormone. Results were mixed in trials of oral NADH and melatonin as well as in the studies of steroid therapy and MAOIs. A trial of dexamphetamine found significant improvements in fatigue in the treated patients but reduced food consumption was a side effect. Adverse events serious enough to cause people to withdraw from the study were also noted with galanthamine hydrobromide, phenelzine, fludrocortisone and fluoxetine.

Immunological/antiviral treatment

Several immunological and antiviral treatments were evaluated in 11 retrieved studies. There were mixed results in three RCTs of the effects of immunoglobulin in adults: one found improvements in symptom scores and functional capacity; a second found improvements in immune measurements but not functional or symptom measures; and a third found no improvement in any outcomes. The methodological quality of these studies was between 13 and 16 out of 20 on the validity assessment. One study of interferon showed an increase in physical activity (p value not provided) and another showed improvements only in immune measurements but not in QoL measures. Use of Ampligen showed an improvement in functional ability and cognitive function but not in depression scores. The combination of leukocyte extract and CBT appeared to improve general health in one study of 49 patients, but not physical or functional capacity. In one RCT of acyclovir, a significant negative effect was

reported for anxiety, depression and confusion. No differences in trials of gancyclovir, inosine pranobex, the antihistamine terfenadine or vaccination with staphylococcus toxoid were found.

People with severe CFS/ME

Very limited numbers of studies indicated the degree of severity of CFS/ME in participants. Two RCTs compared people who had been ill for shorter or longer times. There was no significant difference in response to fludrocortisone in one study or to a broad-based management programme in the other.

Children

Only two RCTs of children with CFS/ME were retrieved. One RCT of immunoglobulin G showed a significant improvement in functional score of 25% or more in the intervention group.

6.4.2.2 Additional clinical evidence

No new evidence was found in the update searches.

6.4.3 Health economics evidence summary

The management of symptoms is an important consideration in cost effectiveness as both costs and benefits are likely to stretch recurrently into the future. The table shows the potential costs of the types of pharmacological intervention..

Type of intervention	Detail (NP, non-proprietary)	Dose	Annual cost (£)*
SSRI	Fluoxetine (Prozac)	20 mg/day	201
Thyroxine	Levothyroxine (NP)	25 µg/day	12
Tricyclic	Amitriptyline (NP)	25 mg/day	13
Skeletal muscle relaxant/antispasmodic	Diazepam (NP)	2 mg/day	12
	Baclofen (NP)	10 mg/day	10
	Clonazepam (Rivotril)	500 µg/day	14

*Data sourced from the BNF (2006)

Apart from SSRIs, the cost implications of the pharmacological interventions referred to in the table above not ruled out in GDG ratings are small. Therefore, cost is unlikely to be a valid reason for deeming these interventions to be inappropriate.

Although there is some evidence regarding infectious triggers for CFS/ME, there is no research evidence on how such triggers might influence clinical management (including pharmacological treatment). While this must be acknowledged, the application of health economics to this evidence poses significant methodological problems. Good cost-effectiveness work is necessarily predicated on good-quality clinical studies, and for the results to be most useful, the outcome of an intervention should be given in a quantified QoL format (such as through an SF-36 or EQ5D questionnaire). While evidence of this kind may be available in the future, the literature search did not retrieve anything substantial at the present time. Therefore, health economics has little to say on this school of interventions other than that they should be judged using the standard core components of health economics.

6.4.4 Clinical scenario questionnaire to GDG and wider group

So that consistent principles were applied in rating the evidence statements, the GDG and the wider group assumed the following.

1. The person with CFS/ME and healthcare professionals involved in their care will make decisions in partnership. These are directed by the patient's personal preferences and build on the existing experience and skills of the professional.

2. All treatments are offered allowing the person with CFS/ME to refuse without compromising the further therapeutic relationship.

3. There is a good rapport in which the patient and their families/carers feel believed and validated.

4. Treatment is provided by the NHS in the context of availability of adequate numbers of competent, appropriately trained healthcare professionals.

5. Minimal waiting times for good-quality services are adhered to.

For the GDG's first rating round, the wording of the evidence statements was consistent with those in other sections, that is 'The use of …… is appropriate.' However, in discussion following the round 1 ratings, it became clear that the GDG believed that while many of these therapies should not be routinely prescribed, they may be appropriate in certain circumstances for certain individuals. The objective of these statements was to determine which drugs the GDG agreed should *not* be used to manage particular symptoms for patients with CFS/ME. Therefore many of the statements were clarified to detail the circumstances, and the GDG changed the statement wording from 'appropriate' to 'inappropriate'. All questions that were changed were re-rated in round 2 regardless of their rating in round 1.

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
2(a)		The use of thyroxine where the individual has LOW thyroxine levels is appropriate….			
	1. for adults with CFS/ME with mild symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for adults with CFS/ME with moderate symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for adults with CFS/ME with severe symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. for children with CFS/ME with mild symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for children with CFS/ME with moderate symptoms	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for children with CFS/ME with severe	Agree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

	symptoms				
2(b)		The use of thyroxine where the individual has NORMAL thyroxine levels is appropriate….			
	1. for adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2.
	2. for adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. for children with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for children with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for children with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
2(c)		The use of SSRIs where the individual is depressed is appropriate….	The use of selective serotonin re-uptake inhibitors (SSRIs) (for example fluoxetine/Prozac or paroxetine/Seroxat) where the individual is moderately		In the first round the GDG was unclear about the severity of symptoms of depression, the

			or severely depressed is INAPPROPRIATE….		statement was clarified and went to round 2. See discussion about appropriate and inappropriate above.
	1. for adults with CFS/ME with mild symptoms	Uncertain	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	2. for adults with CFS/ME with moderate symptoms	Uncertain	Disagree	Uncertain	Random selection for wider survey
	3. for adults with CFS/ME with severe symptoms	Agree	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	1. for children with CFS/ME with mild symptoms	Not included	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	2. for children with CFS/ME with moderate symptoms	Not included	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	3. for children with CFS/ME with severe symptoms	Not included	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
2(c)			The use of venlafaxine where the individual has pain difficulties AND is moderately or severely depressed is INAPPROPRIATE		This statement was added following the 1st round discussion

	1. for adults with CFS/ME with mild symptoms	Not included	Disagree	….	The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	2. for adults with CFS/ME with moderate symptoms	Not included	Disagree	….	The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	3. for adults with CFS/ME with severe symptoms	Not included	Disagree	….	The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
2(c)			The use of venlafaxine where the individual has sleep and pain difficulties AND is NOT moderately or severely depressed is INAPPROPRIATE		This statement was added following the 1st round discussion
	1. for adults with CFS/ME with mild symptoms	Not included	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	2. for adults with CFS/ME with moderate symptoms	Not included	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	3. for adults with CFS/ME with severe symptoms	Not included	Agree	Agree	Random selection for wider survey
2(d)		The use of Tricyclics where the individual is depressed is appropriate….	The use of tricyclics (for example amitriptyline) where the individual has sleep and pain difficulties AND is moderately or severely depressed is INAPPROPRIATE		In the first round the GDG was unclear about the severity of symptoms of depression, the statement was clarified to indicate and progressed to round 2. See

					discussion about appropriate and inappropriate above.
	1. for adults with CFS/ME with mild symptoms	Uncertain	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	2. for adults with CFS/ME with moderate symptoms	Uncertain	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	3. for adults with CFS/ME with severe symptoms	Uncertain	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	4. for children with CFS/ME with mild symptoms	Uncertain	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	5. for children with CFS/ME with moderate symptoms	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	6. for children with CFS/ME with severe symptoms	Uncertain	Uncertain	Disagree	GDG was uncertain at round 2, progressed to wider survey
2(e)			The use of tricyclics (for example amitriptyline) where the individual has sleep and pain difficulties AND is NOT moderately or severely depressed is INAPPROPRIATE……..		This statement was added following the 1st round discussion to test use without depression

	1. for adults with CFS/ME with mild symptoms	Not included	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	2. for adults with CFS/ME with moderate symptoms	Not included	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	3. for adults with CFS/ME with severe symptoms	Not included	Disagree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	4. for children with CFS/ME with mild symptoms	Not included	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	5. for children with CFS/ME with moderate symptoms	Not included	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	6. for children with CFS/ME with severe symptoms	Not included	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
2(f)		The use of gabapentin where the individual is depressed is appropriate….	The use of gabapentin where the individual has pain difficulties is INAPPROPRIATE……..		This statement was clarified following the 1st round discussion. See discussion about appropriate and inappropriate above.
	1. for adults with CFS/ME with mild	Disagree	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey

	symptoms				
	2. for adults with CFS/ME with moderate symptoms	Disagree	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	3. for adults with CFS/ME with severe symptoms	Disagree	Uncertain	Disagree	GDG was uncertain at round 2, progressed to wider survey
	4. for children with CFS/ME with mild symptoms	Disagree	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	5. for children with CFS/ME with moderate symptoms	Disagree	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	6. for children with CFS/ME with severe symptoms	Disagree	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
2(g)		The use of Monoamine oxidase inhibitors where the individual is depressed is appropriate….	The use of monoamine oxidase inhibitors (for example phenelzine or isocarboxazid) where the individual has pain difficulties AND the individual is moderately or severely depressed is INAPPROPRIATE….		This statement was clarified following the 1st round discussion. See discussion about appropriate and inappropriate above.
	1. for adults with CFS/ME with mild symptoms	Disagree	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	2. for adults with CFS/ME	Disagree	Agree		The GDG reached a consensus in the round 2 and the statement did

	with moderate symptoms				not progress to wider survey.
	3. for adults with CFS/ME with severe symptoms	Disagree	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	4. for children with CFS/ME with mild symptoms	Disagree	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
	5. for children with CFS/ME with moderate symptoms	Disagree	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
	6. for children with CFS/ME with severe symptoms	Disagree	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
2(g)			The use of monoamine oxidase inhibitors (for example phenelzine or isocarboxazid) where the individual has pain difficulties AND the individual is NOT moderately or severely depressed is INAPPROPRIATE…. T		This statement was added following the 1st round discussion to clarify the above.
	1. for adults with CFS/ME with mild symptoms	Not included	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
	2. for adults with CFS/ME with moderate symptoms	Not included	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey

	3. for adults with CFS/ME with severe symptoms	Not included	Agree	Agree	Random selection for wider survey
	4. for children with CFS/ME with mild symptoms	Not included	Agree		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for children with CFS/ME with moderate symptoms	Not included	Agree		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for children with CFS/ME with severe symptoms	Not included	Agree		The GDG reached a consensus in the first round and the statement did not progress to Round 2
2(h)		The use of glucocorticoids (such as hydrocortisone) where the individual's primary symptom is pain is appropriate….			
	1. for adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for adults with CFS/ME with severe	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

	symptoms				
2(i)		The use of mineralocorticoids (such as fludrocortisone) where the individual's primary symptom is pain is appropriate….			
	1. for adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
2(i)		The use of Dexamphetamine where the individual's primary symptom is fatigue is appropriate….			
	1. for adults with CFS/ME with mild symptoms	Disagree			The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for adults with CFS/ME with moderate symptoms	Disagree			The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for adults with CFS/ME	Disagree			The GDG reached a consensus in the first round and the statement did

	with severe symptoms				not progress to Round 2
2(j)		The use of methylphenidate where the individual's primary symptom is fatigue is appropriate….			
	1. for adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. for children with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for children with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for children with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
2(k)		The use of Melatonin is appropriate….	The use of melatonin where the individual has sleep difficulties is INAPPROPRIATE….		See discussion about appropriate and inappropriate above.

	1. for children with CFS/ME with mild symptoms	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	2. for children with CFS/ME with moderate symptoms	Uncertain	Uncertain	Disagree	GDG was uncertain at round 2
	3. for children with CFS/ME with severe symptoms	Uncertain	Disagree	Disagree	GDG was uncertain at round 2
2(l)		The use of anti-herpes agents (such as acyclovir) where the individual has had herpes viral infection is appropriate….			
	1. for adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. for children with CFS/ME with mild	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

	symptoms				
	5. for children with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for children with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
2(m)	T	he use of anti-herpes agents (such as acyclovir) where the individual has NOT had herpes viral infection is appropriate….			
	1. for adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. for children with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for children with CFS/ME	Disagree	…		The GDG reached a consensus in the first round and the statement did

	with moderate symptoms				not progress to Round 2
	6. for children with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
2(n)		The use of gut anti-spasmodics (such as mebeverine, alverine and peppermint oil) where the individual has bowel symptoms is appropriate….	The use of gut anti-spasmodics (such as mebeverine, alverine and peppermint oil) where the individual has bowel symptoms is INAPPROPRIATE.		See discussion about appropriate and inappropriate above.
	1. for adults with CFS/ME with mild symptoms	Uncertain	Disagree	Disagree	Random selection for wider survey
	2. for adults with CFS/ME with moderate symptoms	Uncertain	Disagree	Disagree	Random selection for wider survey
	3. for adults with CFS/ME with severe symptoms	Uncertain	Disagree		The GDG reached a consensus in the first round and the statement did not progress to wider survey.
	4. for children with CFS/ME with mild symptoms	Uncertain	Disagree	Disagree	Random selection for wider survey
	5. for children with CFS/ME with moderate symptoms	Uncertain	Disagree		The GDG reached a consensus in the first round and the statement did not progress to wider survey.

	6. for children with CFS/ME with severe symptoms	Uncertain	Disagree		The GDG reached a consensus in the first round and the statement did not progress to wider survey.
2(o)		The use of gut anti-spasmodics (such as mebeverine, alverine and peppermint oil) where the individual has NO bowel symptoms is appropriate….			The GDG reached a consensus in the first round and the statement did not progress to Round 2
	1. for adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. for children with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for children with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for children with CFS/ME with severe	Disagree	…		The GDG reached a consensus in the first round and the statement did

	symptoms				not progress to Round 2
2(p)		The use of skeletal anti-spasmodics (such as diazepam, baclofen, and clonazepam) where the individual has muscle pain, cramps or twitching is appropriate….	The use of skeletal anti-spasmodics (such as diazepam, baclofen, and clonazepam) where the individual has MODERATE OR SEVERE muscle pain, cramps or twitching is INAPPROPRIATE….		This statement was clarified following the 1st round discussion. See discussion about appropriate and inappropriate above.
	1. for adults with CFS/ME with mild symptoms	Disagree	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	2. for adults with CFS/ME with moderate symptoms	Uncertain	Uncertain	Disagree	GDG was uncertain at round 2, progressed to wider survey
	3. for adults with CFS/ME with severe symptoms	Disagree	Disagree		The GDG reached a consensus in the first round and the statement did not progress to wider survey.
	4. for children with CFS/ME with mild symptoms	Disagree	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	5. for children with CFS/ME with moderate symptoms	Disagree	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	6. for children with CFS/ME with severe symptoms	Disagree	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey

2(p)			The use of skeletal anti-spasmodics (such as diazepam, baclofen, and clonazepam) where the individual has NO muscle pain is INAPPROPRIATE….		This statement was clarified following the 1st round discussion to separate from above.
	1. for adults with CFS/ME with mild symptoms	Not included	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	2. for adults with CFS/ME with moderate symptoms	Not included	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	3. for adults with CFS/ME with severe symptoms	Not included	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	4. for children with CFS/ME with mild symptoms	Not included	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	5. for children with CFS/ME with moderate symptoms	Not included	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.
	6. for children with CFS/ME with severe symptoms	Not included	Agree		The GDG reached a consensus in the round 2 and the statement did not progress to wider survey.

1

6.4.5 Recommendations

Note: numbers in square brackets are as in the NICE guidelines.

General management strategies after diagnosis [1.4]

Symptom management [1.4.1]

There is no known pharmacological treatment or cure for CFS/ME. However, symptoms of CFS/ME should be managed as in usual clinical practice. [1.4.1.1]

No research evidence was found to support the experience of some people with CFS/ME that they are more intolerant of drug treatment and have more severe adverse/side effects. However, if people with CFS/ME have concerns, healthcare professionals may consider starting drug treatment for CFS/ME symptoms at a lower dose than in usual clinical practice. The dose may be increased gradually, in agreement with the patient. [1.4.1.2]

Drug treatment for children and young people with CFS/ME should be started by a paediatrician. However, prescribing may be continued in primary care, depending on the preferences of the patient and their carers, and local circumstances. [1.4.1.3]

See also recommendations in section 6.5.5.

Strategies that should not be used for CFS/ME [1.4.6]

The following drugs should not be used for the treatment of CFS/ME:

- monoamine oxidase inhibitors
- glucocorticoids (such as hydrocortisone)
- mineralocorticoids (such as fludrocortisone)
- dexamphetamine
- methylphenidate
- thyroxine
- antiviral agents. [1.4.6.1]

Pharmacological interventions for symptom control [1.6.3 – note after referral for specialist CFS/ME care]

If chronic pain is a predominant feature, healthcare professionals should consider referral to a pain management clinic. [1.6.3.1]

Prescribing of low-dose tricyclic antidepressants, specifically amitriptyline, should be considered for people with CFS/ME who have poor sleep or pain. Tricyclic antidepressants should not be offered to people who are already taking selective serotonin reuptake inhibitors (SSRIs) because of the potential for serious adverse interactions. [1.6.3.2]

Melatonin may be considered for children and young people with CFS/ME who have sleep difficulties, but only under specialist supervision because it is not licensed in the UK. [1.6.3.3]

6.4.6 Deriving recommendations

Discussion of the evidence

Before beginning their review of the evidence, the GDG agreed that they would be sceptical of any intervention that was supported by one small trial only and would not make an evidence statement on this basis. The GDG did not find strong evidence for any pharmacological or immunological therapies. The number of patients in each trial was generally small and many diverse outcomes were measured, making it difficult to reach conclusions or to compare trials.

In addition, particularly with immunoglobin studies, there were large dosage variations across the studies which made any comparison difficult; there is not necessarily a dose–response effect and different doses may elicit very different effects. It was agreed that the *Staphylococcus* toxoid papers should be rejected as the patients studied were women with muscle pain/fibromyalgia and thus not representative of a CFS/ME population. The complication and side-effect rates

were also very high in the immunoglobin studies. The GDG agreed that they did not want to make any evidence statements on immunotherapy.

The GDG was also mindful of the side effects or adverse effects of many of the treatments reviewed. The GDG felt unable to exclude the use of pharmacological interventions for which evidence is lacking to support or reject their use and included these in the questionnaire. It is felt that much research is needed to evaluate appropriate pharmacological interventions, with an emphasis on adverse effects and safety.

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

Expert co-optees

The GDG invited co-optees with expertise in the management of CFS/ME in children to a meeting to discuss difficult areas. The co-optees' view was that the drugs primarily used for the management of the condition in children were:

- melatonin
- amitriptyline
- gabapentin
- non-steroidal anti-inflammatory drugs (NSAIDs)
- other pain killers.

The GDG discussed with them the use of SSRIs as this is an area of uncertainty. The co-optees' view was that SSRIs, in particular fluoxetine, are used for adolescents but not for younger children. Their view was that opinion varied on using them for low mood as opposed to comorbid clinical depression. They were

sometimes used in patients who have low mood and have tried other treatments. As opinion varied the GDG decided to include SSRIs in the questionnaire.

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

Questionnaire

As is demonstrated by the results of the questionnaire, there is a great deal of uncertainty within both the GDG and the wider group regarding the appropriateness of many of the drug treatments for the symptoms of CFS/ME. There was some consensus that some drugs may be helpful in particular circumstances, and recommendations were made for these. The GDG agreed that the general principles of care when prescribing drugs to a person with CFS/ME in order to manage symptoms were to:

- use any drug with caution
- start with low doses
- discuss prescription with the patient, who must give informed consent.

The GDG's discussion of the questionnaire results concluded as follows.

SSRIs: It appears from the questionnaire that there was reasonable consensus that SSRIs are no less useful for people with CFS/ME than for those with other conditions. There was consensus that SSRIs were the preferred first-line treatment for mood disorders in line with the NICE depression guideline (www.nice.org.uk/CG023). Caution should be exercised due to the sensitivity of many CFS/ME patients to drugs.

Venlafaxine: There was a strong consensus from the GDG and both patients and healthcare professionals that venlafaxine was generally inappropriate but further research is needed. The GDG decided not to make a negative recommendation as venlafaxine may be appropriate in some situations.

Tricyclics: The wider group consensus was that tricyclics were inappropriate for children with severe pain and sleep problems and depression. The GDG decided that tricyclics at low dose should be considered as a treatment option for adults and children to relieve pain and sleep symptoms. If depression was present, the use of low-dose tricyclics was not considered an appropriate option as they are only effective at higher doses. However, the prescribing of tricyclics should only be undertaken after referral to specialist CFS/ME care.

Gabapentin: The GDG noted that the wider survey was supportive of gabapentin in people with severe CFS/ME. The GDG was uncertain why this was the case. Because of its side effects, the GDG did not think that gabapentin should be used for mild pain, but there will be certain individual cases where it might be considered despite its relatively high side-effect profile. The GDG decided not to make a positive or negative recommendation.

Monoamine oxidase inhibitors: There was agreement on the questionnaires that these should not be used and the GDG made a negative recommendation.

Melatonin: The wider survey group was strongly in favour of its use. The view of the GDG was that the use of melatonin might be considered for sleep disorders, although it is not licensed.

Gut antispasmodics: NICE is currently developing a clinical guideline on the management of irritable bowel syndrome. Gut antispasmodics should be used as normal.

Antivirals and immunoglobins: The consensus was that they do not have benefit in the treatment of CFS/ME.

6.5 Dietary interventions and supplements

6.5.1 Evidence statements

*6.5.1.1 **At present, evidence is insufficient to support a beneficial effect of dietary supplements, including essential fatty acids in CFS/ME. (Evidence level 1++)***

6.5.2 Clinical evidence summary

*6.5.2.1 **Summary of evidence presented in Appendix 1***

Eleven studies were reviewed that addressed the treatment of CFS/ME patients with supplements. Only three of these studies had validity ratings > 10 and all sample sizes were < 90. No significant effects were noted in RCTs of general supplements, pollen extract and medicinal mushrooms. There was no effect on symptoms nor any general improvement with use of acclydine and amino acids. Studies that examined essential fatty acid supplements were conflicting, with one good-quality RCT reporting no improvements and one slightly larger controlled trial conducted in patients with postviral syndrome reporting an overall beneficial effect. This trial showed greater shifts towards normal levels of fatty acid concentration in treatment groups, most of which were statistically significant, as well as improvements in symptom measures. One small good-quality RCT showed that magnesium supplements had an overall positive effect of improvements in measures of energy and pain, emotional reactions, general health and laboratory measures, but not in sleep, physical mobility or social isolation. However, two of 34 participants in this study developed a rash and dropped out.

*6.5.2.2 **Additional clinical evidence***

No new evidence was found.

6.5.3 Health economics evidence summary

No evidence was found.

6.5.4 Clinical scenario questionnaire to GDG and wider group

So that consistent principles were applied in rating the evidence statements, the GDG and the wider group assumed the following.

1. The person with CFS/ME and healthcare professionals involved in their care will make decisions in partnership. These are directed by the patient's personal preferences and build on the existing experience and skills of the professional.

2. All treatments are offered allowing the person with CFS/ME to refuse without compromising the further therapeutic relationship.

3. There is a good rapport in which the patient and their families/carers feel believed and validated.

4. Treatment is provided by the NHS in the context of availability of adequate numbers of competent, appropriately trained healthcare professionals.

5. Minimal waiting times for good-quality services are adhered to.

6. Doses were in line with the recommended daily allowance where available.

In reviewing the results of the first round, the GDG had assumed in general that any food supplement was considered as a treatment for CFS/ME, not as a contribution to general health. This needed to be made explicit, and therefore statements progressing to Round 2 were clarified.

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	Dietary Supplements				
4(a)		**Vitamin B12 injections should be used in….**			
	1. adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. children with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. children with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. children with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
4(b)		**Vitamin C should be used in…..**			The GDG reached a consensus in the first round and the statement did not progress to Round 2
	1. adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. children with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. children with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. children with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
4(c)		**Co-enzyme Q10 should be used in….**			
	1. adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. children with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. children with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. children with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
4(d)		**Magnesium should be used in….**			

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	1. adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. children with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. children with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. children with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
4(e)		**Echinacea should be used in….**			
	1. adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
					progress to Round 2
	2. adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. children with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. children with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. children with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
4(f)		**Nicotinamide adenine dinucleotide (NADH) should be used in….**			
	1. adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	2. adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. children with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. children with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. children with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
4(g)		**Essential Fatty acids should be used in….**	**Essential fatty acids are appropriate for the treatment of….**		**Question reworded to make clear that it was about treatment of CFS/ME not general health.**
	1. adults with CFS/ME with mild symptoms	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	2. adults with CFS/ME with moderate symptoms	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	3. adults with CFS/ME with severe symptoms	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	4. children with CFS/ME with mild symptoms	Disagree	Disagree		The GDG reached a consensus in Round 2 and the statement did not progress to Wider survey
	5. children with CFS/ME with moderate symptoms	Disagree	Disagree		The GDG reached a consensus in Round 2 and the statement did not progress to Wider survey
	6. children with CFS/ME with severe symptoms	Disagree	Disagree	Uncertain	Random inclusion
4(h)	**Multivitamin and mineral supplements are appropriate for the treatment of…...**				
	1. for adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. for adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. for adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	4. for children with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. for children with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. for children with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	Diets				
4(i)	**An anti-candida (low yeast, low sugar) diet is appropriate for….**				
	1. adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	4. children with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. children with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. children with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
4(j)		**An exclusion diet followed by food challenges where the individual has bowel symptoms should be used in...**	**An clinically supervised exclusion diet followed by food challenges where the individual has moderate or severe bowel symptoms is appropriate for….**		**Statement was modified to make clear the severity of the symptoms and clinical supervision.**
	1. adults with CFS/ME with mild symptoms	Uncertain	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
	2. adults with CFS/ME with moderate symptoms	Uncertain	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
	3. adults with CFS/ME with severe symptoms	Uncertain	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
	4. children with CFS/ME with mild symptoms	Disagree	Uncertain	Agree	GDG was uncertain at round 2, progressed to wider survey
	5. children with CFS/ME with moderate symptoms	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	6. children with CFS/ME	Uncertain	Uncertain	Agree	GDG was uncertain at round

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
	with severe symptoms				2, progressed to wider survey
4(k)		**An exclusion diet followed by food challenges where the individual is has no bowel symptoms should be used in….**			
	1. adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. children with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. children with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. children with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not

		GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Group Question and Results	Discussion
					progress to Round 2

6.5.5 Recommendations

Note: numbers in square brackets are as in the NICE guidelines.

Symptom management [1.4.1]

If a person experiences nausea as part of CFS/ME, this should be managed conventionally, including giving advice on eating little and often, snacking on dry starchy foods and sipping fluids. The use of anti-emetic drugs should be considered only if the nausea is severe. [1.4.1.4]

Although exclusion diets are not generally recommended for managing CFS/ME, many people find them helpful in managing symptoms, including bowel symptoms. If a person with CFS/ME undertakes an exclusion diet or dietary manipulation, healthcare professionals should seek advice from a dietitian because of the risk of malnutrition. [1.4.1.5]

Complementary and supplementary therapies [1.4.7]

See also section 6.6.5.

There is insufficient evidence for the use of supplements – such as vitamin B_{12}, vitamin C, co-enzyme Q10, magnesium, NADH (nicotinamide adenine dinucleotide) or multivitamins and minerals – for people with CFS/ME, and therefore they should not be prescribed for treating the symptoms of the condition. However, some people with CFS/ME have reported finding these helpful as a part of a self-management strategy for their symptoms. [1.4.7.2]

People with CFS/ME who are using supplements should be advised not to exceed the safe levels recommended by the Food Standards Agency[†††]. [1.4.7.3]

[†††] See www.food.gov.uk

Some people with CFS/ME need supplements because of a restricted dietary intake or nutritional deficiencies. Healthcare professionals should seek advice from a dietitian about any concerns. [1.4.7.4]

6.5.6 Deriving recommendations

Discussion of the evidence

When the GDG reviewed the evidence for nutritional supplements, it was regarded as weak and inconclusive. The studies were small and the outcome measures diverse and in many cases not clearly defined. Therefore no conclusions could be reached.

This view was supported by the questionnaire responses. While supplements may be useful for general health, the GDG agreed that they could not be recommended for the management of CFS/ME.

Although weight loss may occur in people with CFS/ME, it was not considered to be a defining symptom of the condition. The GDG noted that profound weight loss is often a symptom of a serious underlying disorder so should not be attributed to CFS/ME without appropriate assessment and investigation. The GDG also noted the need for expert dietetic input where there is concern about nutritional intake.

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

6.6 Complementary therapies

6.6.1 Evidence statement

6.6.1.1 The evidence found on the effects of complementary therapies for CFS/ME is inadequate in terms of quantity and/or quality.

6.6.2 Clinical evidence summary

6.6.2.1 Summary of evidence presented in Appendix 1

Trials of complementary therapies included studies on the effectiveness of homeopathy, massage therapy and osteopathy in treating CFS symptoms. One high-quality study of homeopathic treatments showed a significant improvement in fatigue and on some physical dimensions of the functional limitations profile. Massage therapy and osteopathy appeared to improve measures of fatigue, back pain and sleep, but the quality of these studies was very poor.

6.6.2.2 Additional clinical evidence

No new evidence was found.

6.6.3 Health economics evidence summary

No evidence was found.

6.6.4 Clinical scenario questionnaire to GDG and wider group

So that consistent principles were applied in rating the evidence statements, the GDG and the wider group assumed the following.

1. The person with CFS/ME and healthcare professionals involved in their care will make decisions in partnership. These are directed by the patient's personal preferences and build on the existing experience and skills of the professional.

2. All treatments are offered allowing the person with CFS/ME to refuse without compromising the further therapeutic relationship.

3. There is a good rapport in which the patient and their families/carers feel believed and validated.

4. Treatment is provided by the NHS in the context of availability of adequate numbers of competent, appropriately trained healthcare professionals.

5. Minimal waiting times for good-quality services are adhered to.

Following the first round the GDG decided to use a global statement in the wider questionnaire about complementary therapies in general rather than asking about specific techniques.

	Complementary Therapies	GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Survey Question and Results	Discussion
4(l)		**Acupuncture should be used in….**	**Acupuncture by a registered therapist is appropriate for symptom control in…….**		Question refined for second round
	1. adults with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	2. adults with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	3. adults with CFS/ME with severe symptoms	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	4. children with CFS/ME with mild symptoms	Disagree			The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. children with CFS/ME with moderate symptoms	Disagree			The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. children with CFS/ME with severe symptoms	Disagree			The GDG reached a consensus in the first round and the statement did not progress to Round 2
4(m)	**Homeopathy by a registered therapist is appropriate for symptom control in…**	**Homeopathy should be used in….**	**Homeopathy by a registered therapist is appropriate for symptom control in…**		
	1. adults with CFS/ME with mild symptoms	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	2. adults with CFS/ME with moderate symptoms	Uncertain	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	3. adults with CFS/ME with severe symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2 The GDG reached a consensus in the first round and the statement did not progress to Round 2
	4. children with CFS/ME with mild symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	5. children with CFS/ME with moderate symptoms	Disagree	…		The GDG reached a consensus in the first round and the statement did not progress to Round 2
	6. children with CFS/ME with severe symptoms	Disagree	…		

	Complementary Therapies	GDG Round 1 Question and Results	GDG Round 2 Question and Results	Wider Survey Question and Results	Discussion
4(m)		**Other complementary therapies by a registered therapist are appropriate for symptom control in…**			This statement was developed by the GDG to abridge statements above and represent complementary therapies.
	1. adults with CFS/ME with mild symptoms	Not included	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey progressed to wider survey progressed to wider survey
	2. adults with CFS/ME with moderate symptoms	Not included	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	3. adults with CFS/ME with severe symptoms	Not included	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	4. children with CFS/ME with mild symptoms	Not included	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	5. children with CFS/ME with moderate symptoms	Not included	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey
	6. children with CFS/ME with severe symptoms	Not included	Uncertain	Uncertain	GDG was uncertain at round 2, progressed to wider survey

6.6.5 Recommendations

Note: numbers in square brackets are as in the NICE guidelines.

Complementary and supplementary therapies [1.4.7]

See also section 6.5.5.

There is insufficient evidence that complementary therapies are effective treatments for CFS/ME and therefore their use is not recommended. However, some people with CFS/ME choose to use some of these therapies for symptom control, and find them helpful. [1.4.7.1]

6.6.6 Deriving recommendations

Discussion of the evidence

As with drug therapy, the GDG agreed that they would view with scepticism evidence supported by only one small trial and would not make an evidence statement in these circumstances. It was therefore decided not to make an evidence statement on homeopathy.

After consultation on the draft guideline was complete, the GDG continued discussions on the recommendations, based on the comments from the stakeholders. For details of changes and responses to stakeholder comments, please see the comments table which can be found on the NICE website at www.nice.org.uk

Questionnaire

The questionnaire confirmed a high level of uncertainty about the benefit of complementary therapies in the management of CFS/ME. The GDG decided that whilst such therapies may be helpful for individuals as part of their own management, they could not be recommended as part of treatment for CFS/ME.

6.7 Review and ongoing management

No evidence was found regarding review and ongoing management. The GDG agreed the following recommendations.

6.7.1 Recommendations

Note: numbers in square brackets are as in the NICE guidelines.

Review and ongoing management [1.8]

Regular, structured review should be undertaken for all people with CFS/ME. The review should include, if appropriate:

- Assessing improvement or deterioration in symptoms.
- Assessing any adverse or unwanted effects of therapy.
- Ongoing investigations.
- Considering the need to repeat investigations (for children and young people, repeating investigations should be considered if there is no improvement after 1 year).
- Reviewing the diagnosis, especially if signs and symptoms change (see recommendation 1.2.1.4).
- Considering referral to specialist CFS/ME care.
- Reviewing equipment needs.
- Assessing any additional support needs (see sections 1.1 and 1.4). [1.8.1.1]

The timing of the reviews should depend on the severity and complexity of symptoms, the effectiveness of any interventions, and the needs of the person with CFS/ME. [1.8.1.2]

7 People with severe CFS/ME

7.1 Introduction

No definitive studies have been carried out in the UK to determine the prevalence of severe CFS/ME in people with CFS/ME, but estimates range from 25%[4] (population and setting not clear) to a lower figure experienced in general clinical practice.‡‡‡ People who have severe CFS/ME may be unable to carry out activities of daily living and may spend a significant proportion, or all, of the day in bed.

The symptoms experienced by patients with severe CFS/ME are diverse and debilitating, and these may fluctuate and change, both in type and in severity. It is therefore important that the management and care plan is flexible and reviewed regularly. In the clinical experience of several members of the GDG, some people with severe CFS/ME do improve and, after being bedridden for a number of years, now have mild/moderate symptoms and are active. However some people may have severe CFS/ME for years, and some may never recover. Reports have also been published of people with severe CFS/ME that has responded well to individually designed and supported activity management programmes.[48;49]

7.2 Purpose and context of this chapter

In the past, this group of patients have either received healthcare that is inappropriate and even harmful, or been unable to access healthcare services. There are anecdotal reports of people with severe CFS/ME not seeing medical practitioners for many years.

‡‡‡ As noted, there are no cited epidemiological data to support these figures in the UK.

The purpose of this chapter is to highlight where there are additional needs or additional caution is required specifically in the care of people with severe CFS/ME. However, this is not intended as a definitive guide to the specialist CFS/ME care needed for this patient group, and further reading is recommended.[50]

This chapter does not address issues that commonly arise in conditions where individuals are severely and chronically ill, for example access to care and the stresses put on carers. These are addressed in other publications such as the National Service Framework for Long Term Conditions www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/LongTermConditions/fs/en (England only, no equivalent available for Wales). Although the NSF for Long Term Conditions does not refer specifically to CFS/ME, it is the GDG's opinion that the standards and examples of best practice included are generalisable to the care of people with CFS/ME. The NHS Patient Advice and Liaison Services (PALS; www.pals.nhs.uk) also provide a general source of information and support to patients and carers.

People with severe CFS/ME should, in general, have the same access to services as would any person with CFS/ME. All of the recommendations in this chapter relating to people with severe CFS/ME should be read in the context of all the recommendations and be specially tailored to individual choice, need and level of severity. For reference, only those recommendations exclusively relevant to people with severe CFS/ME are repeated in this chapter.

7.3 General recommendations

Note: numbers in square brackets are as in the NICE guidelines.

Key principles of care for people with severe CFS/ME [1.9]

General principles of care [1.9.1]

Management of severe CFS/ME is difficult and complex and healthcare professionals should recognise that specialist expertise is needed when planning and providing care for people with severe CFS/ME. [1.9.1.1]

Diagnosis, investigations, management and follow-up care for people with severe CFS/ME should be supervised or supported by a specialist in CFS/ME. [1.9.1.2]

People with severe CFS/ME may need to use community services at times. These services may include nursing, occupational therapy, dietetics, respite care, psychology and physiotherapy (see the 'National service framework for long-term conditions'[§§§]). The input of different professionals should be coordinated by a named professional. [1.9.1.3]

People with severe CFS/ME should be offered a summary record of every consultation because of their cognitive difficulties. [1.9.1.4]

Most people with CFS/ME will not need hospital admission. However, there may be circumstances when a planned admission should be considered. The decision to admit should be made with the person with CFS/ME and their family, and be based on an informed consideration of the benefits and disadvantages. For example, a planned admission may be useful if assessment of a management plan and investigations would require frequent visits to the hospital. [1.9.1.5]

[§§§] Available from www.dh.gov.uk

Rest [1.9.2]

When making decisions about prolonged bed rest, healthcare professionals should seek advice from a specialist experienced in the care of people with severe CFS/ME. The significant physical and psychological risks associated with prolonged bed rest should be taken into account. [1.9.2.1]

Healthcare professionals working with people with severe CFS/ME who are in bed most (or all) of the time, should explain the associated risks (such as postural hypotension, deep venous thrombosis, osteoporosis, pressure sores and deconditioning) and monitor these. [1.9.2.2]

Management approaches [1.9.3]

People with severe CFS/ME should be offered an individually tailored activity management programme (see recommendation 1.6.2.22) as the core therapeutic strategy, which may:

- be delivered at home, or using telephone or email if appropriate
- incorporate the elements of recommendation 1.6.2.22 and draw on the principles of CBT and GET (see recommendations 1.6.2.1–21). [1.9.3.1]

An activity management programme should be reviewed regularly and frequently. [1.9.3.2]

7.4 Additional information related to Chapter 4 – General principles of care

People with severe CFS/ME should be given information about their condition and management in a format that is accessible to them. Patients with severe cognitive difficulties may benefit from an audio tape or written summary of the consultation. Contact and communication with the Department for Work and Pensions and other relevant benefit agencies may be an issue and this should be discussed and advice provided, if appropriate.

7.4.1 Support

The guideline has highlighted the impact that severe CFS/ME may have on many aspects of life and the following section highlights the support needs of patients and their carers. It is recognised that people with severe CFS/ME face particular difficulties and barriers when accessing care and that they have specific needs.

Home support

Patients with severe CFS/ME may require domiciliary visits by the CFS/ME multidisciplinary team with reviews from the GP and specialist clinician as appropriate. Regular home reviews and the use of telephone, video link, email or text messaging, as appropriate, may facilitate good communication and therapeutic support.

A mutually agreed key worker should be appointed, and an understanding, supportive and trusting relationship should be established early in the process of care.

A full functional assessment of the personal and domestic needs of the patient within the home should be completed (for example, people with severe CFS/ME are often sensitive to light, noise and chemicals, so may require quiet, dark surroundings with no or limited use of household products such as cleaning products or air fresheners), as well as an assessment of the carer's needs. Carers for people with severe CFS/ME will need support and healthcare professionals should provide information on the sources noted above.

The provision of equipment and environmental adaptation as part of an agreed management plan should be considered in order to increase independence, allow dignity, and increase overall functioning for patients with severe CFS/ME. As with any intervention, the use of equipment and adaptations should be reviewed regularly.

There may, however, be occasions when patients with severe CFS/ME are unable to make progress at home (despite input from the CFS/ME team) and

may benefit from a period of admission to specialist CFS/ME services. This provides an opportunity to review management and provide a higher level of support. It is also an opportunity to review symptom presentation and medication, and to access further investigations if needed.

Children and young people, and adults in further or higher education, who have severe CFS/ME will be unable to access conventional education and therefore individualised learning plans need to be developed. This will require close liaison between those providing education at home (home tuition and virtual learning) and the clinical team. It is important to make sure that cognitive activities are included in the management plan and it may be necessary to provide some training about CFS/ME for the teachers involved. See the exemplar on Chronic Fatigue Syndrome (CFS) and Myalgic Encephalopathy (ME) which forms part of the National Service Framework in England for children, young people and maternity services[51] (available at www.dh.gov.uk/assetRoot/04/09/81/25/04098125.pdf). See also the Wales National Service Framework for children, young people and maternity services at www.wales.nhs.uk.

Impact on families and carers

Caring for a person with severe CFS/ME can be overwhelming for the family and carers. Healthcare professionals need to be aware of the impact that symptoms can have on family life, including the disruption of family routine, isolation, lack of support and changes in family roles. As with other illnesses, appropriate support should be offered to the family and carer. Please refer to the National Service Framework for Long Term Conditions (available at www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/LongTermConditions/fs/en for England; Wales does not yet have a specific NSF for long term care) which outlines what help and support carers and families can expect to receive.

7.4.2 Other considerations

Child protection

A lack of understanding and knowledge about CFS/ME, or lack of a clear diagnosis of CFS/ME, may lead to child protection concerns, as may disagreement between parents and professionals over preferred treatments.

Child protection should be considered as in any other chronic illness or disability. However healthcare professionals should be aware that:

- unexplained symptoms in a child or young person do not constitute evidence of abuse
- the exercising of choices about treatment or education by parents/carers and/or a young person does not constitute evidence of abuse
- rapport with the family and a cooperative relationship using a flexible approach is essential to successful management. A child protection referral is likely to be destructive if based on flimsy or ill-reasoned evidence
- the differential diagnosis of fabricated or induced illness (FII) is difficult. Paediatricians should follow the Department of Health guidelines and RCPCH guidelines on FII.

Key documents that address the issue of child protection include The Chief Medical Officer's Working Group Report on CFS/ME[4] and the Royal College of Paediatrics and Child Health Evidence Based Guideline for the Management of CFS/ME.[1]

Sectioning under the Mental Health Act

Whilst mental health professionals may have a role to play in the treatment of CFS/ME, both in assessment and management of the condition and in the treatment of comorbid psychiatric illness, use of the Mental Health Act in management of the condition is extremely rare. This is likely to occur where

CFS/ME is complicated by severe eating disorders, depression, psychosis or other forms of severe mental illness.

Healthcare professionals should be aware that the stringencies and protocols that apply to use of the Mental Health Act for any condition should be followed if its use is being considered for a patient who also has CFS/ME.

7.5 Additional information related to Chapter 5 – Making a diagnosis of CFS/ME

7.5.1 Investigations

Patients should have as many as possible of the initial screening tests done at home. If further tests are necessary, the different options should be discussed with the patient so they can make an informed choice. The options are likely to include outpatient or inpatient assessment and timing of the tests. In such settings outside the home, people with severe CFS/ME may require additional provisions, such as an area to rest, as appropriate to their needs.

7.5.2 Diagnosis

As discussed in Chapter 5, a diagnosis of CFS/ME is made on the basis of exclusion of other conditions, and the assessment of symptoms indicative of CFS/ME. There is anecdotal evidence that, in the past, it has taken years for some patients to have a diagnosis of CFS/ME confirmed, and the recommendations should be used by healthcare professionals to raise the suspicion of CFS/ME early in the diagnostic process.

There is a risk in attributing new or unusual symptoms to existing CFS/ME. The healthcare professional must be alert to alternative diagnoses and conditions. Regular review should be carried out to identify and assess both ongoing and new or unusual symptoms in patients with severe CFS/ME.

7.5.3 Referral

As discussed in the management section of the guideline, people with severe symptoms should be referred immediately to specialist CFS/ME care for specific care and support. Early referral may minimise the progression of the illness.

7.6 Additional information related to Chapter 6 – Management

Because of the severity and complexity of symptoms, people with severe CFS/ME are often not able to contribute to, or may be excluded from or under-represented in, research trials. It is acknowledged that there is a lack of research for this patient subgroup. However, there is a growing understanding of how to manage severe CFS/ME from the experience of patients and carers, support groups and health practitioners specialising in this area.

7.6.1 Pharmacological interventions

For people with severe CFS/ME, symptom management is a useful form of management. Although there is no research evidence about greater intolerance to and more severe side effects from drug treatment in people with CFS/ME, some patients with severe CFS/ME have reported being sensitive to medication and experiencing more side effects. Where patients have concerns healthcare professionals should discuss this and may consider starting drug treatment used for the control of CFS/ME symptoms at a lower dose than in usual clinical practice. The dose may then be increased slowly, in agreement with the patient.

7.6.2 General management strategies and non-pharmacological programmes

Any management programme devised for people with severe CFS/ME must be developed and implemented with great care in order to lessen the chance of exacerbation or setback/relapse. People with severe symptoms may be more susceptible to the cumulative effect, with their bodies being unable either to undertake or to sustain activity. In devising a management programme,

healthcare professionals should be aware of the level of disability of patients; for example, being able to sit up or hold a conversation may be very difficult.

7.6.3 Dietary interventions and supplements

While many people with CFS/ME gain weight as a result of reductions in activity, others may lose weight poor nutritional status. However, weight loss should be assessed, and investigated as appropriate, to exclude other possible causes.

People with severe CFS/ME may face many difficulties in achieving adequate and balanced dietary intake including:

- pain and fatigue making the physical process of eating difficult and possibly requiring help with feeding
- sensitivity to the smell or taste of food
- difficult or painful swallowing
- sore throat making eating difficult
- nausea affecting the ability to eat
- bowel symptoms affecting food choices
- food intolerances leading to a restricted diet
- disturbed sleep patterns causing meal patterns to be disrupted
- the need for carers to help with all aspects of food purchase and preparation.

The healthcare professional should work with the patient and carers to address these problems. In some extreme cases, this may include the use of tube feeding, if appropriate.

Referral to a dietitian should be made where there are concerns about weight maintenance or the adequacy of nutritional intake or fluid balance. Dietary

advice should be individualised, depending on the symptoms experienced. Advice on how to combine foods to maximise absorption of nutrients may be useful. Particular attention should be paid to calcium and vitamin D intake in this group, as they are potentially at long-term risk of developing osteoporosis due to the lack of exposure to sunlight, the lack of weight-bearing exercise and possible self-restriction of diet due to food intolerances. There may be a need for use of prescribable supplements where requirements cannot be met by conventional means.

7.6.4 Review

As with other people with CFS/ME the timing of reviews should be based on the needs of the patient. Because of the complexity of the condition, reviews should be carried out under the supervision of a specialist in CFS/ME.

It can be difficult to identify new and potentially serious or fatal comorbidities, and any changes in symptoms or increases in severity should be considered for investigation.

The individual with severe CFS/ME may find it difficult to cope with seeing a number of different people in a multidisciplinary team and efforts should be made to minimise the number of contacts, noise and disruption to the individual. As noted previously, it is important that the patient has a mutually agreed key worker and that they have established an understanding, supportive and trusting relationship.

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